La terapia sistemica antitumorale: quali novità nel setting (neo)adiuvante?

Sessione 4: Il carcinoma mammario nelle donne con mutazione patogenetica *BRCA*1-2

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Disclosure Information

Relationship Relevant to this Session

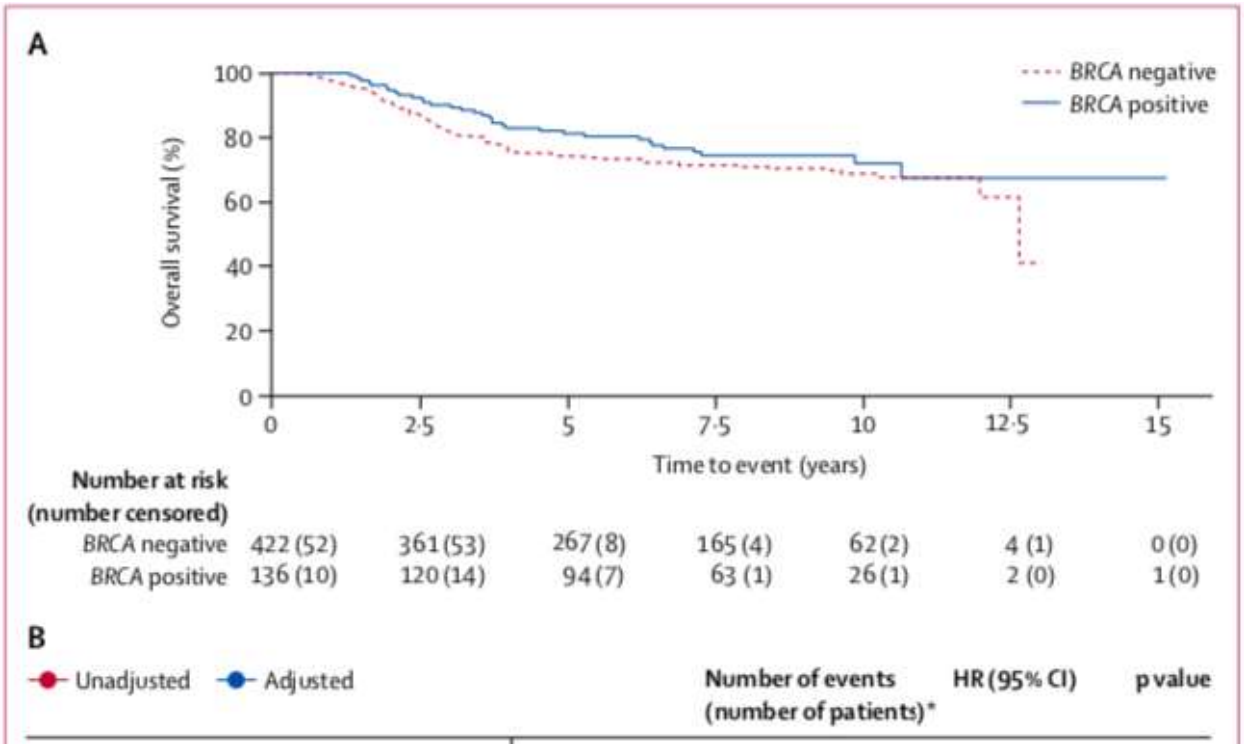
Poggio, Francesca:

No relevant relationship to disclose.

Agenda

- **Introduction**
- Neoadjuvant: platinum agents
- Neoadjuvant: PARPi
- (Neo)Adjuvant setting: ongoing trials
- Conclusions

BRCA mutations carriers: The POSH study



POSH is the largest prospective cohort study to compare breast cancer outcomes of patients with a *BRCA1* or *BRCA2* mutation with patients with sporadic cancer.

Our findings showed that patients with young-onset breast cancer who have a *BRCA* mutation have a similar overall survival to non-carriers.

Copson ER, Lancet 2018

BRCA mutations carriers: Guidelines

- The overall prognosis of BC in BRCA carriers is similar to sporadic breast cancer…Standard prognostic features should be used to decide treatment (BRCA in breast cancer: ESMO clinical practice guidelines. Balmana S et al. Ann Oncol 2011; 21, Suppl 5: v20-22)
- The decision concerning the type of chemotherapy or hormonal therapy should be based on established prognostic and predicitive factors normally used for the treatment of sporadic forms (Breast cancer and genetic counselling: 2017 Guidelines of the Italian Association of Medical Oncology (A.I.O.M.)

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- Introduction
- **Neoadjuvant: platinum agents**
- Neoadjuvant: PARPi
- (Neo)Adjuvant setting: ongoing trials
- Conclusions

Neoadjuvant setting: Geparsixto

JAMA Oncology | Original Investigation

JAMA Oncol. 2017;3(10):1378-1385.

Germline Mutation Status, Pathological Complete Response, and Disease-Free Survival in Triple-Negative Breast Cancer

Secondary Analysis of the GeparSixto Randomized Clinical Trial

Table 1. pCR Rates According to *BRCA1* and *BRCA2* Germline Mutation Status and Treatment

	pCR[a]		Mutant vs Wild-type *BRCA*	
Type of Treatment	Yes	No	OR (95% CI)	*P* Value
Noncarboplatin arm, No. (%)				
Overall (n = 145)	60 (41.4)	85 (58.6)		
Mutant (n = 24)	16 (66.7)	8 (33.3)	3.50 (1.39-8.84)	.008
Wild-type (n = 121)	44 (36.4)	77 (63.6)		
Carboplatin arm, No. (%)				
Overall (n = 146)	83 (56.8)	63 (43.2)		
Mutant (n = 26)	17 (65.4)	9 (34.6)	1.55 (0.64-3.74)	.33
Wild-type (n = 120)	66 (55.0)	54 (45.0)		

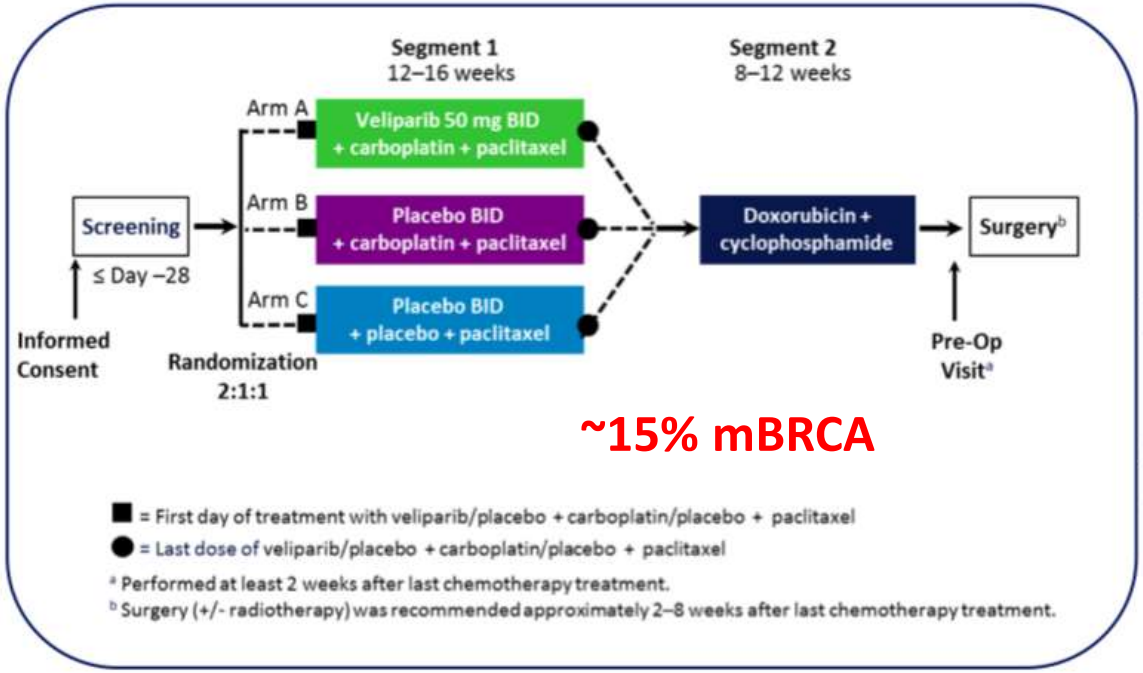
Table 2. Comparison of pCR Rates by Treatment Arms and by *BRCA1* and *BRCA2* Germline Mutation Status

Type of Treatment in Cb vs NonCb Arm	pCR[a]	
	OR (95% CI)	*P* Value
Cb vs nonCb, overall	1.87 (1.17-2.97)	.009
Cb vs nonCb, mutant	0.94 (0.29-3.05)	.92
Cb vs nonCb, wild-type	2.14 (1.28-3.58)	.004

86% of patients were gBRCA1 m and 14% gBRCA2m

Hahnen E, JAMA Oncol 2017

Neoadjuvant setting: BrighTNess



Study Objectives

Primary objectives:

- Pathologic complete response (pCR) in breast and ipsilateral axillary lymph nodes

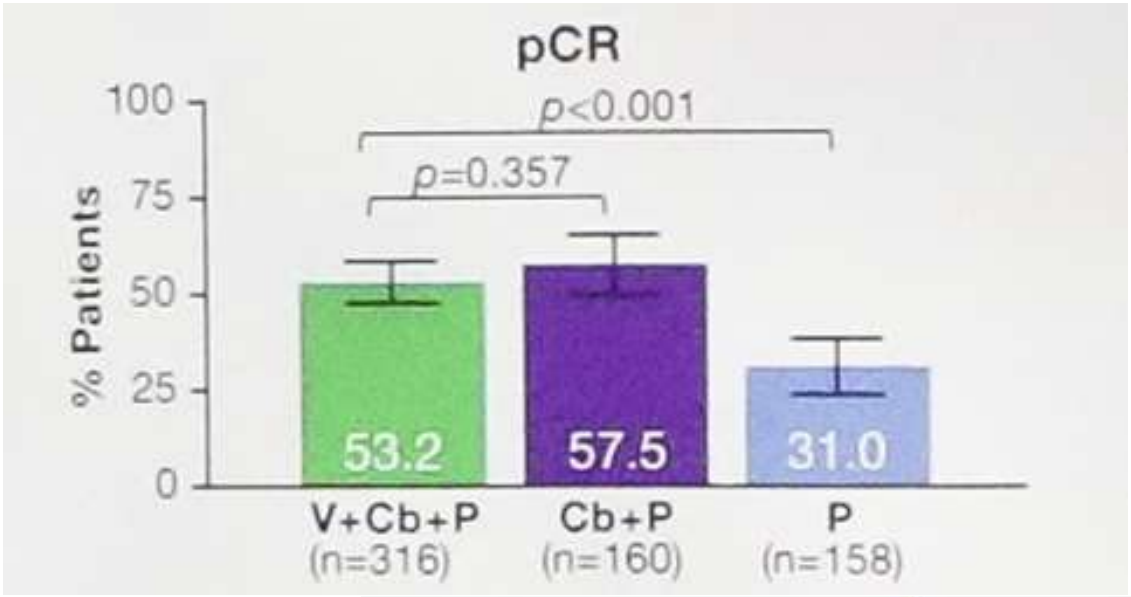
Secondary objectives:

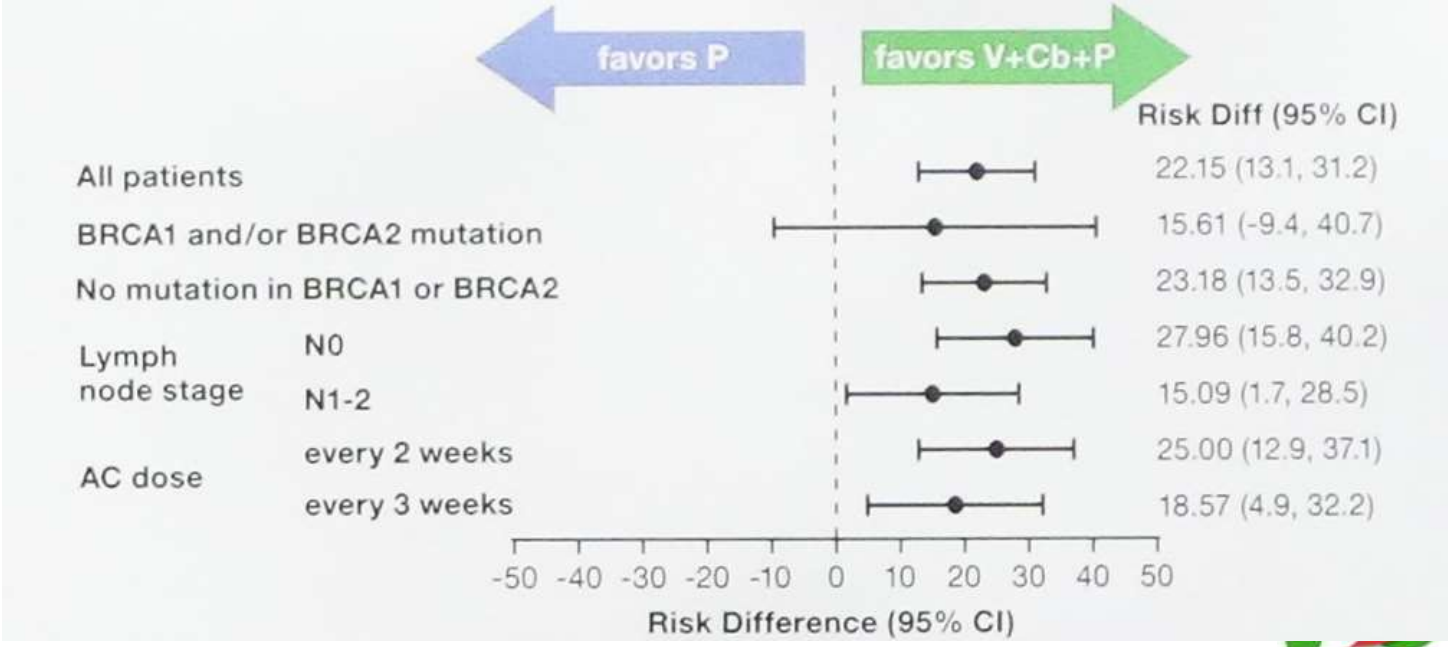
- EFS, OS, and rate of eligibility for breast conservation after therapy

EFS, event free survival; P, paclitaxel; OS, overall survival; V, veliparib

Loibl S, Lancet 2018

Neoadjuvant setting: BrighTNess





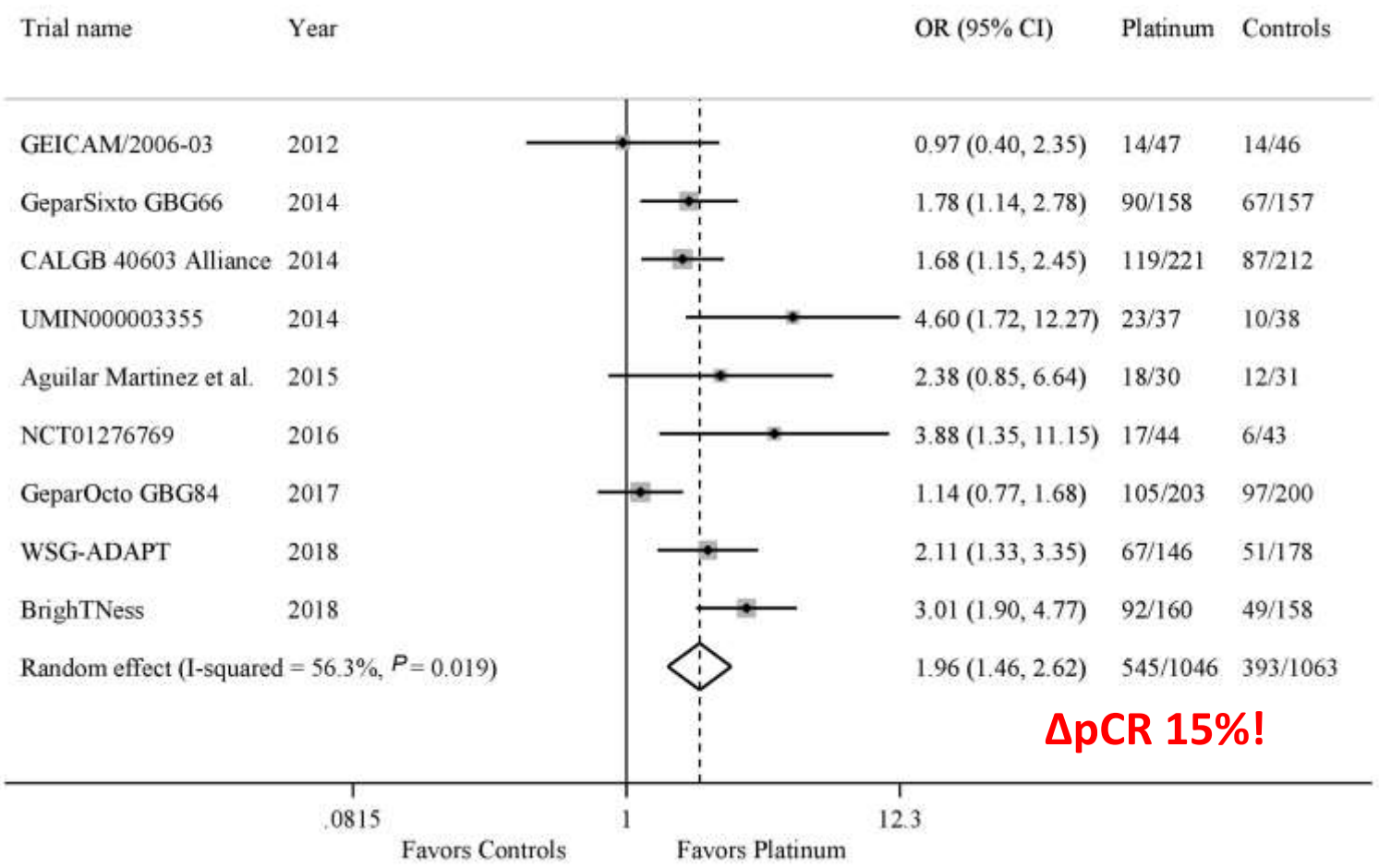
Loibl S, Lancet 2018

Neoadjuvant setting: BrighTNess

- Addition of V and Cb to P followed by AC demonstrated a significant improvement in pCR compared with P followed by AC (53.2% vs 31.0%, *P*<.001) confirming results of I-SPY-2
- However, addition of V to Cb and P followed by AC did not show improvement in pCR, compared to Cb+P followed by AC (53.2% vs 57.5%, *P* = .36), demonstrating improvement in pCR was due to carboplatin, without apparent contribution from veliparib at the 50 mg BID dose
- Increase in pCR with addition of carboplatin was independent of g*BRCA* mutation status

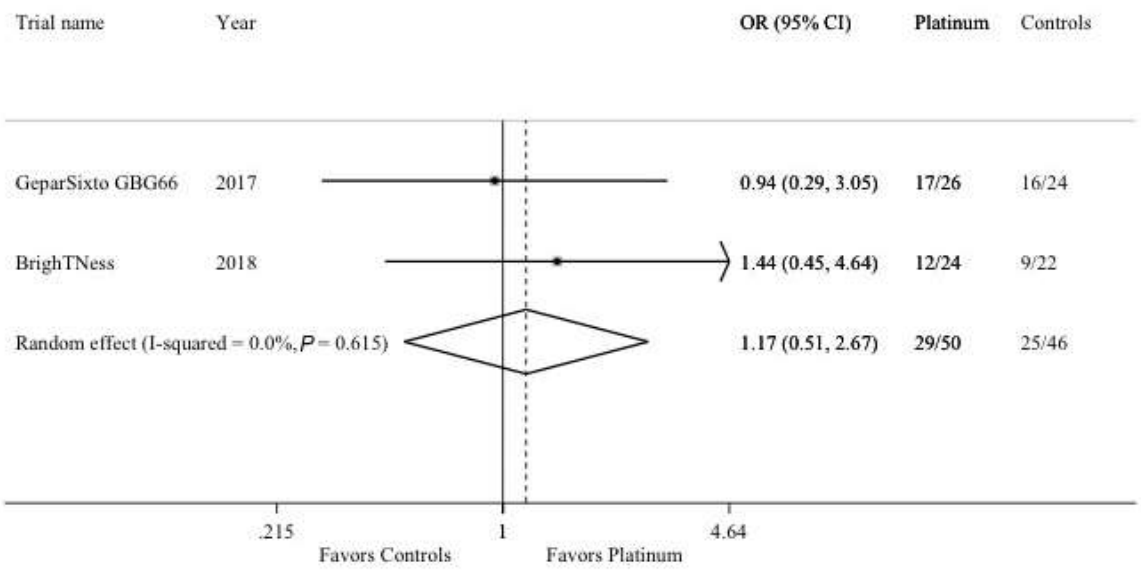
Loibl S, Lancet 2018

Meta-analysis platinum agents

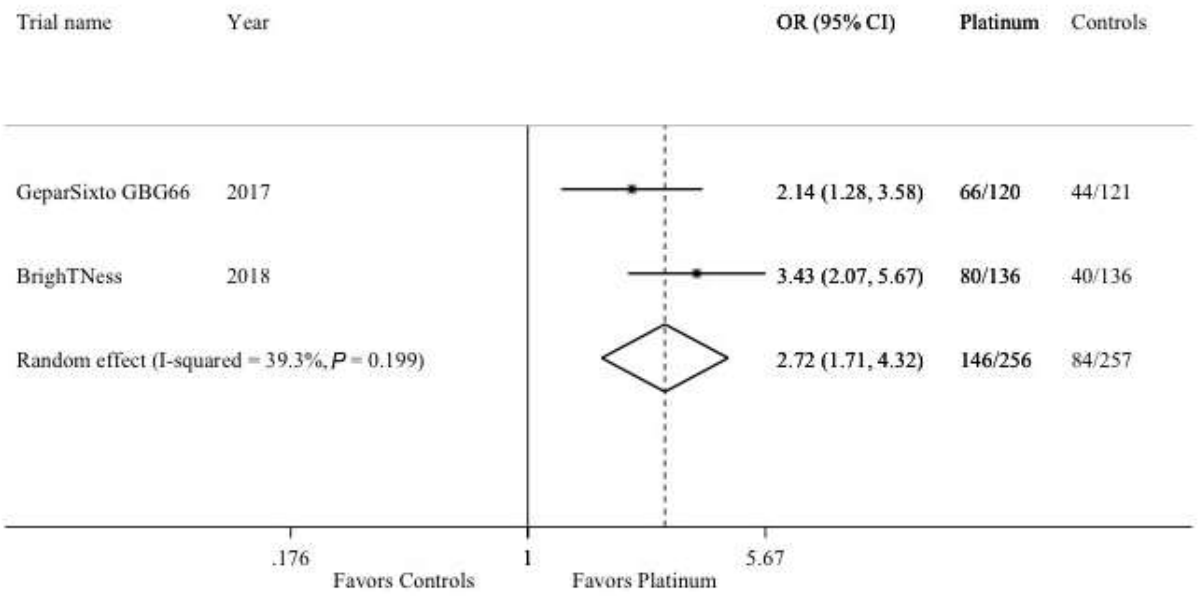


Poggio F, Ann Oncol 2018

Meta-analysis platinum agents



***BRCA*-mutated patients**



***BRCA*-negative patients**

Poggio F, Ann Oncol 2018

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- **Neoadjuvant: PARPi**
- (Neo)Adjuvant setting: ongoing trials
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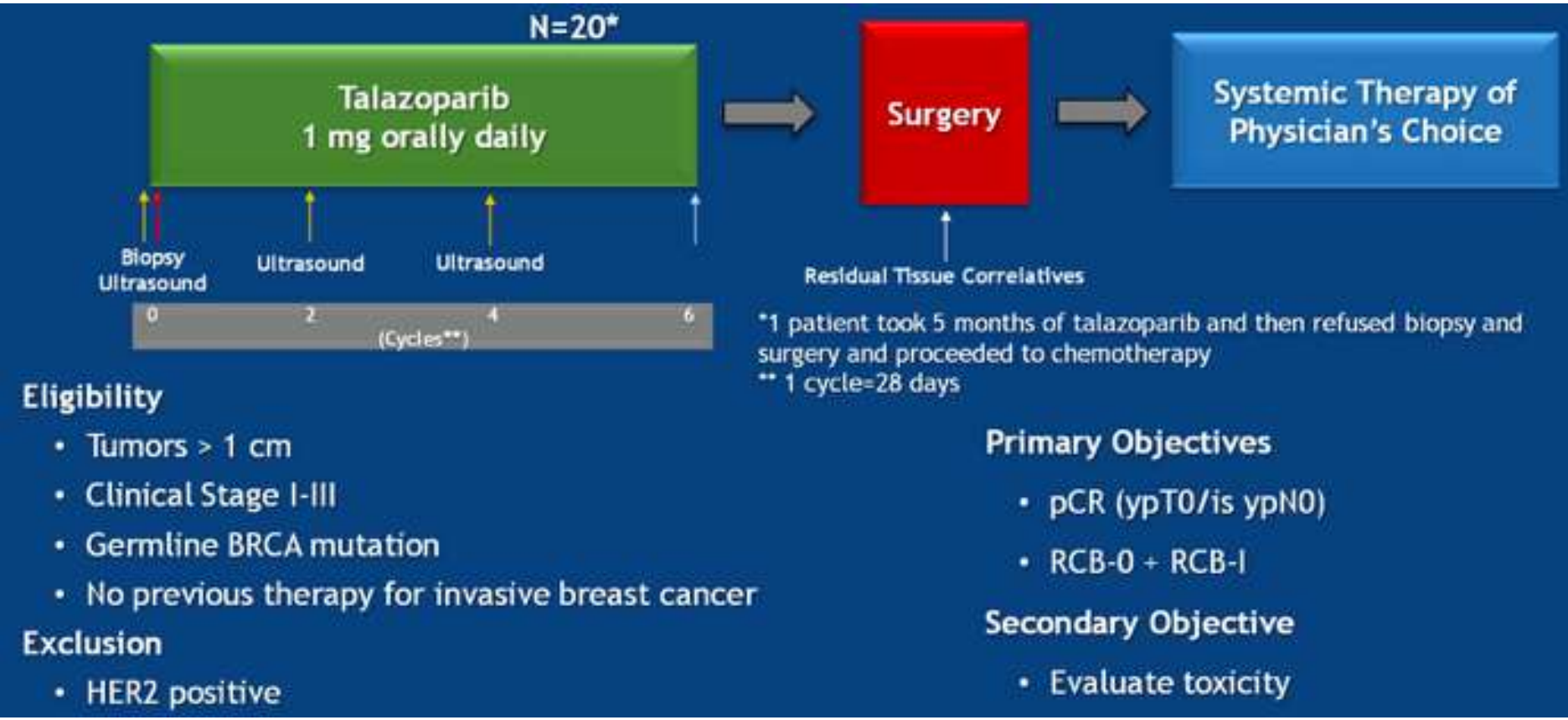
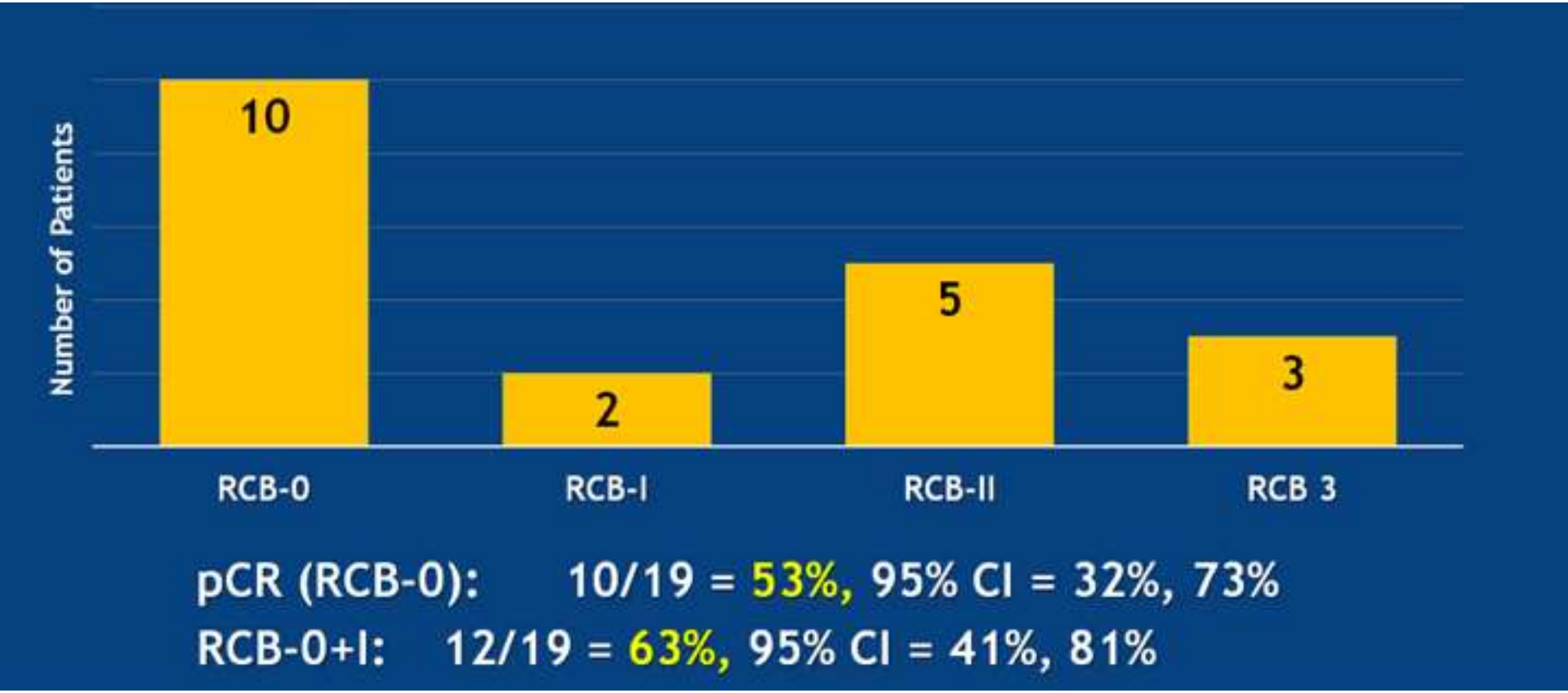
PARPi single agent



Litton J, J Clin Oncol 2019

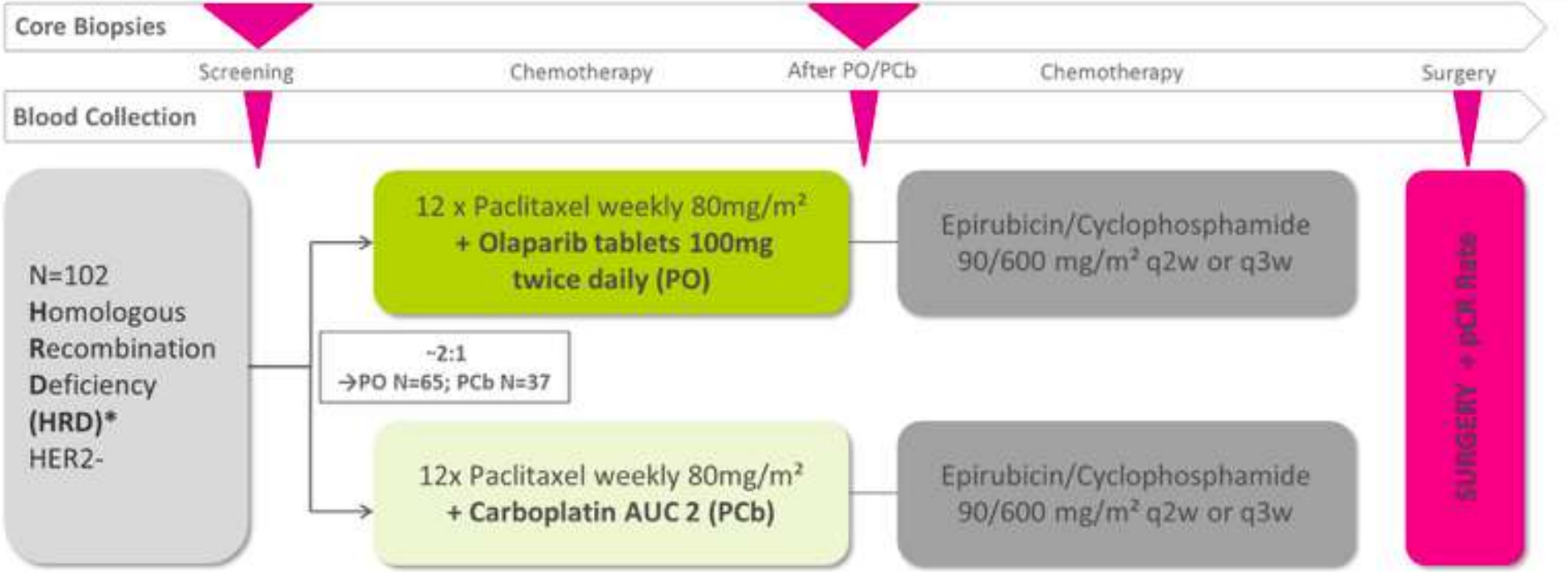
PARPi single agent: results



First study of a single targeted therapy to achieve pCR in BRCA+ patients, including TNBC
Talazoparib was well tolereted with acceptable adherence
This study warrants the larger confirmatory trial

Litton J, J Clin Oncol 2019

GeparOla



Stratification Factors:

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

* Patients with either a known somatic or germline *BRCA*1/2 mutation or HRD score[1] high

[1]Timms 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 t*BRCA1/2* mutation and/or HRD score high and/or known g*BRCA* mutation).

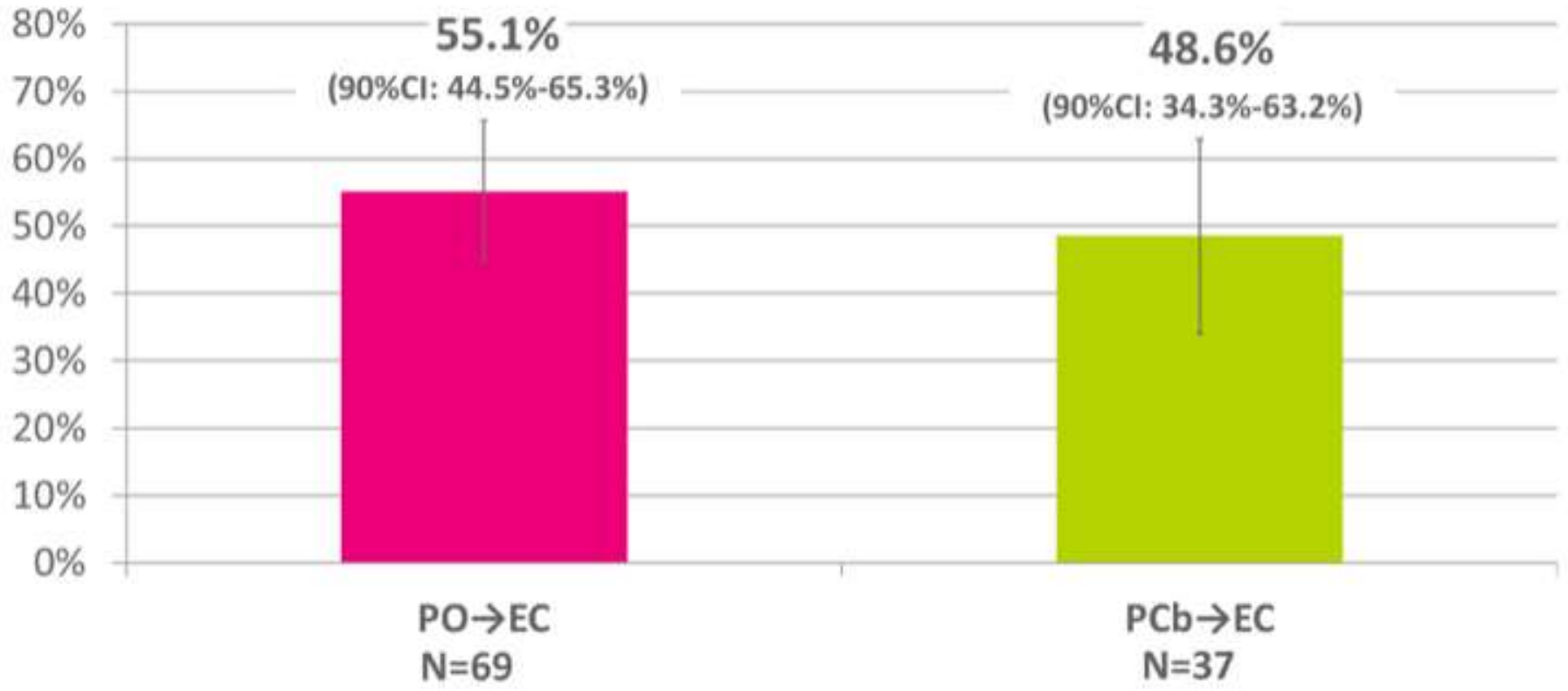
Fasching AP, J Clin Oncol 2019

GeparOla: results

GBG GERMAN BREAST GROUP

Primary Endpoint – pCR ypT0/is ypN0

GEPAR-OLA



Fasching AP, J Clin Oncol 2019

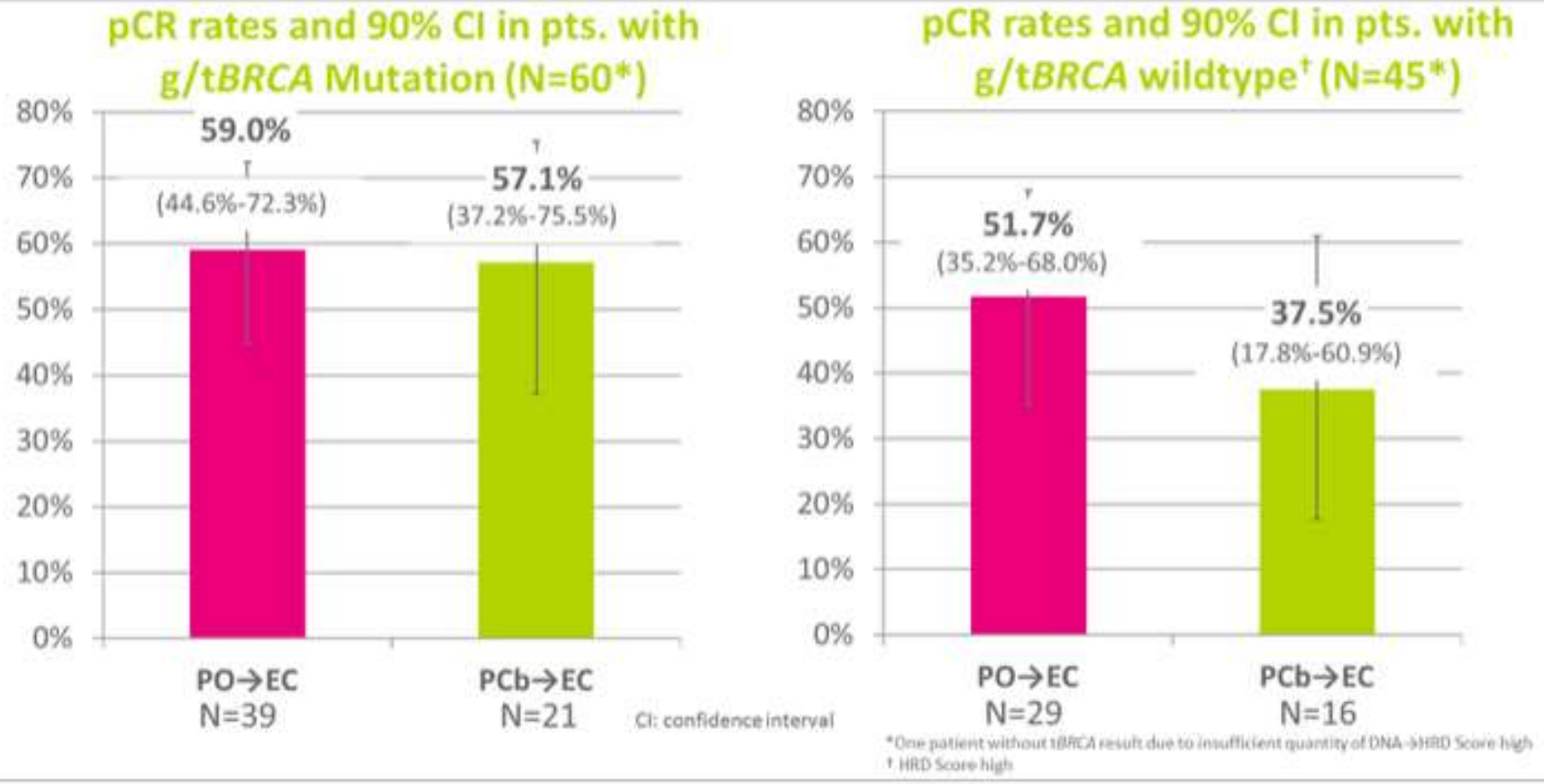
GeparOla: results

GBG GERMAN BREAST GROUP

Predefined Subgroup Analysis (ypT0/is ypN0)

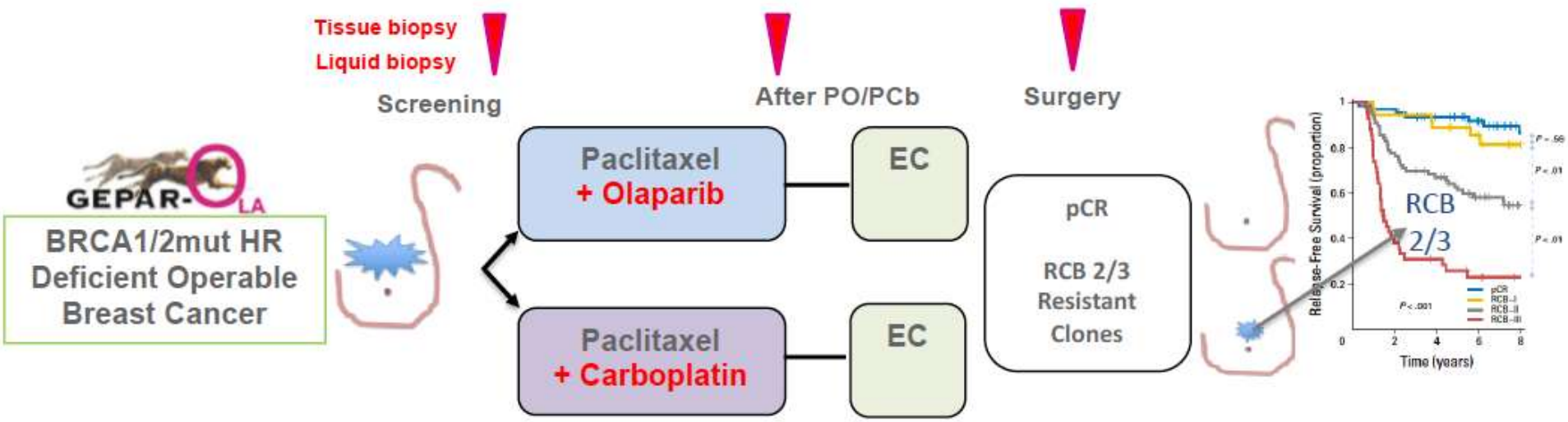
BRCA Mutation

GEPAR-OLA



Fasching AP, J Clin Oncol 2019

GeparOla: results



Fasching AP, J Clin Oncol 2019

(Neo)adjuvant setting

Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

- The addition of a platinum compound may be considered in triple-negative tumours and/or in patients with deleterious *BRCA1/2* mutations [I, C].

Qualità Globale delle evidenze GRADE	Raccomandazione clinica	Forza della raccomandazione clinica
Moderata	Nelle donne con carcinoma mammario triplo negativo (recettori ormonali negativi ed HER2 negativo) candidate a ricevere chemioterapia primaria/neoadiuvante, l'aggiunta del platino ad uno schema standard con antracicline e taxani può essere preso in considerazione.	**Positiva debole**

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- **(Neo)Adjuvant setting: ongoing trials**
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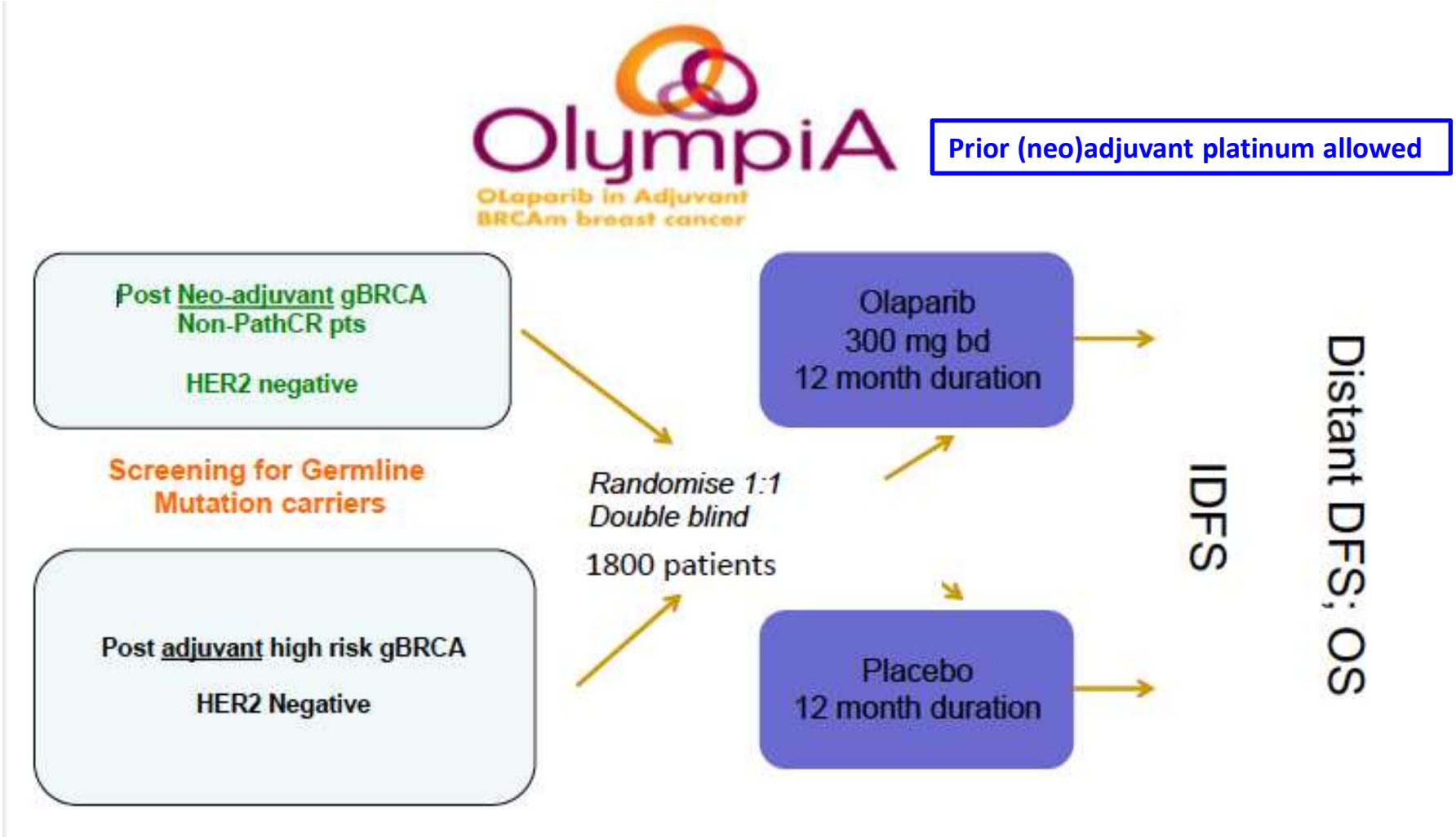
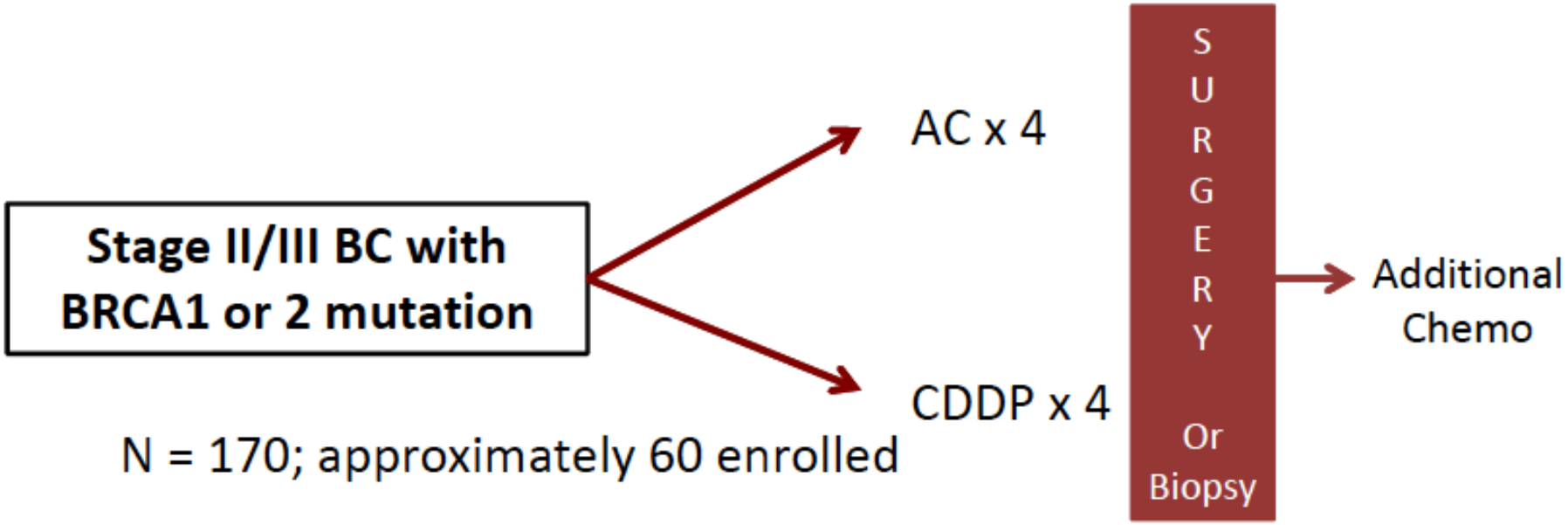
PARPi in the adj setting
OlympiA trial



Recently completed → 1836 BRCA carriers enrolled

INFORM trial: perioperative CDDP vs. AC



- Multicenter study
- Designed to show 20% improvement in pCR with cisplatin over AC

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Conclusions

- **How big is the issue: nearly 6% of all BC and nearly 15% in the subgroup ≤ 45 years or TNBC regardless the age**
- **Current guidelines did not recommend a specific treatment for *BRCA*-mutated in the early setting**
- **Tha addition of platinum to neoadjuvant chemotherapy may be considered an option for unselected TNBC**
- **Results of ongoing trials are awaited to clarify the role of PARPi in the (neo)adjuvant setting**