

Case #5
**Metastatic Triple-Negative
Breast Cancer**

Ahmad Awada, MD, PhD
Institute Jules Bordet
Brussels, Belgium

Issues to be Discussed

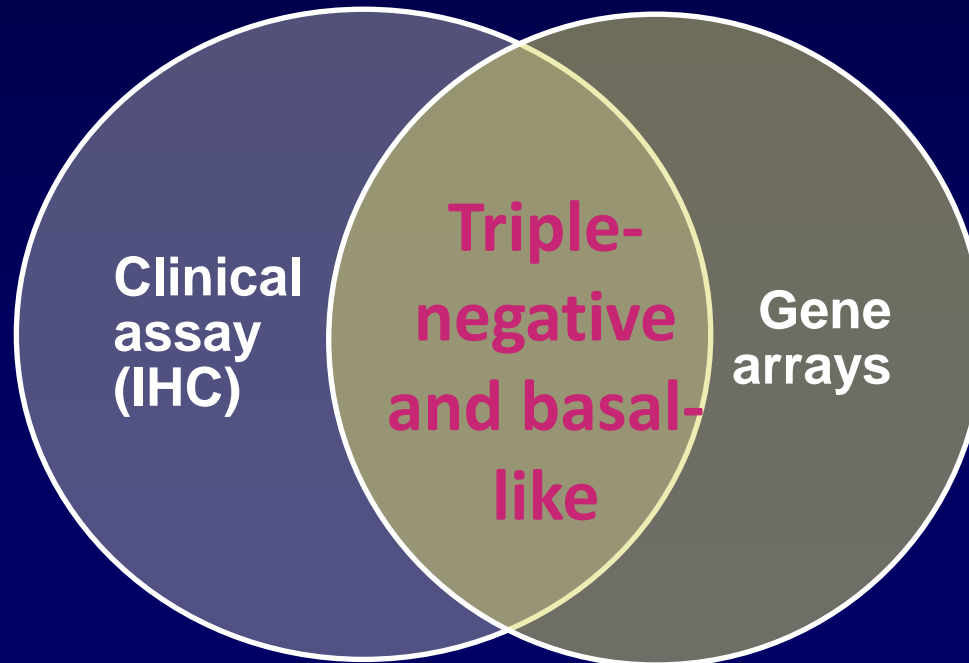
- **BRCA testing in TNBC patients**
- **Biopsy of the metastatic lesions**
- **Systemic therapy for symptomatic metastatic TNBC following TAC adjuvant therapy:**
 - **Chemotherapy combinations, mainly platinum-based**
 - **Chemotherapy + molecular-targeted therapy**

Triple-Negative: Definition

- ER- / PgR- / HER2-
- ~15% of all breast cancers
- Poorly differentiated; express cytokeratins 5/6, 17

- **Triple-negative but not basal**

- 10-30% can also include “claudin-low,” a subtype notable for high expression of stem cell markers



- **Basal but not triple-negative**

- 15-40% are ER+, PR+ or HER2+

TNBC Shares Clinical and Pathologic Features with BRCA1-Related Breast Cancers

Characteristics	Hereditary <i>BRCA1</i>	Triple-Negative/Basal-Like ¹⁻³
ER/PR/HER2 status	Negative	Negative
TP53 status	Mutant	Mutant
BRCA1 status	Mutational inactivation*	Diminished expression*
Gene expression pattern	Basal-like	Basal-like
Tumor histology	Poorly differentiated (high grade)	Poorly differentiated (high grade)
Chemosensitivity to DNA-damaging agents	Highly sensitive	Highly sensitive

*BRCA1 dysfunction due to germline mutations, promoter methylation, or overexpression of HMG or ID4⁴

1. Perou CM, et al. *Nature*. 2000;406(6797):747-752.
2. Cleator S, et al. *Lancet Oncol*. 2007;8(3):235-244.

3. Sørlie T, et al. *Proc Natl Acad Sci U S A*. 2001;98(19):10869-10874.
4. Miyoshi Y, et al. *Int J Clin Oncol*. 2008;13(5):395-400.

Expanding the Criteria for *BRCA* Mutation Testing in Breast Cancer Survivors

Janice S. Kwon, Angelica M. Gutierrez-Barrera, Diana Young, Charlotte C. Sun, Molly S. Daniels, Karen H. Lu, and Banu Arun

CONCLUSIONS:

Testing women with TN breast cancers who were younger than 50 years for *BRCA* mutations is a cost-effective strategy and should be adopted into current guidelines for genetic testing.

TNBC: Clinical Characteristics

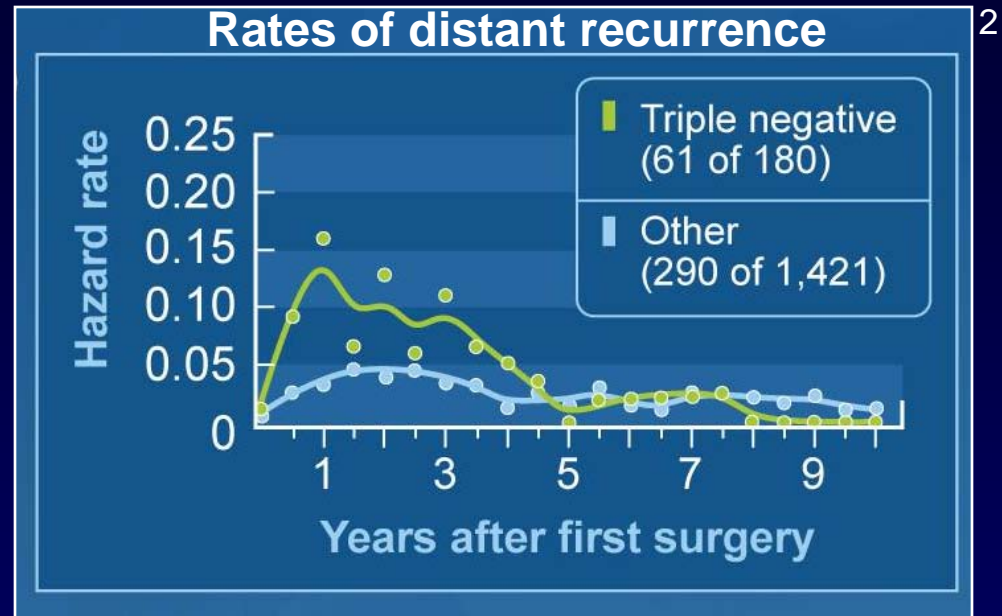
* Risk Factors:

- Young
- African American
- BRCA1 carriers (80%)

* No consistent association with nodal status or stage

* Relapse pattern:

- Higher risk
- Early timing
- Sites differ from luminal:
 - e.g., CNS 46% over time¹



	N	Bone	Soft Tissue	Viscera
TNBC	79	13%	13%	74%
ER+	123	39%	7%	54%
HER+	78	7%	12%	81%

1. Lin NU. *Cancer*. 2008;113(10):2638-2645. 2. Dent R. *Clin Cancer Res*. 2007;13(15 Pt1):4429-4434.

3. Liedtke C. *J Clin Oncol*. 2008;26(8):1275-1281.

ASCO 2010: Significant Rate of Discordancy Between Primary and Metastases

Studies	#1007 Amir et al. N = 271	#CRA 1008 Locatelli et al. N = 255	#1009 Karlsson et al. N = 477
	prospective	retrospective (liver)	retrospective
ER+ primary with loss in recurrence	21/174 (12%)	22/197 (11%)	123/336 (36%)
ER- primary with gain in recurrence	8/57 (14%)	15/58 (25%)	32/141 (22%)
Overall ER discordance rate	12%	14.5%	32%
Overall PR discordance rate	34%	48%	43%
HER2- primary with gain in recurrence	9/197 (4.6%)	7/118 (5.9%)	n.d.
HER2+ primary with loss in recurrence	3/24 (12.5%)	17/54 (31.5%)	n.d.
Change in management from results of recurrence biopsy	15%	12%	n.d.

Chemotherapy for Metastatic Breast Cancer (MBC)

- **Sequential single agents preferred for most patients**
 - Variety of options—no single ‘gold standard’
 - Limited toxicity regimens are preferred
- **Combinations appropriate for rapidly progressive and symptomatic disease**
 - Reduction in disease symptoms outweighs potential toxicity
 - May not be candidate for subsequent therapy if progression continued

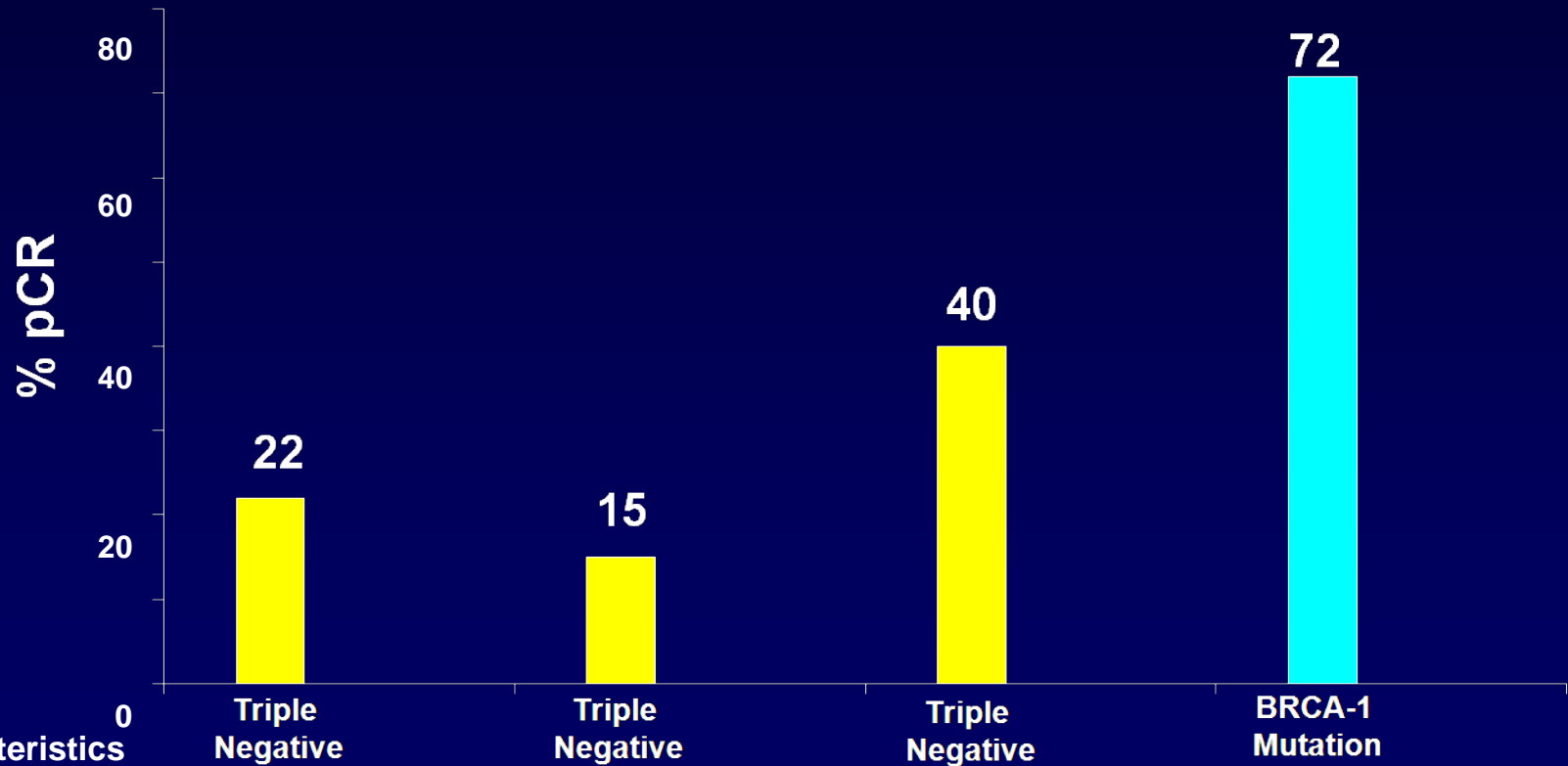
Neoadjuvant Chemotherapy with Platinum Compounds: Phase II Trials

Garber JE
2006¹
CDDP → Sx
N = 28

Ryan PD
2009²
CDDP + BEV → Sx
N = 51

Torrise R
2008³
ECF → P → Sx
N = 30

Gronwald J
2009⁴
CDDP → Sx
N = 25



CDDP, cisplatin; Sx, surgery; BEV, bevacizumab; ECF, epirubicin-cisplatin-5FU; P, paclitaxel; pCR, pathologic complete response

1. Garber JE, et al. *Breast Cancer Res Treat.* 2006;100(Suppl 1): Abstract 3074. 2. Ryan PD, et al. *J Clin Oncol.* 2009;27(15S): Abstract 551. 3. Torrise R, et al. *Cancer Chemother Pharmacol.* 2008;62(4):667-672. 4. Gronwald J, et al. *J Clin Oncol.* 2009;27(15S): Abstract 502.

Bevacizumab for TNBC

Trial / Arm	Median PFS (mo) in TNBC Subset
E2100	
Paclitaxel (n = 110)	5.3
Paclitaxel + bev (n = 122)	10.6
AVADO	
Docetaxel + placebo (n = 52)	5.4
Docetaxel + bev 15 mg/kg (n = 58)	8.2
RIBBON-1	
Taxane/anthracycline + placebo (n = 46)	6.2
Taxane/anthracycline + bev (n = 96)	6.5
Capecitabine + placebo (n = 50)	4.2
Capecitabine + bev (n = 87)	6.1
ATHENA	
Taxane-based regimen + bev (n = 577)	7.2*

OS in TNBC population showed no difference between bev- and non-bev-treated groups (HR = 0.96; 95% CI: 0.79-1.16)

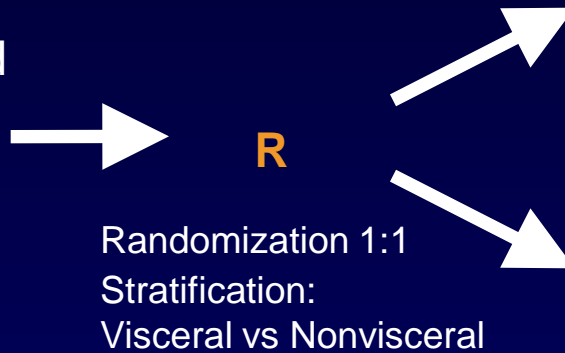
O'Shaughnessy et al. ASCO 2010

SOLTI-0701: Study Design

Multinational, double-blind, randomized, placebo-controlled, phase IIB

Locally Advanced
or
Metastatic
Breast Cancer

N = 220



Sorafenib 400 mg PO BID
+
Capecitabine 1000 mg/m²
PO BID 14 of every 21 days

Until disease progression/toxicity

Placebo PO BID
+
Capecitabine 1000 mg/m² PO
BID 14 of every 21 days

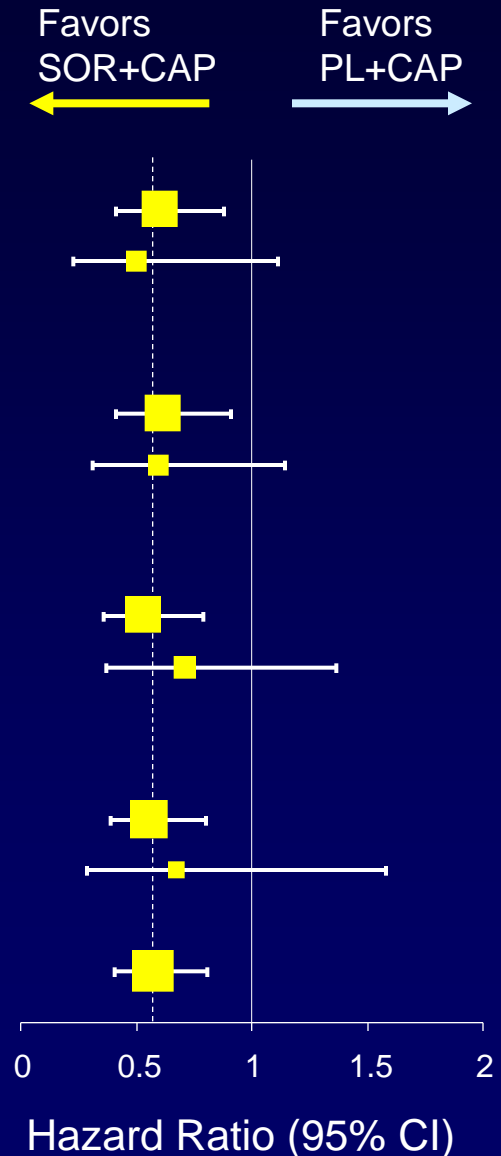
BID = twice daily; PO = oral

- 1° endpoint: PFS
- 2° endpoints: OS, TTP, RR, duration of response, safety
- Target enrollment: N = 220
- Sample size calculation: 90% power at hazard ratio (HR) of 0.65 (1-sided $\alpha = 0.14$)
- Countries: Spain, France, Brazil

SOLTI-0701: PFS

Prespecified Subgroup Analyses

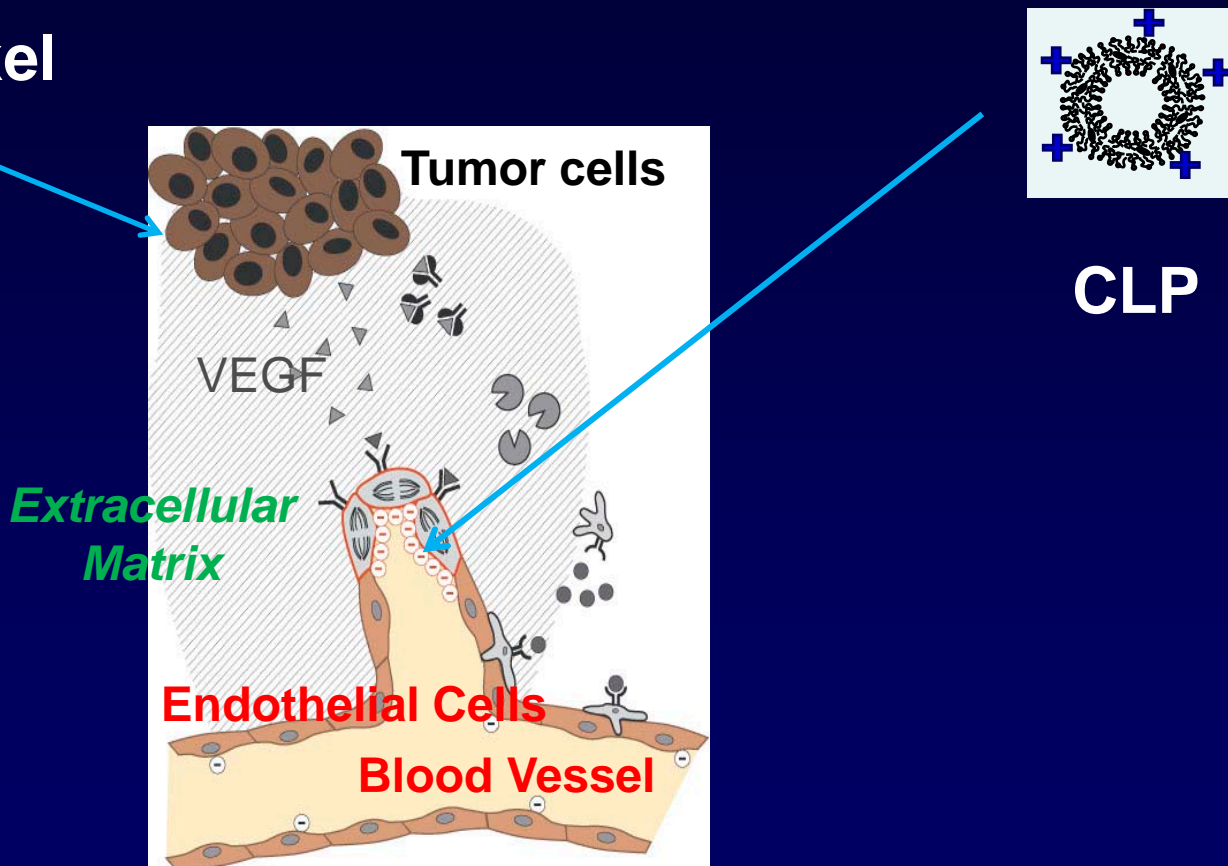
Subgroup, n	PFS, months		HR
	SOR+CAP	PL+CAP	
Age, years			
<65 (175)	6.0	4.1	0.606
≥65 (54)	9.2	4.1	0.503
Hormone receptor status*			
Positive (173)	7.6	5.5	0.615
Negative (53)	4.3	2.5	0.596
Visceral disease*			
Yes (171)	7.2	5.0	0.532
No (58)	4.3	3.0	0.713
Measurable disease			
Yes (191)	6.4	4.1	0.558
No (37)	5.8	4.0	0.678
Overall ITT (229)	6.4	4.1	0.576



*Subgroup of main interest

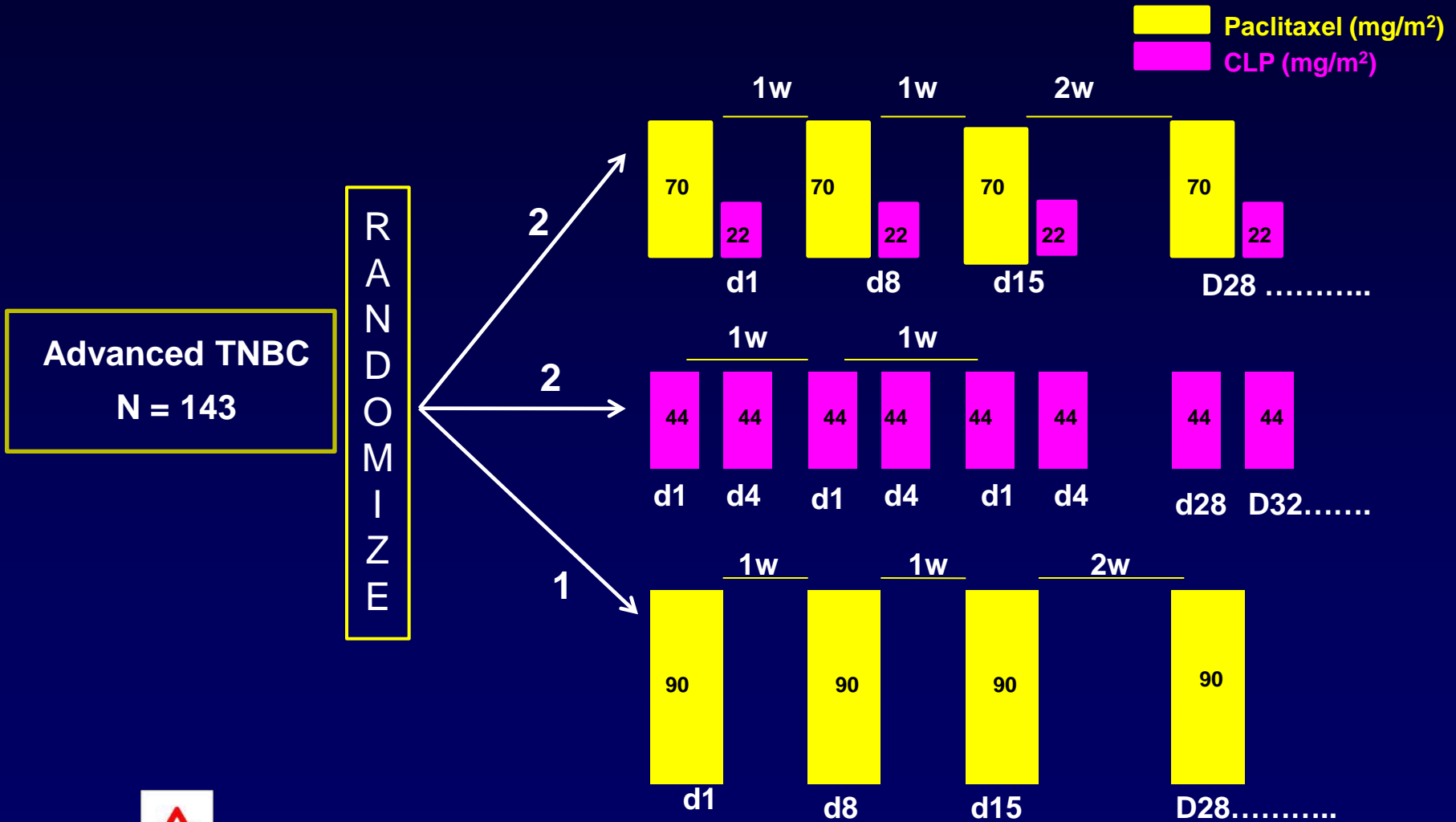
Positively Charged Cationic Liposomal Paclitaxel (CLP) Targets Activated Tumor Endothelial Cells With Negative Surface Charge (= Vascular Disrupting Agent)

Paclitaxel



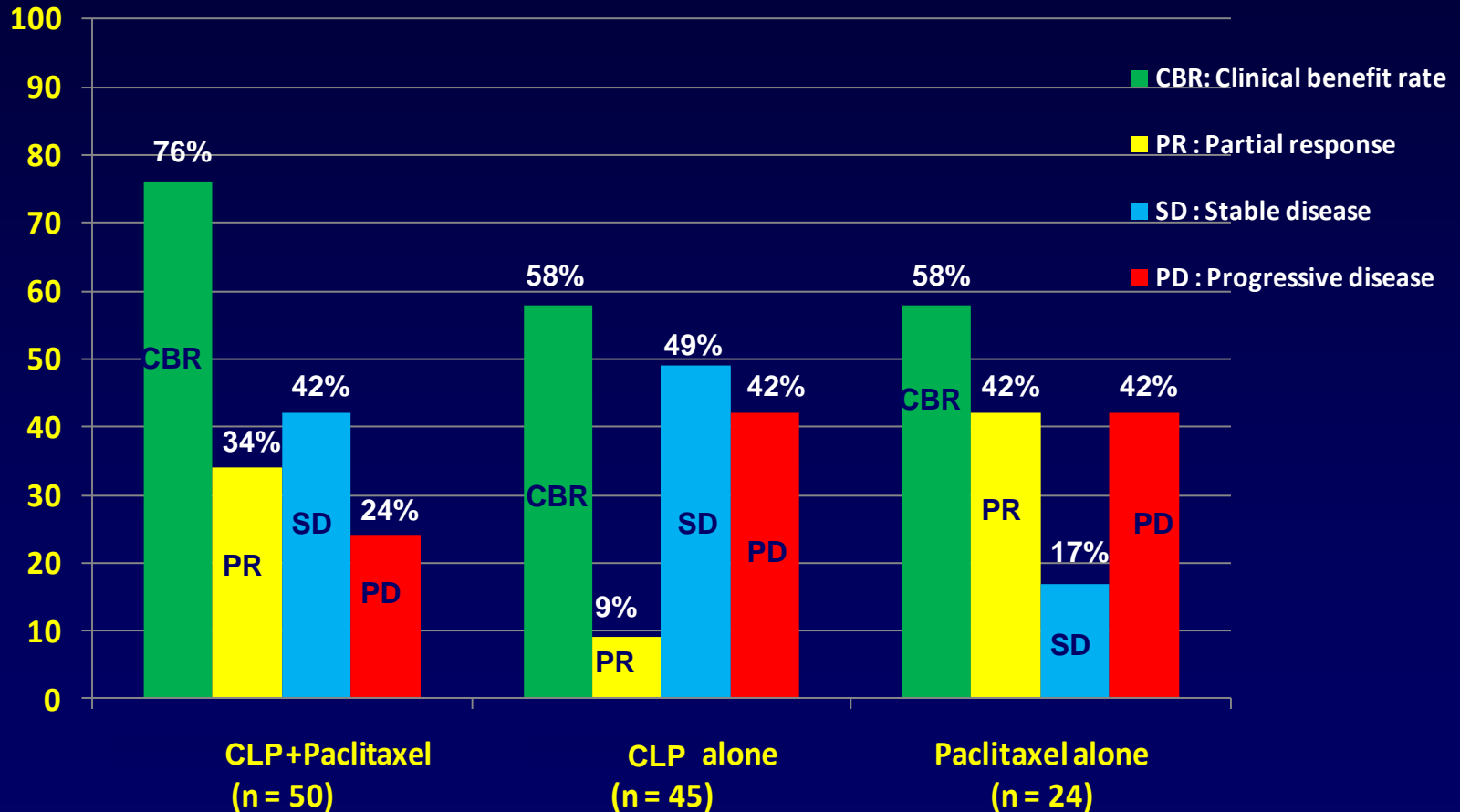
CLP

Cationic Liposomal Paclitaxel (CLP) Study in TNBC: Treatment Scheme



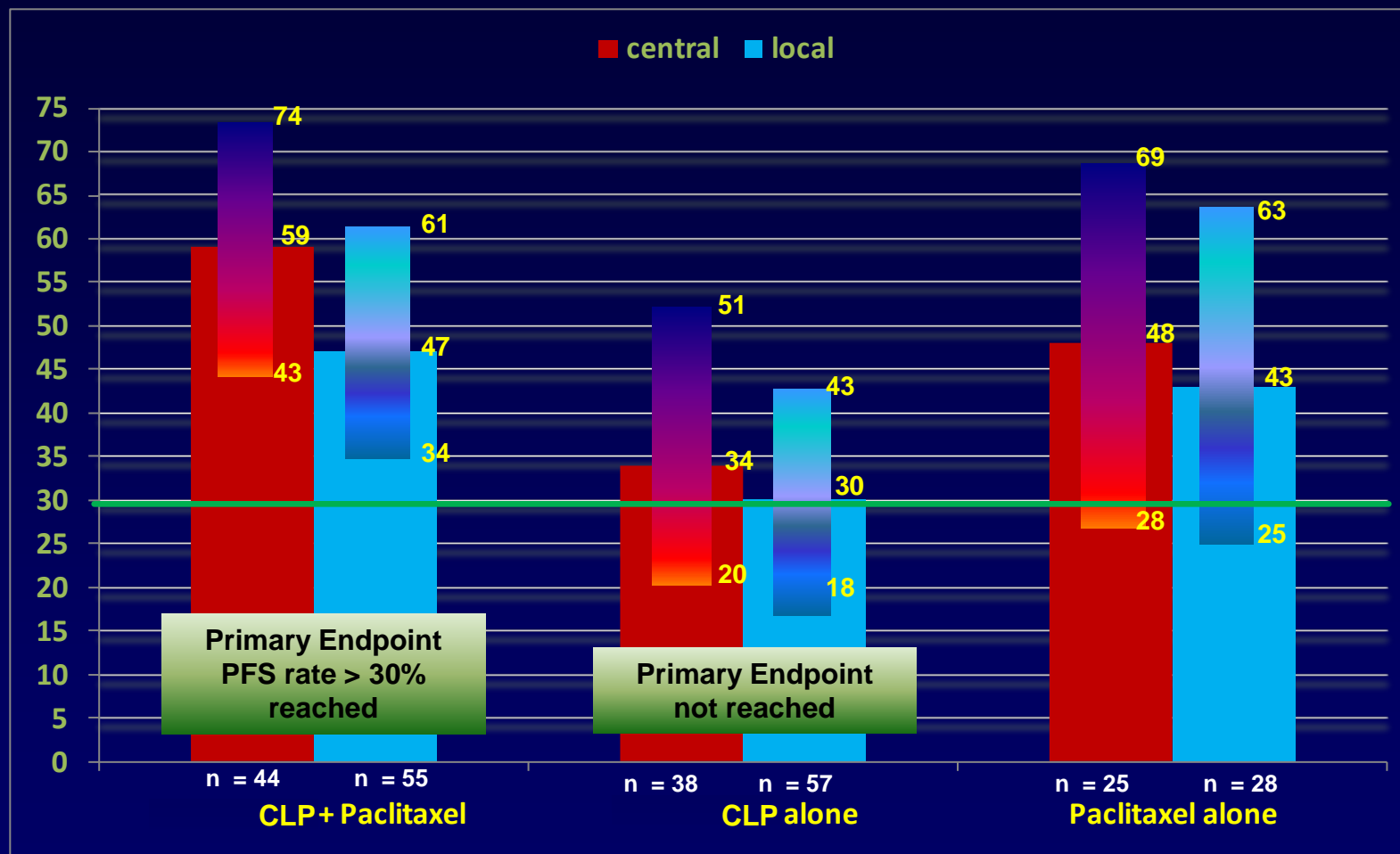
Absolute Paclitaxel concentration is equal in the 3 treatment arms

Cationic Liposomal Paclitaxel (CLP) Study in TNBC: Best Overall Response (Central Assessment*)



*blinded

Primary Endpoint: PFS Rate at Week 16



Two-sided 95% confidence interval

PARP Repair System

- Poly(ADP-ribose) polymerase (PARP) is a key enzyme involved in the repair of single-strand breaks in DNA via the Base Excision Repair pathway
- Cells deficient for either BRCA1 or BRCA2 are particularly sensitive to the inhibition of PARP enzymatic activity; this results in chromosomal instability, cell cycle arrest, and subsequent apoptosis.

Mechanisms of DNA Repair

Environmental factors

(UV, radiation, chemicals)

Normal physiology

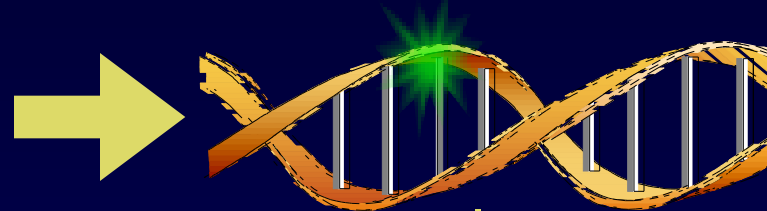
(DNA replication, ROS)

Chemotherapy

(alkylating agents, antimetabolites)

Radiotherapy

DNA DAMAGE



---> Cell Death

MAJOR DNA REPAIR PATHWAYS

Single Strand Breaks

- Nucleotide excision repair
- Base excision repair
- PARP1

Replication Lesions

- Base excision repair
- PARP1

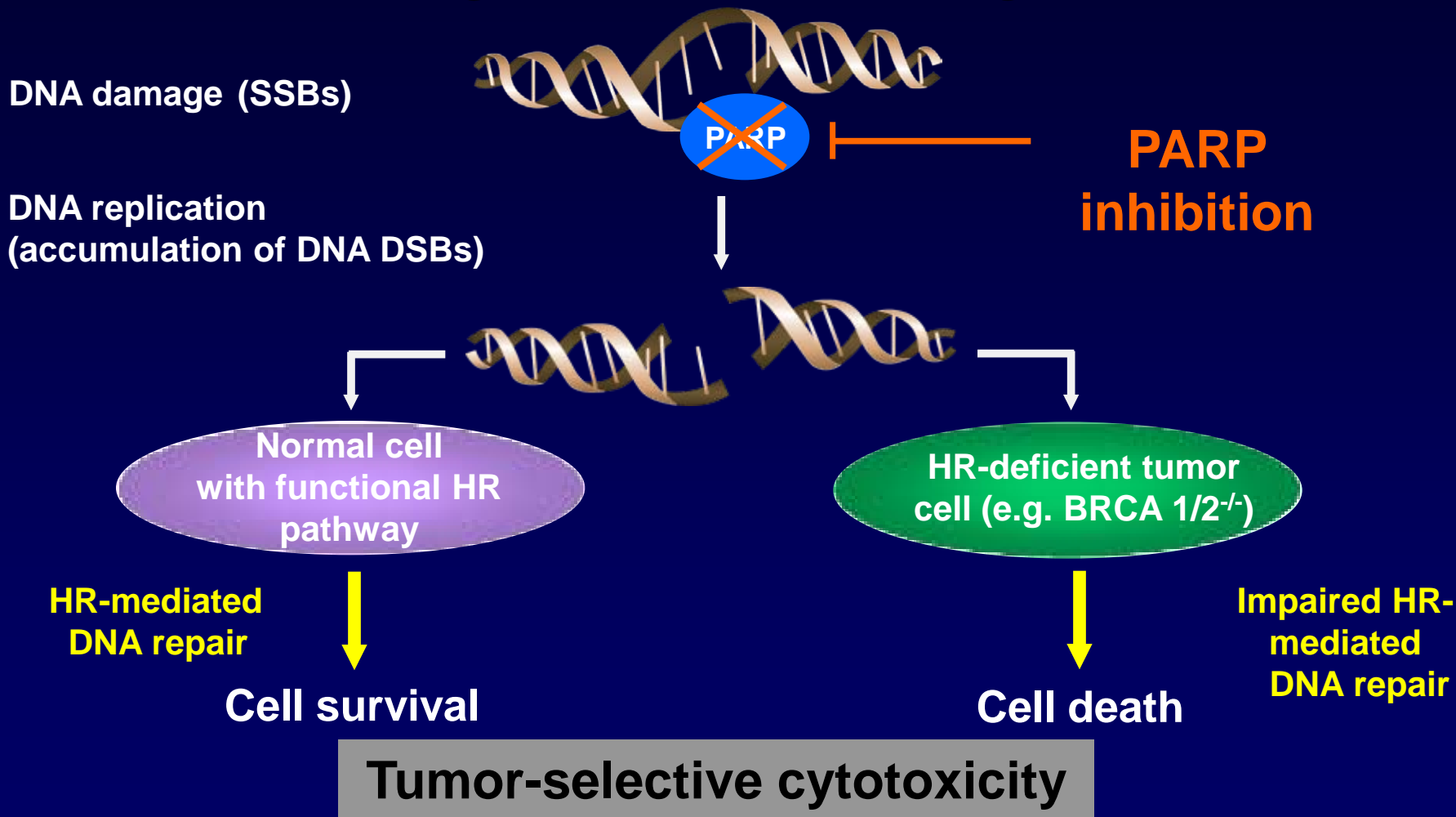
Double Strand Breaks

- Non-homologous end-joining
- Homologous recombination
 - BRCA1/BRCA2
- Fanconi anemia pathway
- Endonuclease-mediated repair

DNA Adducts/Base Damage

- Alkyltransferases
- Nucleotide excision repair
- Base excision repair
- PARP1

PARP Inhibition and Tumor-Selective Synthetic Lethality



Farmer H, et al. *Nature* 2005;434(7035):917-921.
Bryant HE, et al. *Nature* 2005;434(7035):913-917.
McCabe N, et al. *Cancer Res* 2006;66(16):8109-8115.

DSB, double-strand break; HR, homologous recombination
SSB, single-strand break

Rationale for Iniparib (BSI-201) in TNBC

- **PARP1**
 - Upregulated in triple-negative human breast cancers
- **Iniparib (BSI-201)**
 - Small molecule with PARP inhibitory activity
 - Potentiates effects of platinum- and gemcitabine-induced DNA damage
 - No maximum tolerated dose (MTD) reached in Phase I studies of iniparib alone or in combination with chemotherapy

Multicenter Open-Label Randomized Phase II Gem/Carbo ± Iniparib (BSI-201) in TNBC

- Metastatic TNBC (ie, hormone receptor and HER2 negative) with measurable disease
- 0-2 prior chemotherapy regimens for metastatic disease
- No prior treatment with gemcitabine, carboplatin, cisplatin, PARP inhibitor
- Stable brain metastases allowed
- ECOG PS 0–1

Randomization (1:1)

**Gemcitabine (1000 mg/m², IV, d 1, 8)
Carboplatin (AUC 2, IV, d 1, 8)*
Every 3 weeks**

N = 62

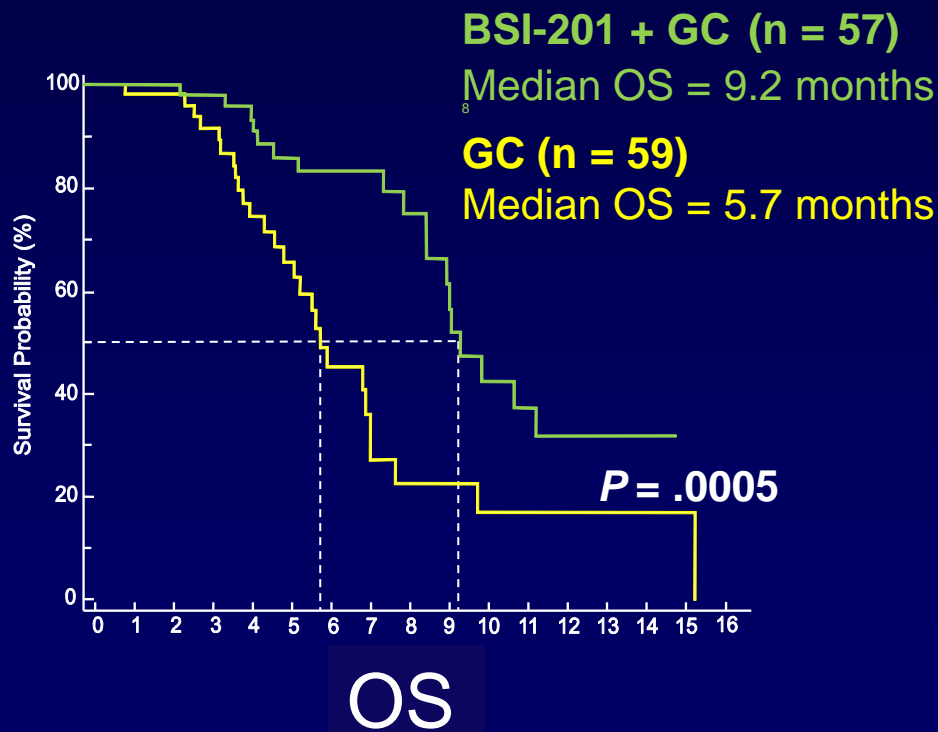
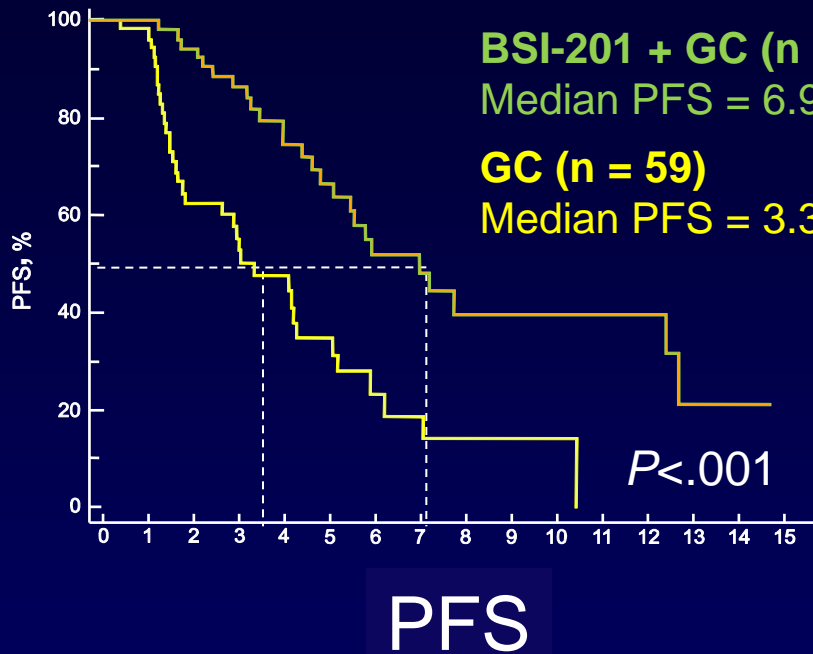
**Iniparib (5.6 mg/kg, IV, d 1, 4, 8, 11)
Gemcitabine (1000 mg/m², IV, d 1, 8)
Carboplatin (AUC 2, IV, d 1, 8)
Every 3 weeks**

N = 61

**RESTAGING
Every 2 Cycles**

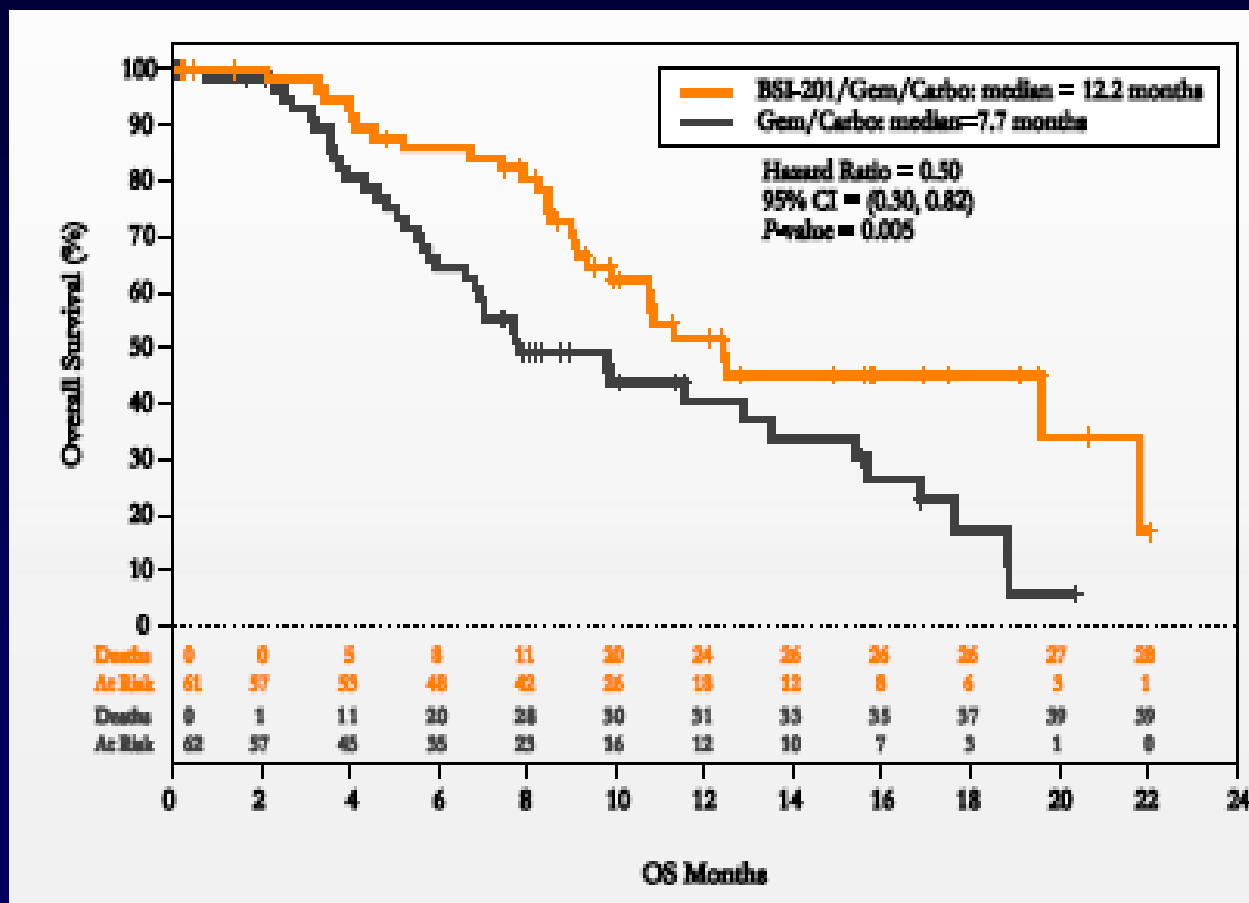
* Patients randomized to gem/carbo alone could crossover to receive gem/carbo + Iniparib (BSI-201) at disease progression

Phase II Gem/Carbo + IV PARP Inhibitor BSI-201 in Triple-Negative Breast Cancer (TNBC)



PHASE III TRIAL OF THIS APPROACH – RESULTS LIKELY IN 2011

BSI 201: OS Update SABCS 2009



A Phase II Trial Testing Olaparib (a PARP 1 Inhibitor) in BRCA-Deficient Advanced (Heavily Pretreated) Breast Cancer

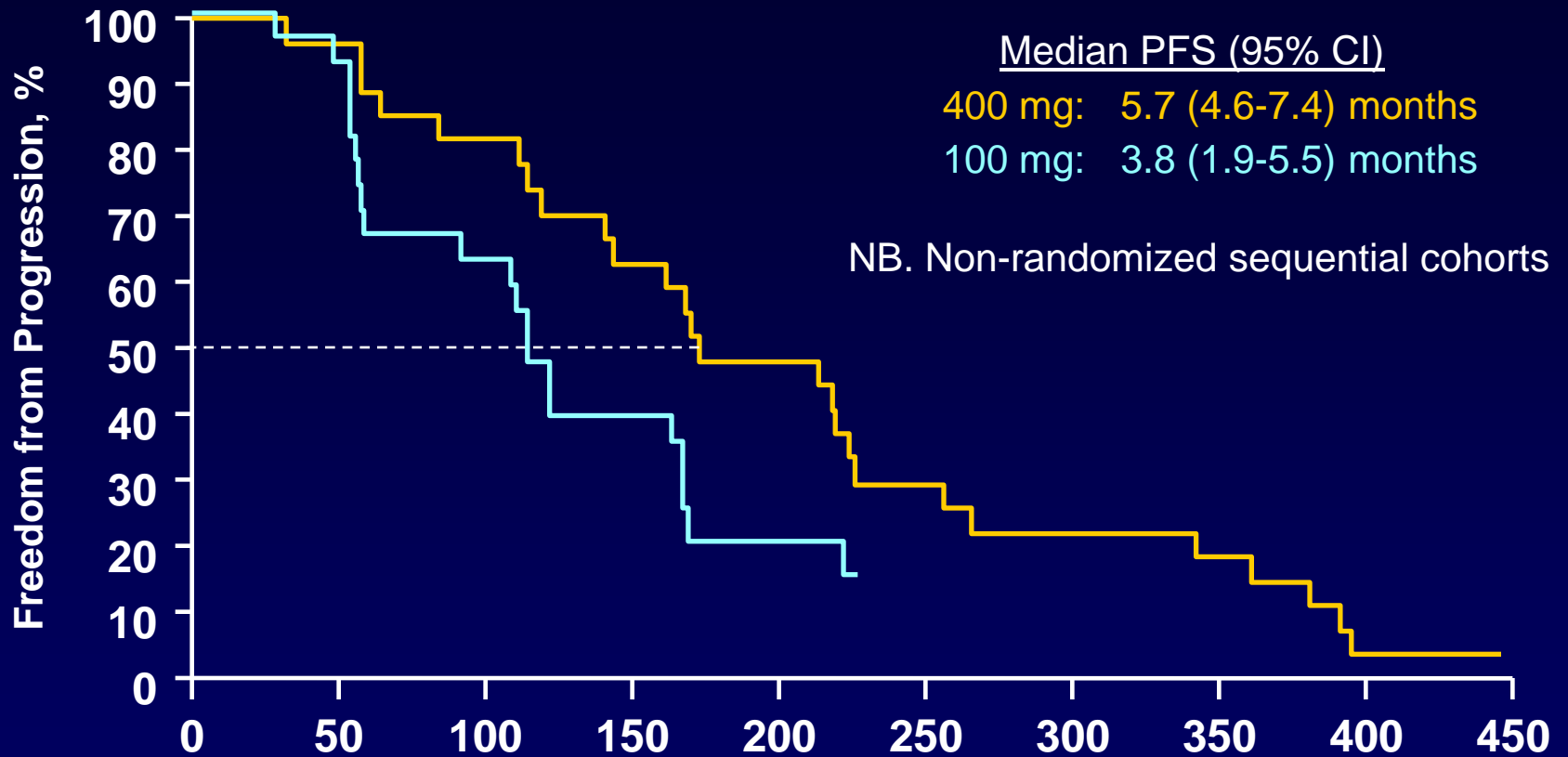
Cohort 1 : N = 27 Olaparib (400 mg) PO bid

Cohort 2 : N = 27 Olaparib (100 mg) PO bid

	Cohort 1 400 mg	Cohort 2 100 mg
% Overall response rate	41	22
% Complete/partial response rate	4/37	0/22

Main G3 side-effects : fatigue (6 patients), nausea (5 patients), vomiting (3 patients)

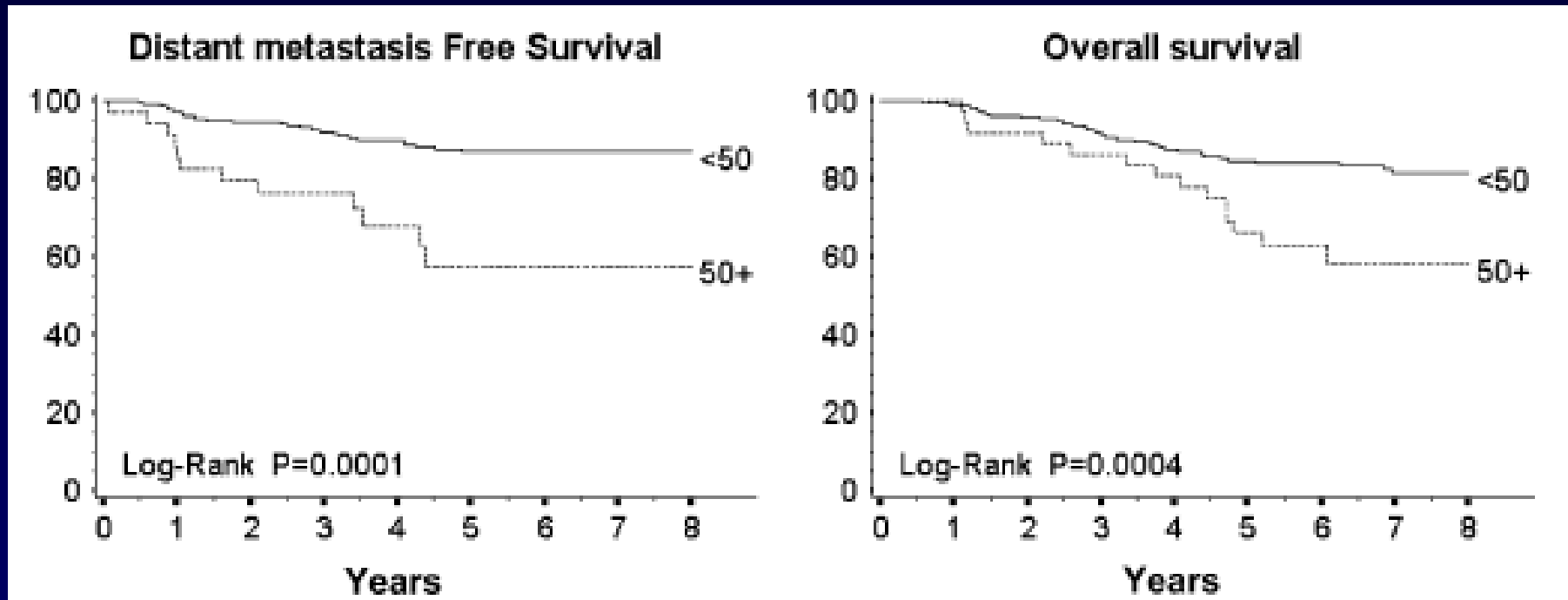
Progression-Free Survival



Patients at risk:	PFS, days									
400 mg:	27	26	22	17	13	8	6	5	1	0
100 mg:	27	25	17	10	4	0	0	0	0	0

EGFR Expression and Outcome in TNBC Patients

[284 patients, pT1-3, pN1-3, M0]



Worse outcome for EGFR immunoreactivity in $\geq 50\%$ cells

DFS: HR 2.39 (95% CI, 1.32–4.34, $P = .004$)

OS: HR 2.34 (95% CI, 1.20–4.59, $P = .01$)

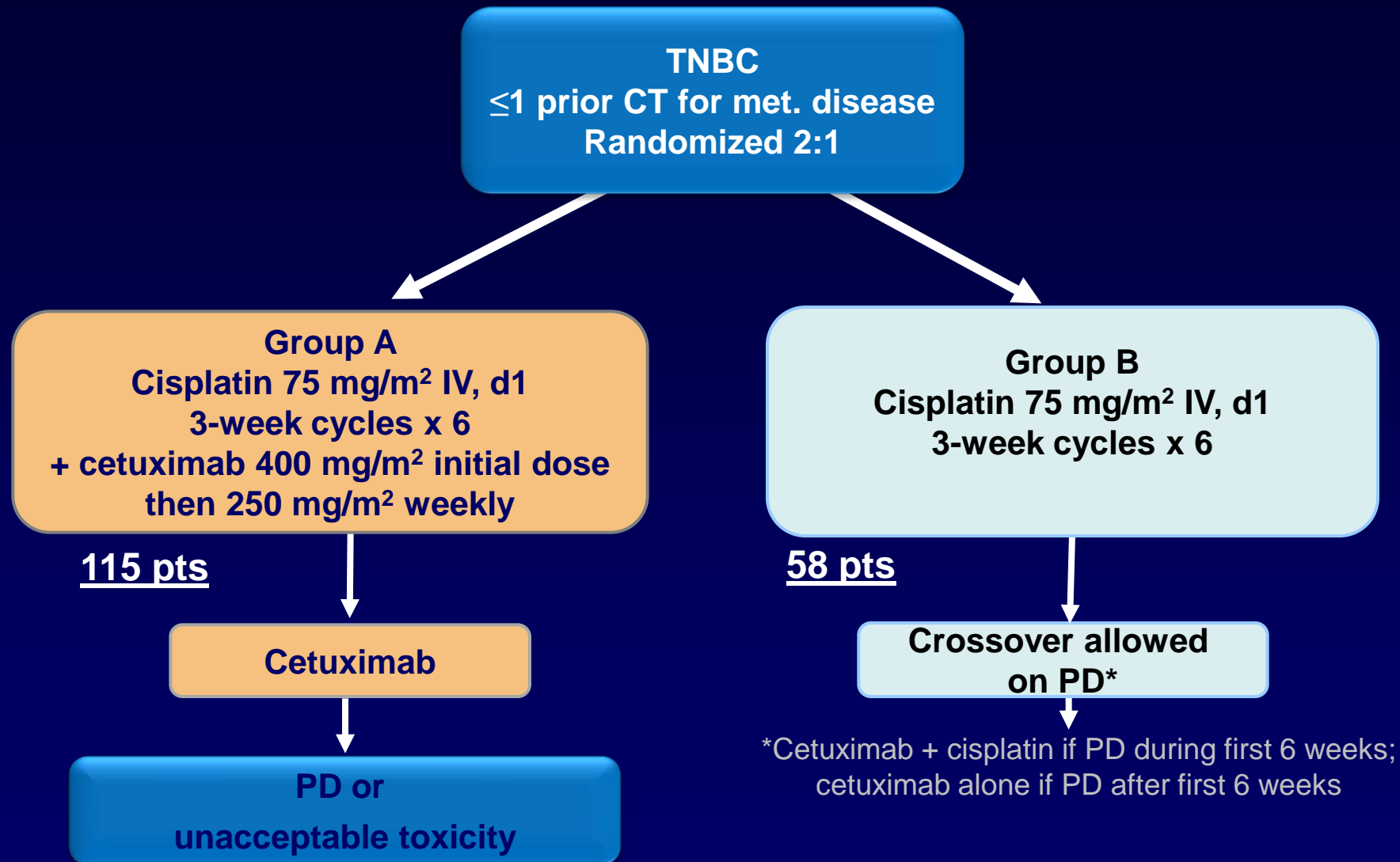
Cetuximab + Chemotherapy in Triple-Negative MBC

TBCRC001 Phase II R 116 pts		US Oncology Phase II R 72 TN pts		
	CBDCA + Cet	Cetuximab	CBDCA/CPT + Cet.	CBDCA/CPT
RR	33%	6%	49%	30%
			No ↑ PFS	

Carey LA, et al. *J Clin Oncol*. 2008;26(Suppl): Abstract 1009.

O'Shaughnessy J, et al. *Breast Cancer Res Treat*. 2007;106(Suppl 1): Abstract 308.

BALI-1: Study Design

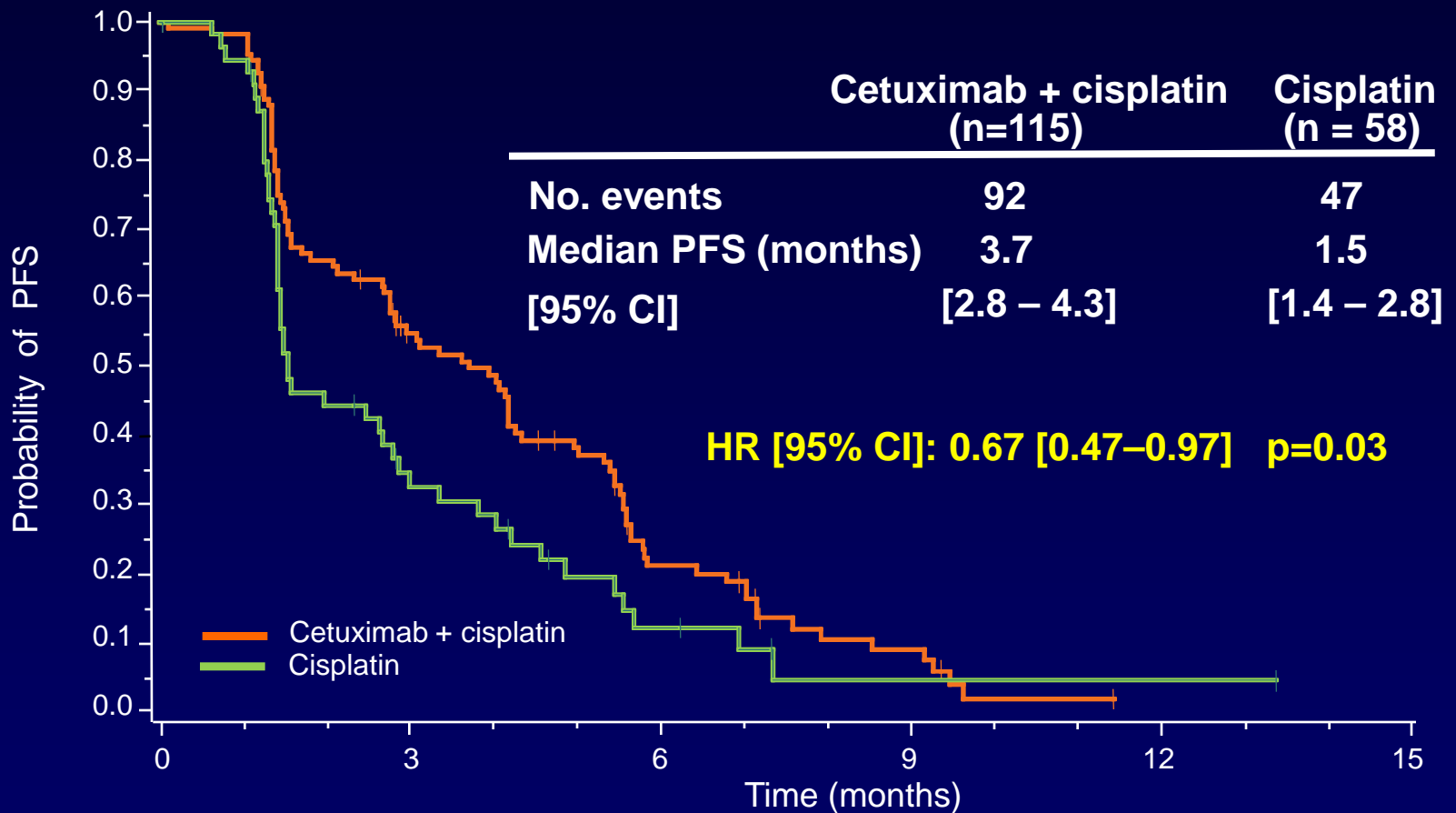


BALI-1: Primary Efficacy Analysis

ORR

Response assessed by investigator	Cetuximab + cisplatin n=115 (100%)	Cisplatin n=58 (100%)
Complete response	2 (1.7%)	1 (1.7%)
Partial response	21 (18.3%)	5 (8.6%)
Stable disease	48 (41.7%)	18 (31.0%)
Progressive disease	34 (29.6%)	31 (53.4%)
Not evaluable	10 (8.7%)	3 (5.2%)
ORR	23 (20.0%)	6 (10.3%)
[95% CI]	[13.1% – 28.5%]	[3.9% – 21.2%]

BALI-01: Secondary Efficacy PFS



	Cetuximab + cisplatin (n=115)	Cisplatin (n = 58)
No. events	92	47
Median PFS (months)	3.7	1.5
[95% CI]	[2.8 – 4.3]	[1.4 – 2.8]

Patients at risk	0	3	6	9	12	15
Cetuximab + cisplatin	115	53	18	6	0	0
Cisplatin	58	16	5	1	1	0

Androgen Receptors in TNBC

1. TNBC series with long-term follow-up:

- AR expression, nodal status, tumor size most useful prognostic markers
- In LN+ tumors, AR and tumor size retained prognostic value

2. AR may be a potential target in TNBC

3. Neoadjuvant TAC efficacy correlated with presence of AR, ER/PR, grade, & age

- Response (pCR) in TNBC by AR expression:
AR+ 33.3%; AR- 43.5%

AR as a Therapeutic Target in TNBC

Phase II Feasibility Study of Bicalutamide

Patient Population

- MBC
- ER- and PR-
- AR+
- If HER2+, must have received prior trastuzumab

Treatment

Target N=28

Bicalutamide PO QD x 4 wk*

*Treatment repeats every 4 weeks x 6 mo in absence of progression or unacceptable toxicity. Pts with CR/PR/SD may continue to receive bicalutamide per investigator.

Endpoints:

- Primary: 6-mo response rate for pts with measurable and non-measurable disease
- Secondary: median PFS, safety

MY OPINION (Part I)

Do you think BRCA testing should be performed in this patient?

1. Yes

2. No

MY OPINION (Part II)

Would you perform liver biopsy for purposes of repeating ER/PR and HER2 status?

1. Yes

2. No

MY OPINION (Part III)

Biopsy of the liver metastases confirms recurrence of triple-negative breast cancer.

Which of the following systemic therapy options would you recommend at the time of progression?

1. Platinum-based chemotherapy
2. Combination therapy with capecitabine and docetaxel
3. Other conventional chemotherapy for metastatic disease
4. Chemotherapy + bevacizumab

MY OPINION (Part IV)

The patient was treated with capecitabine and bevacizumab. After the third cycle of this therapy, she was asymptomatic and partial response was confirmed. She did well for 5 months when she developed mild cough and pain (5/10) in lumbar spine. Liver function tests were slightly elevated, all other lab tests were normal. With further evaluation, progression in lung, liver, and bone was confirmed. Radiation therapy was administered to the lumbar spine and intravenous (IV) zoledronic acid was begun. ECOG PS = 1.

Which systemic therapy would you recommend for this patient now after progression on chemotherapy and bevacizumab?

1. Conventional chemotherapy for metastatic disease
2. I would change chemotherapy and continue bevacizumab
3. Clinical trial of a PARP inhibitor if available
4. Clinical trial of other targeted agent (eg, sorafenib, dasatinib, everolimus, androgen receptor inhibitor)