Brightness – Wirken PARP-Inhibitoren bei allen TNBCs

GBG Jahrestreffen
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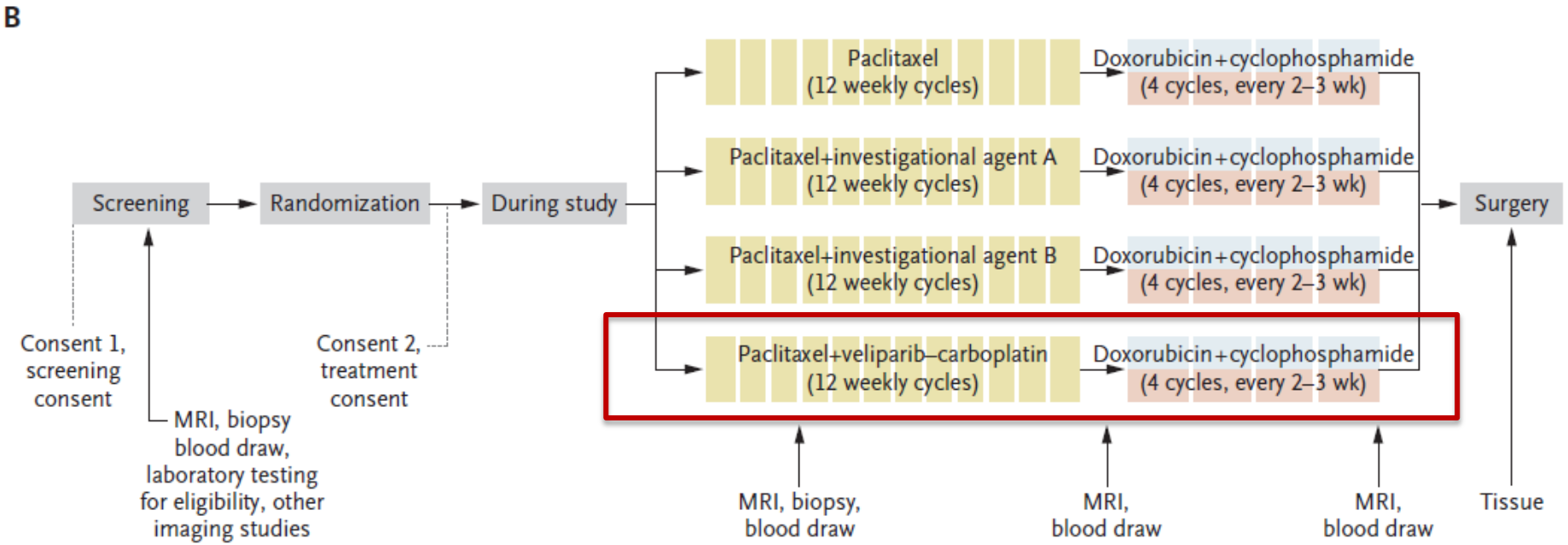
Onkologisches Spitzenzentrum - Ausgezeichnet und gefördert durch

Deutsche Krebshilfe
HELFEN. FORSCHEN. INFORMIEREN.

Brightness - GBG 81 / M14-011

A Randomized, Placebo-Controlled, Double-Blind, Phase 3 Study Evaluating Safety and Efficacy of the Addition of Veliparib Plus Carboplatin Versus the Addition of Carboplatin to Standard Neoadjuvant Chemotherapy Versus Standard Neoadjuvant Chemotherapy in Subjects With Early Stage Triple Negative Breast Cancer (TNBC)

ISPY trial - Platin and PARP Inhibition
Neoadjuvant beim *HER2 negativen* MACA



H Rugo et al. NEJM 2016

ISPY trial - Platin and PARP Inhibition Neoadjuvant

Veliparib/Carboplatin GRADUATES in the Triple Negative Signature

SIGNATURE	Estimated pCR Rate (95% probability interval)		Probability Veliparib + Carbo is Superior to Control	Predictive Probability of Success in Phase 3
	Veliparib/ Carbo	Concurrent Control		
All HER2-	33% (22-43%)	22% (10-35%)	92%	55%
HR+/HER2-	14% (4-27%)	19% (6-35%)	28%	9%
HR-/HER2-	52% (35-69%)	26% (11-40%)	99%	90%

PARP Inhibition in MBC patients With BRCA Mutations

- 62 patients with *BRCA1(37) / 2(25)* mutations
- Stage IV disease
- Median 4,6 previous CHT (68% Platinum)
- Olaparib 400 mg twice daily

OR = 13%	OR prior Platin: 4/42 (10%)
SD = 47%	4/20 (20%)
PFS 3,7 Mo	

Kaufmann JCO 2014

Carboplatin bei Triple Negativem Mammakarzinom

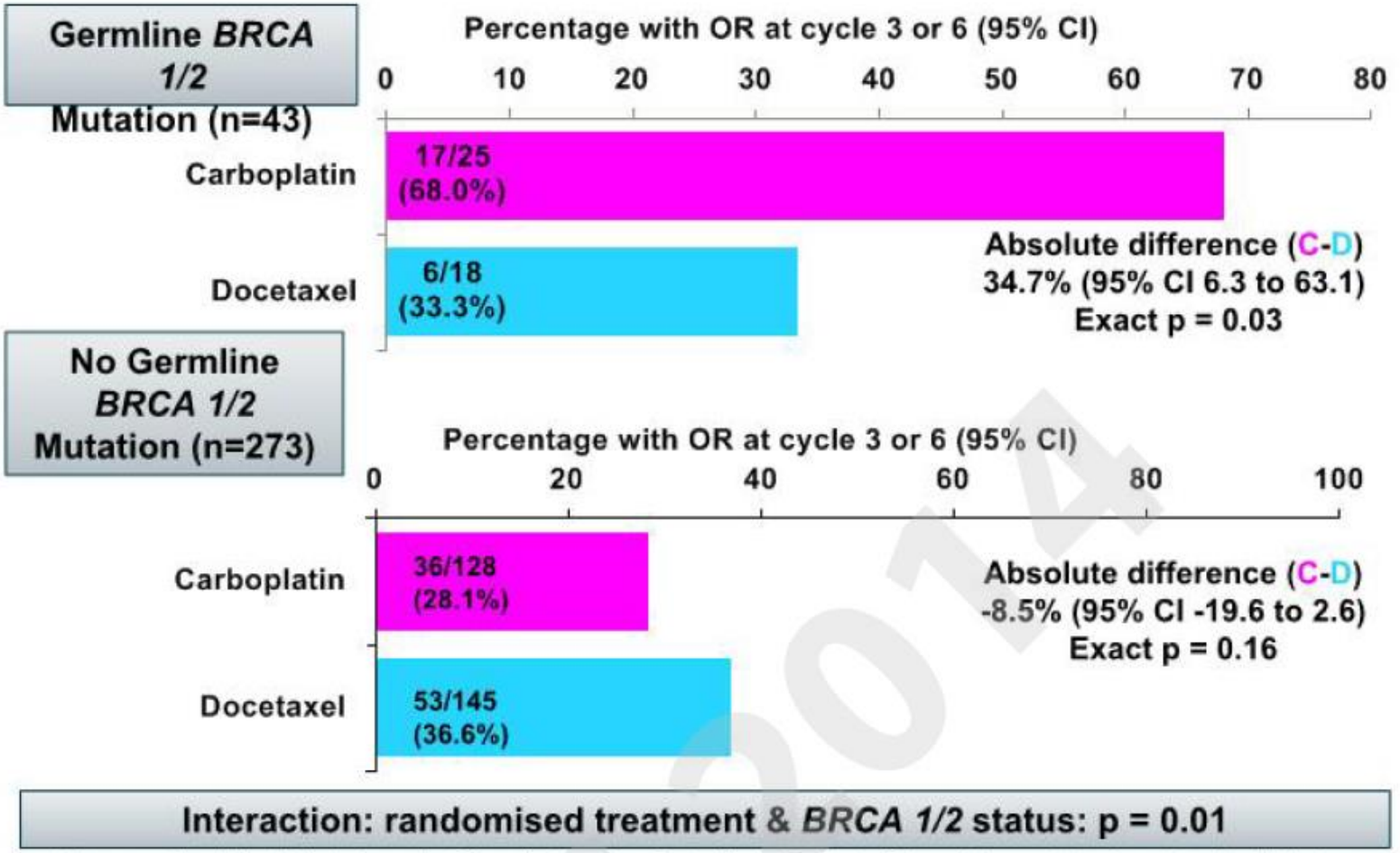
Studien	Anzahl Pat	pCR mit Carbo (ypT0/is N0) (%)	pCR ohne Carbo (ypT0/is N0) (%)		DFS mit Carbo[3] (%)	DFS ohne Carbo (%)	HR
Geparsixto[1]	**315**	**53[3]**	**43**		**85.8**	**76.1**	**0.56[3] P= 0,03**
CALGB[2] 40603	**433**	**54**	**41**		**76**	**71**	**0.84 P=0.36**

[1]18 x **wk** NPLD/Pac/Bev ± Carbo
[2]12 x Pac wk – 4 x ddAC ± Carbo/Bev
[3] Effekt v.a. bei **wt** gBRCA

von Minckwitz et al Lancet Oncol 2014
von Minckwitz et al SABCS 2015
Sikov et al JCO 2015
Sikov et al SABCS 2015

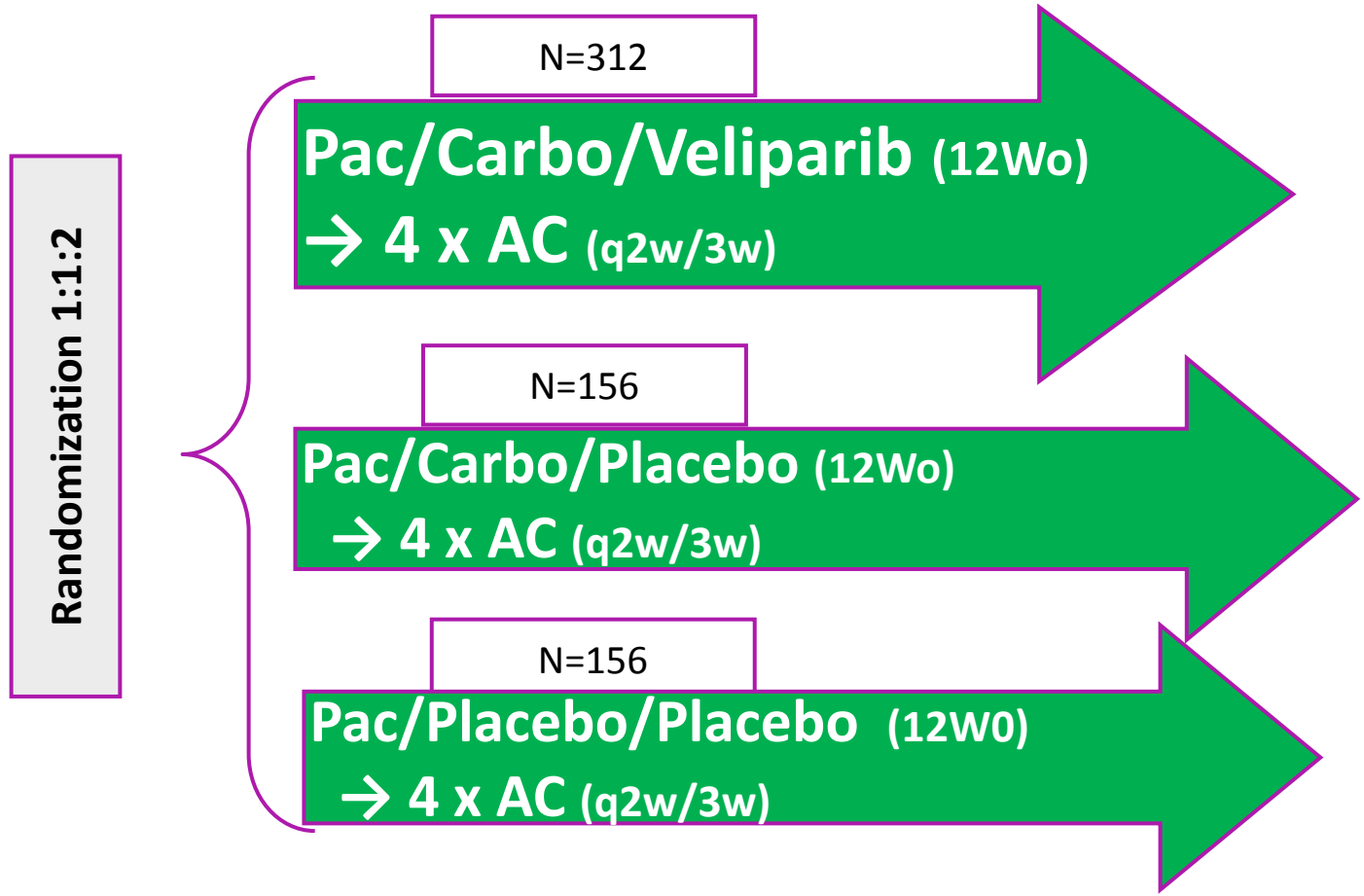
TNT TRIAL

Objective response – *BRCA 1/2* status



A Tutt et al. SABCS 2014

Brightness Studie



Veliparib or Placebo
50 mg BID, daily

Paclitaxel
80 mg/m^2 , q1w

Carboplatin or Placebo
AUC 6, q3w

Doxorubicin
60 mg/m^2 q2w or q3w

Cylcophosphamide
600 mg/m^2 , q2w or q3w

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Inclusion Criteria (main)

- Women ≥ 18 years of age
- Histologically confirmed invasive breast cancer by core needle or incisional biopsy (excisional biopsy is not allowed)
- **Clinical stage cT2-4 cN0-2 or cT1 cN1-2**
- If multiple (up to 2) suspicious lesions are present, each must be biopsied to evaluate for invasive disease and all invasive lesions in the same breast must be triple-negative
- **Documented BRCA germline mutation testing.** All subjects regardless of BRCA mutation status (i.e., wildtype BRCA or germline BRCA mutation) are eligible – BRCA test will be done during screening
- **ER-, PR-, and HER2-negative (triple-negative)** cancer of the breast
- ECOG 0 – 1
- Left ventricular ejection fraction > 50% by MUGA or echocardiogram

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Exclusion Criteria (main)

- Previous anti-cancer treatment with therapeutic intent for current breast cancer
- Previous treatment with carboplatin, paclitaxel, doxorubicin or cyclophosphamide
- Prior therapy with a Poly-(ADP-ribose)-Polymerase (PARP) inhibitor
- Concurrent treatment with an ovarian hormonal replacement therapy or with hormonal agents such as raloxifene, tamoxifen or other selective estrogen receptor modulator (SERM)
- A history of seizure within 12 months prior to study entry
- Pre-existing neuropathy from any cause in excess of Grade 1

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Stratification Factors for Randomization

BRCA Status	Lymph Node Stage+	Planning AC Dosing Schedule
• BRCA 1 and/or BRCA 2* • No BRCA mutation** • Unknown***	• N0 • N1-2	• Q2 weeks (dose dense) • Q3 weeks

* Including subjects with deleterious or suspected deleterious mutations according to core lab

** Including subjects with mutations of uncertain clinical significance according to core lab

*** Subjects will not be denied enrollment due to delays in BRCA testing results. Up to 32 (5%) of subjects will be permitted to enroll with BRCA status unknown

+ During the Screening Axillary Assessment, subjects with suspicious nodes documented by physical exam OR ultrasound will have a biopsy of the nodes (fine needle aspirate or core needle biopsy). Results of the biopsy will determine whether the subject is stratified into the node-positive (cancer present) or node-negative (no cancer present) group

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Endpoints

- **Primär**

  Vergleich der pCR Raten (Brust und Axilla)

  Pac/Carbo/Veliparib –AC vs:

  - Pac/Carbo/Placebo - AC

  - Pac/Placebo/Placebo - AC

- **Sekundär**

  Rate an brusterhaltenden Therapien

- **Tertiär**

  EFS, OS, CRR, Residual Cancer Burden (RCB), ECOG und QoL

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Fragen beim Triple Negativen MACA

- Zusätzliche Wirksamkeit der PARP-Inhibition bei optimalem CHT Regime mit Anthrazyklinen /Taxanen/Platin
- Rolle des Platins zusätzlich zu Taxan/Anthrazyklin
- Einfluss von BRCA auf die Wirksamkeit der unterschiedlichen Regime
- AC q2w vs ACq3w
- Keine „Bev-Kontamination“
- Was fehlt: Pac / Parp-Inhibitor Arm

  (kein head to head Vergleich möglich Parp-Inhibitor vs Carbo)

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Study Status: enrollment (bis März 2016)

Total Rand*	Active (on treatment)	D/C (Pre-surgery)	Completed Surgery	Active (In follow-up)	In Survival
634	246	9	379	357	22

*BRCA mutations = 92; Unk BRCA Mutations = 6

Country	# Sites	# Subjects	% of Total Subjects
Australia	8	19	3%
Belgium	8	25	4%
Canada	5	10	2%
Czech Rep	6	20	3%
France	9	36	6%
Germany	34	55	9%
Hungary	12	20	3%
Israel	4	0	0%
Italy	7	13	2%

Country	# Sites	# Subjects	% of Total Subjects
Netherlands	2	3	0%
Poland	2	0	0%
Russia	7	23	4%
S. Korea	8	73	12%
Spain	19	39	6%
Taiwan	4	8	1%
UK	6	8	1%
USA	77	282	44%

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Aggregate data review: demographics and baseline characteristics (N = 634)

Age	n	%
20-29	16	2.5
30-39	101	15.9
40-49	165	26.0
50-59	197	31.1
60-69	120	18.9
70-79	34	5.4
80 plus	1	0.2

(median age = 51)

Histologic Grade	n	%
High	379	59.8
Intermediate	132	20.8
Low	35	5.5
Unknown	88	13.9

ECOG (baseline)	n	%
0	571	90.1
1	63	9.9

	n	%
Pre-menopause	307	48.4
Post-menopause	314	49.5
(Empty)	13	2.1

Histology/Cytology	n	%
Invasive (infiltrating) ductal	539	85.0
Invasive (infiltrating) lobular	9	1.4
Invasive mammary (NOS)	47	7.4
Invasive mixed ductal/lobular	3	0.5
Medullary	6	0.9
Papillary	1	0.2
Other	29	4.6

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Aggregate data review: clinical stage

Clinical T Stage (baseline)	n	%
cT1a	3	0.5
cT1b	3	0.5
cT1c	66	10.4
cT2	453	71.5
cT3	108	17.0
cT4a	1	0.2

Clinical T Stage (AC1)	n	%
T0	190	30.0
T1	137	21.6
T2	225	35.5
T3	44	6.9
(Empty)	38	6.0

Clinical T Stage (Pre-op)	n	%
T0	233	36.8
T1	118	18.6
T2	207	32.6
T3	41	6.5
(Empty)	35	5.5

Clinical N Stage (baseline)	n	%
N0	366	57.7
N1-2	268	42.3

Clinical N Stage (AC1)	n	%
N0	451	71.1
N1	124	19.6
N2	21	3.3
N3	2	0.3
(Empty)	36	5.7

Clinical N Stage (Pre-op)	n	%
N0	468	73.8
N1	111	17.5
N2	17	2.7
N3	3	0.5
(Empty)	35	5.5

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Aggregate data review: summary of chemotherapy exposure

Paclitaxel

Cycles	n	%
1-8	30	4.8
9	16	2.6
10	20	3.2
11	52	8.3
12	509	81.2
Total	627	100.0

AC

Cycles	n	%
1	15	2.5
2	16	2.7
3	13	2.2
4	557	92.7
Total	601	100.0

Carboplatin bei Triple Negativem Mammakarzinom

Studien	Anzahl Pat	pCR mit Carbo (ypT0/is N0) [3] (%)	pCR ohne Carbo (ypT0/is N0) (%)		DFS mit Carbo[3] (%)	DFS ohne Carbo (%)	HR
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CALBG[2] 40603	433	54	41		76	71	0.84 P=0.36
Brightness	634	?	?				

Ergebnisse pCR und BET Raten

ASCO 2017

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Study Status (April/Mai 2015 - März 2016)

GBG No.	Site	Fully Activated	In Screening	Screened Failure	Randomized (Total)	GBG No.	Site	Fully Activated	In Screening	Screened Failure	Randomized (Total)
108	Huober	29. Apr 15	0	1	7	372	Mau	10. Jul 15	0	1	1
16	Paepke	12.May 15	0	2	7	384	Ober	13. Mar 15	0	0	1
419	Just	11. Jun 15	0	2	6	367	Stefek	29. May 15	0	0	1
619	Wagner	02. Mar 15	0	0	5	737	Stötzer	08. Sep 15	0	0	1
411	Hackmann	23. Mar 15	0	0	4						
574	Kunz	22. Jun 15	0	1	4						
264	Fischer	26. Apr 15	0	1	3						
209	Mundhenke	20. Jul 15	0	1	3						
210	Jackisch	22. Sep 15	0	1	2						
329	Schmatloch	20. Sep 15	0	0	2						
368	Lehnert	20. Jul 15	0	0	2						
459	Heinrich	27. Feb 15	0	0	2						
675	Weigel	14. Apr 15	0	0	2						
348	Möbus	20. Nov 15	0	0	2						

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HERZLICHEN DANK!

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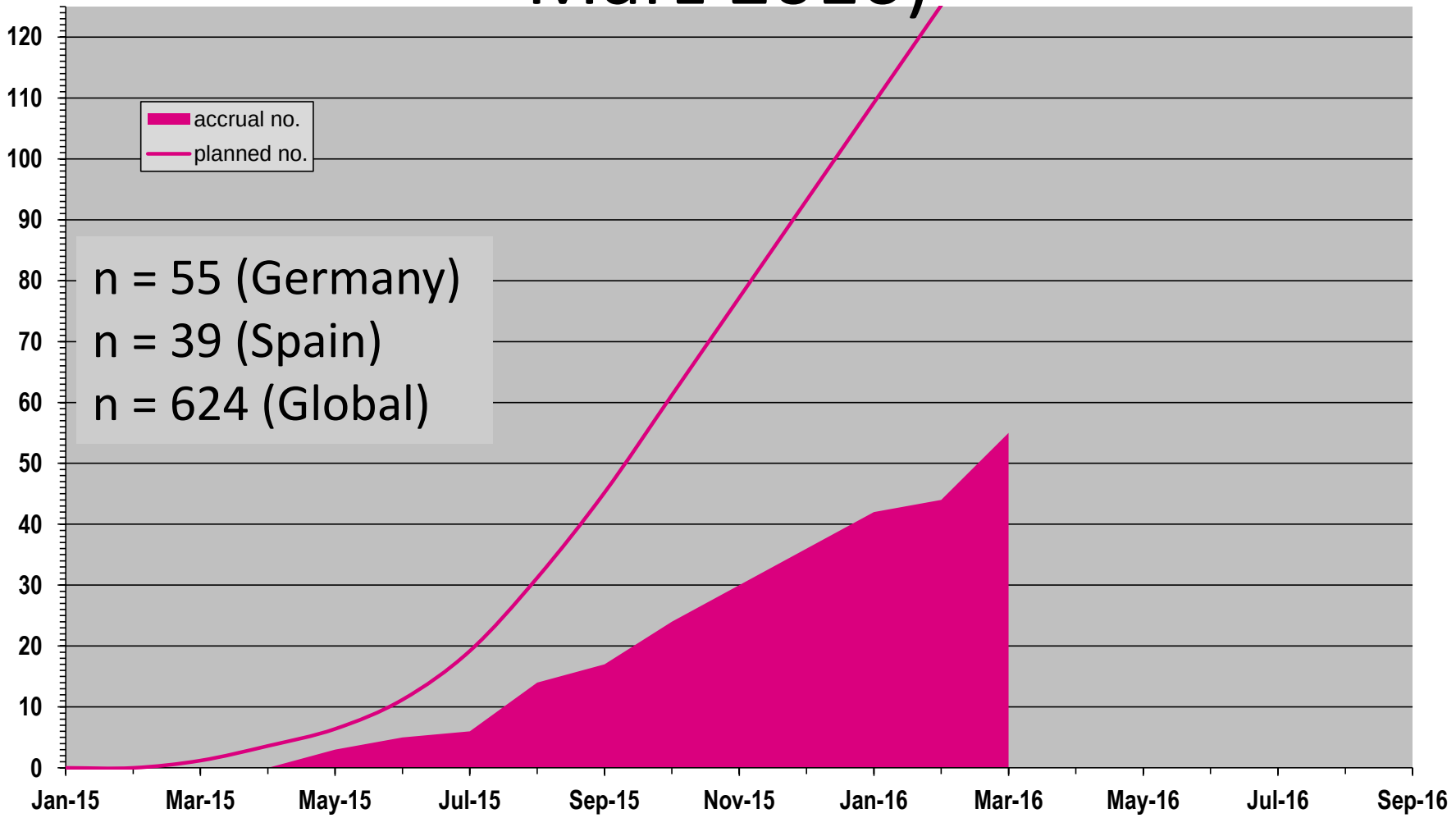
Study Status (finale Rekrutierung 01. März 2016)



Collected Biomaterial

Biomaterial	Visit
Breast tumor biopsies: Core biopsies for histologocal confirmation of TNBC (**randomization upon local result**) (if up to 2 lesions: each must be biopsied to confirm TNBC; preferably 4-2 samples) – FFPE and RNAlater	Screening
BRCA Germline mutation test	Screening,P1
Sample of residual tumor or tumor bed - FFPE and RNAlater	Surgery
Pharmacogenetic blood sample (optional)	P1
Plasma Markers	Screening, P1, P4, AC1
Veliparib pharmacokinetic sample	P1, P4, P7, P10

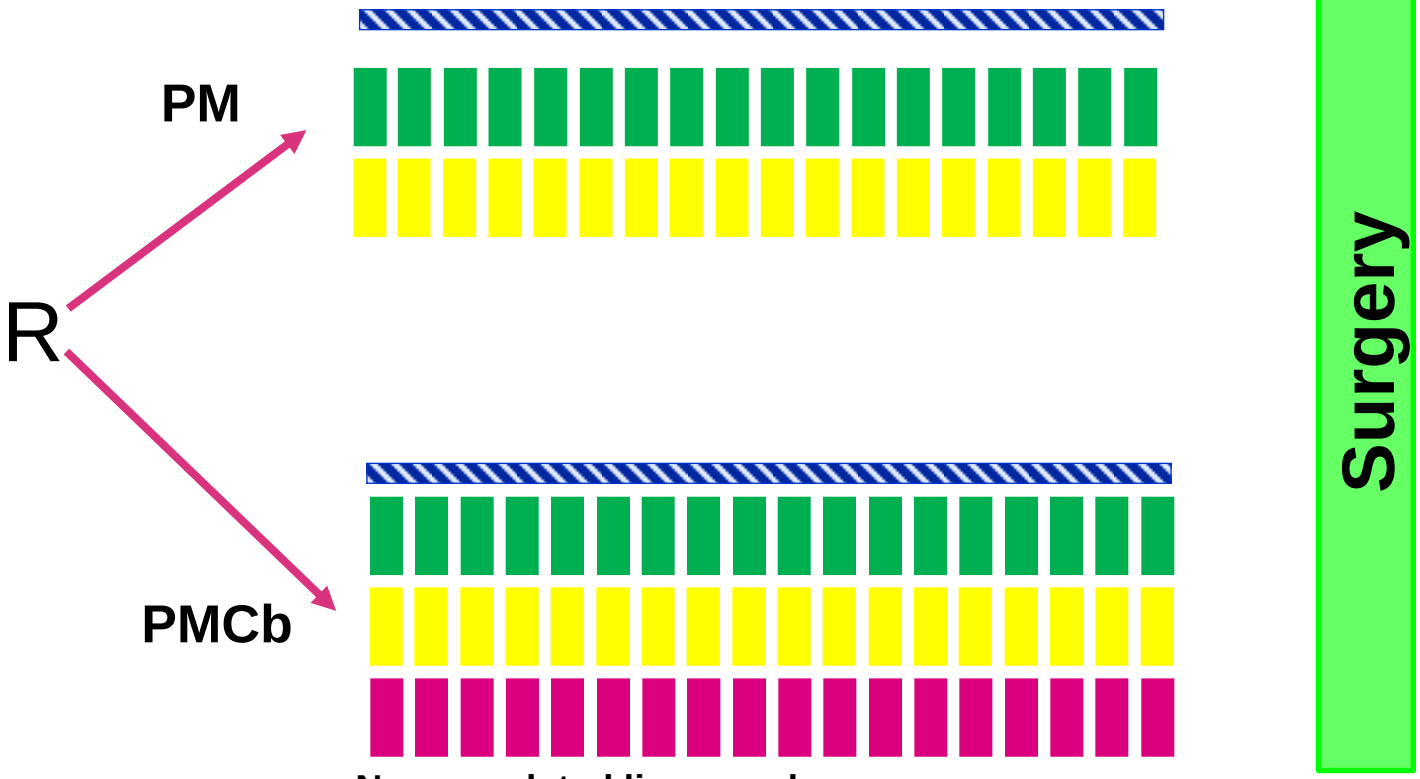
final Study Status (March 2016)

- AbbVie sponsored trial
- Countries activated: 17 (USA, Canada, South Korea, Australia, Taiwan, Czech Republic, Hungary, Italy, Germany, Israel, Belgium, Spain, Russia, France, UK, Netherlands, Poland)
- GBG responsibility:
  - Germany: 37 sites
  - Spain (GEICAM): 19 sites
- Sites initiated 220
- Enrolled: 634
- INC globally, along with Alliance, NSABP, and USO (North American Coop Group Partners): 540 pts. (April 2014-March 2016)
- GBG and GEICAM: 94 pts. (April 2015-March 2016)

TNBC subgroup: LPD+Pac ± Carboplatin

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

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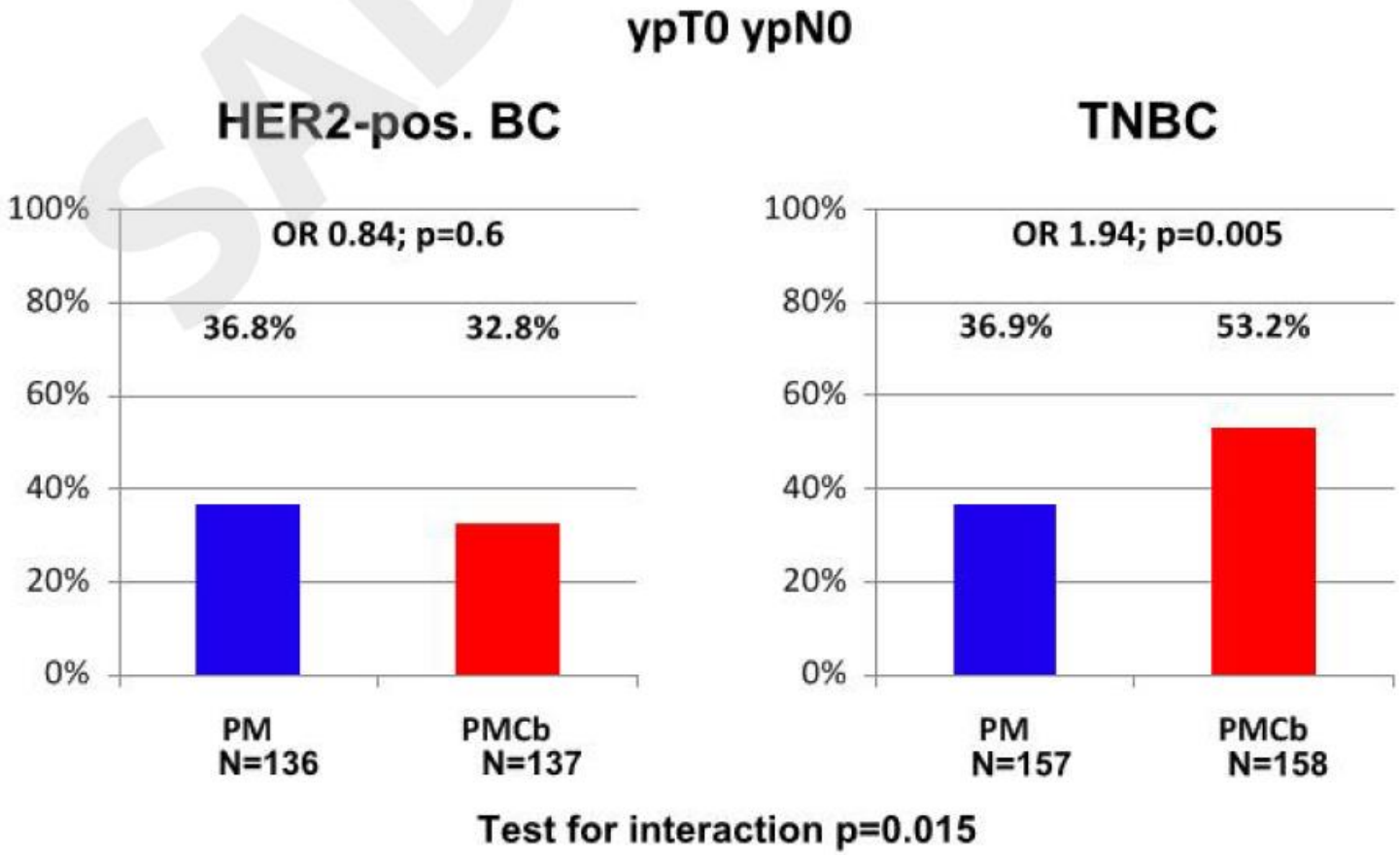
pCR Rates by Subtype



AGO-B BREAST STUDY GROUP

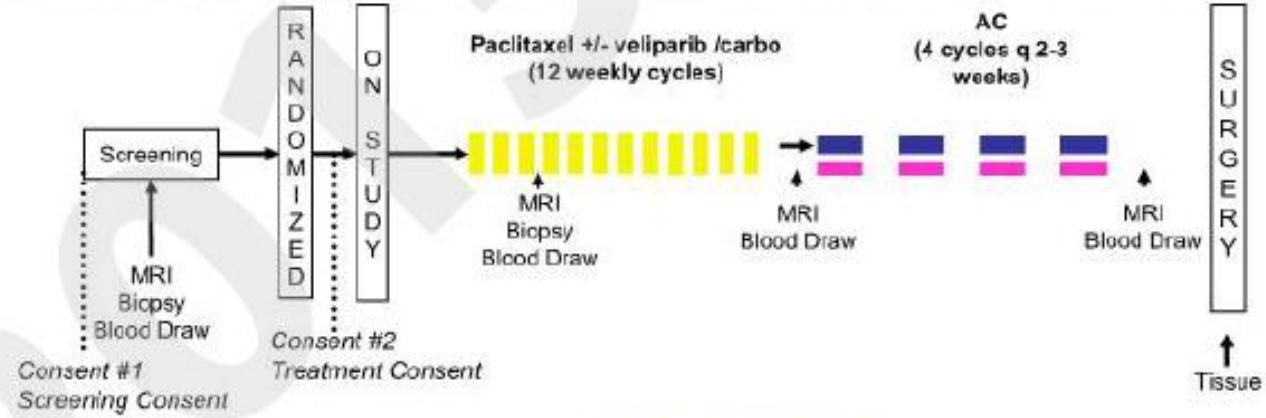
von Minckwitz et al. Lancet Oncology 2014

ISPY trial - Platin and PARP Inhibition Neoadjuvant

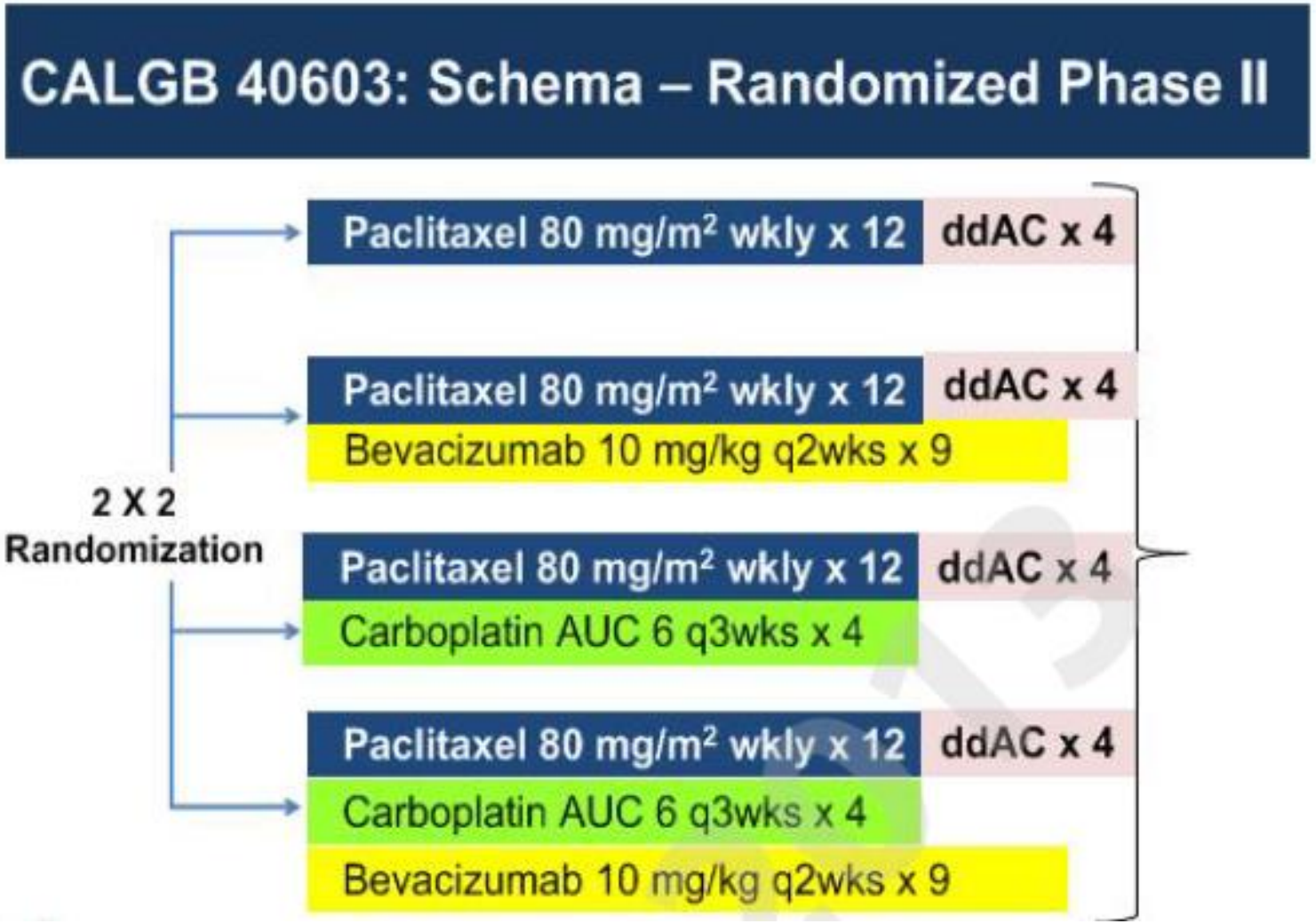
San Antonio Breast Cancer Symposium – Cancer Therapy and Research Center at UT Health Science Center – December 10-14, 2013

Experimental Arm 1: Veliparib/Carboplatin

- Veliparib (ABT888) is a potent PARP inhibitor.
- For this analysis, patients were ADAPTIVELY randomized to receive:
  - Veliparib 50 mg po BID x 12 weeks/carboplatin AUC 6 q 3 weeks x 4
  OR with weekly paclitaxel followed by AC
  - Weekly paclitaxel followed by AC
- Enrollment open **only** to patients **with HER2 negative disease**
- Eligible to graduate in 3 signatures: **all HER2-, HR+/HER2-, TN**



CALGB 40603
AC-Pac ± Carboplatin in TNBC



Sikov et al. JCO 2015;33:13-21