

# Novel Strategies for the Management of Disease Progression Following Standard Chemotherapy

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**Focus on patients with  
hormone-resistant HER2-negative  
advanced breast cancer refractory to  
anthracyclines and taxanes**

# Potential New Options Beyond Capecitabine Single-Agent

- **Platinum compounds  $\pm$  PARP inhibitors**
- **Combination capecitabine-ixabepilone**
- **Eribulin**
- ***Nab*-paclitaxel**

# Platinum-Based Chemotherapy: Rationale

**Triple-negative disease  
(±20% of breast cancer cases)**

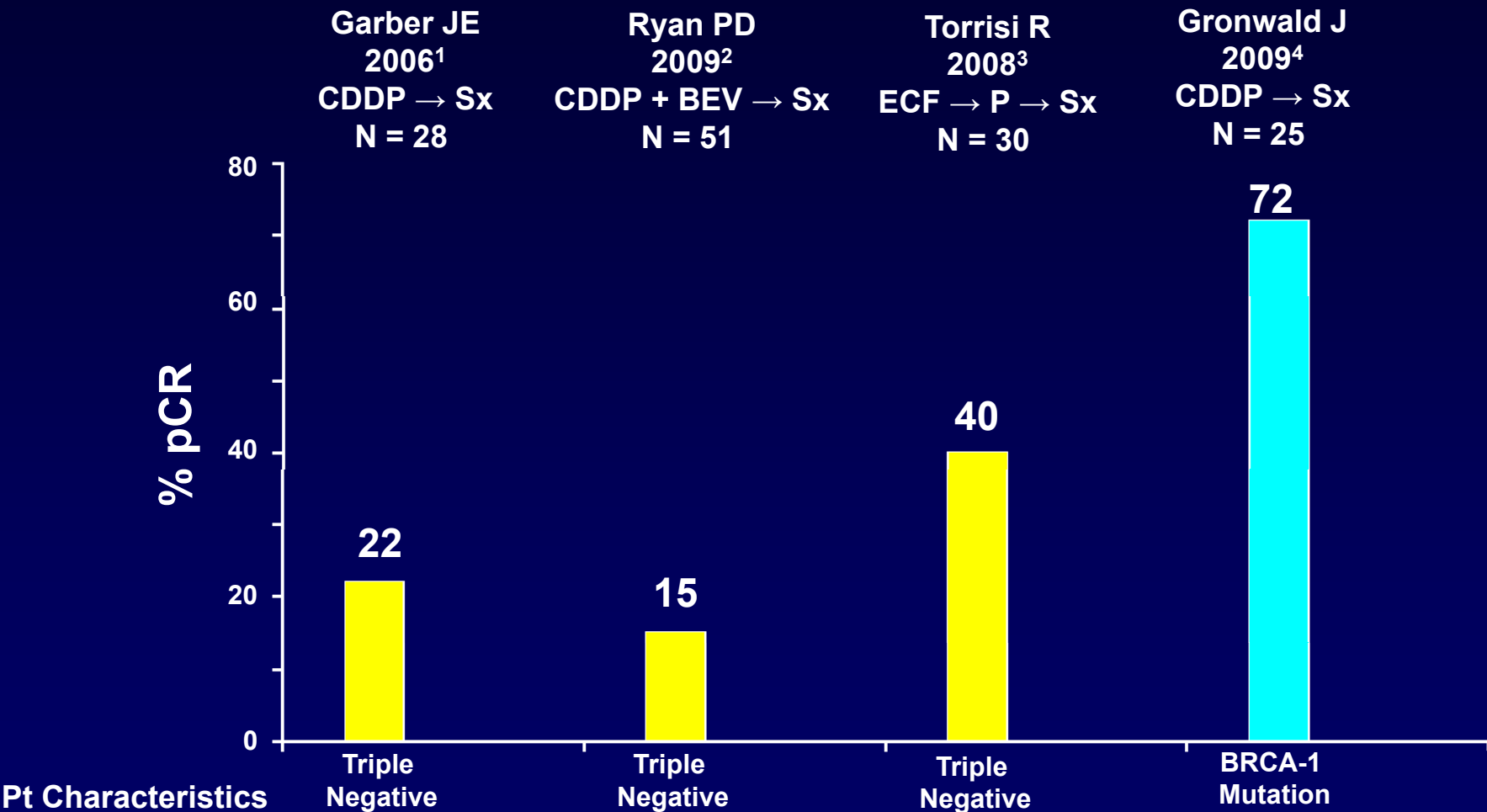


**Basal-like phenotype  
(50% to 80% of triple-negative)**



**BRCA-1 loss-of-function  
(±80% of basal-like)**

# Neoadjuvant Chemotherapy with Platinum Compounds: Phase II Trials



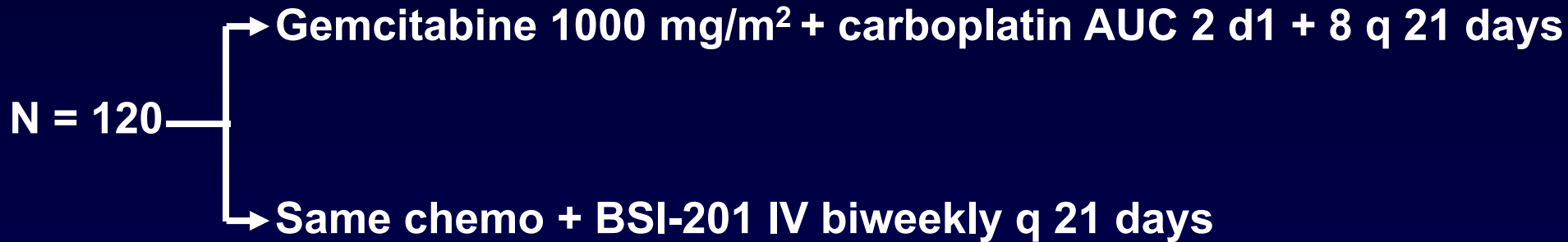
CDDP, cisplatin; Sx, surgery; BEV, bevacizumab; ECF, epirubicin-cisplatin-5FU; P, paclitaxel; pCR, pathologic complete response

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. Torrisi R, et al. *Cancer Chemother Pharmacol.* 2008;62(4):667-672. 4. Gronwald J, et al. *J Clin Oncol.* 2009;27(15S): Abstract 502.

# **Poly (ADP-Ribose) Polymerase-1 (PARP 1) as a Treatment Target in Triple-Negative Breast Cancer**

- **Nuclear enzyme involved in DNA base excision repair**
- **Upregulated in majority of triple-negative breast cancers**
- **Key role in BRCA-1 deficient cell lines\***

# A Phase II Randomized Trial Testing a PARP 1 Inhibitor BSI-201 in Triple-Negative Metastatic Breast Cancer Patients



	Chemo	Chemo + PARP Inhibitor	HR (95% CI)	P Value
Clinical benefit rate, %	21	62	-	.0002
Median PFS, months	3.3	6.9	0.34 (0.20-0.58)	.0001
Median OS, months	5.7	9.2	0.35 (0.19-0.65)	.0005

**No increase in toxicity in the PARP inhibitor arm**

AUC, area under the curve; OS, overall survival; PFS, progression-free survival

O'Shaughnessy J, et al. *J Clin Oncol*. 2009;27(18S): Abstract 3.

# 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**

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

**Main grade 3 side effects: Fatigue (6 patients), nausea (5 patients), vomiting (3 patients)**

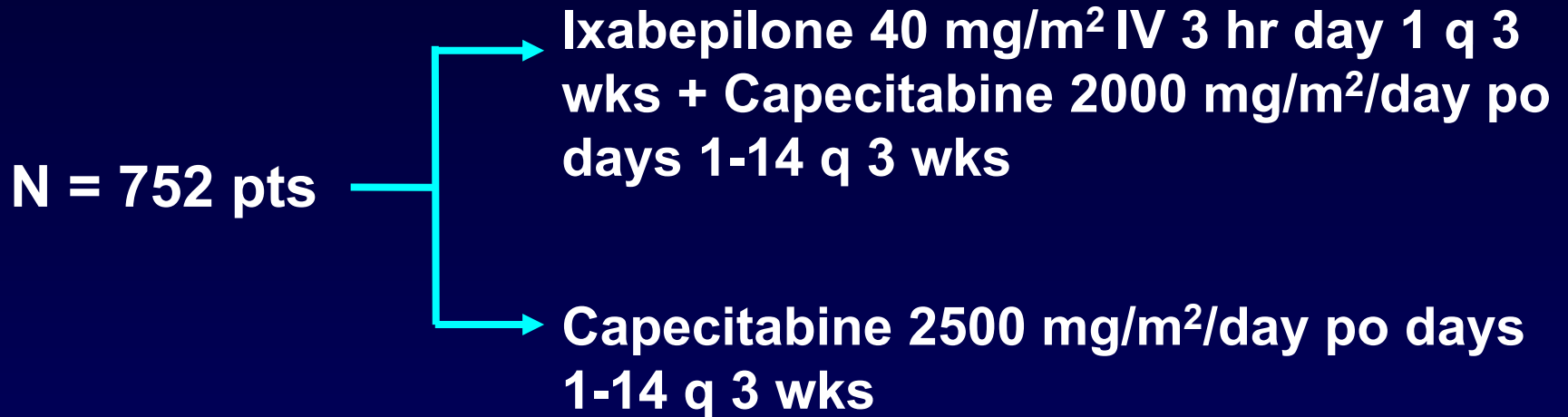
# Open Questions on PARP 1 Inhibitors

- **Clinical activity of PARP 1 inhibitors in combination with cisplatin in BRCA-deficient tumors**
- **Combination of PARP 1 inhibitors with other DNA damaging agents (ie, cyclophosphamide, anthracyclines, doublets or triplets)**
- **Clinical activity of PARP 1 inhibitor in non–triple-negative or non–BRCA-deficient tumors**

# **Ixabepilone in Breast Cancer Phase II Trials**

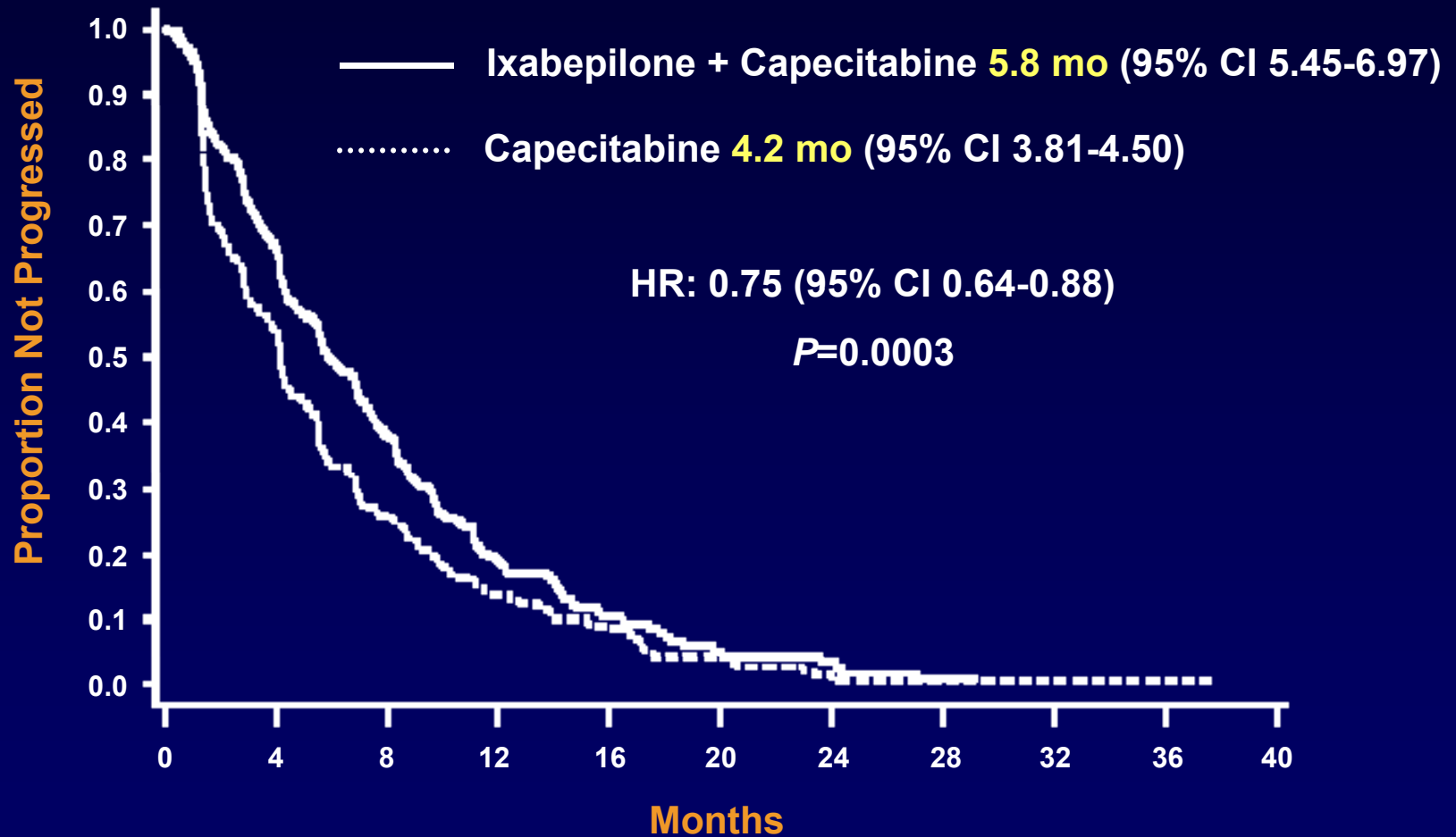
- **Ixabepilone promotes cell death by stabilizing microtubules and inducing apoptosis. Unlike taxanes, epothilones have low susceptibility to multiple mechanisms of drug resistance (PgP and MRP1)**
- **Four trials in M+ patients have shown ORR for ixabepilone ranging from 12% (pretreated) to 42% (first-line)**
- **A neoadjuvant trial has shown a pCR rate of 18% for single-agent ixabepilone**

# A Phase III Trial in M+ Pts Resistant to Anthracyclines and Taxanes



**Stratification by visceral mets, prior CT, anthracycline resistance, study site**

# Progression Free Survival by Treatment Arm (Independent Radiology Review)



# Ixabepilone + Capecitabine Phase III Trial

## Grade 3/4 Treatment-Related Toxicities

Adverse Event Grade 3/4	I + C, % (N = 369)	C, % (N = 368)
Neutropenia	68	11
Febrile Neutropenia	4.8	0.5
Peripheral neuropathy	22.8	0
Resolution of neuropathy*, median wks after dose reduction (range)	6.0 (4.6–7.6)	NA
Hand-foot syndrome	18	17
Fatigue	9	3.3
Myalgia	8	0.3
Diarrhea	6	8.5
Vomiting	4	2.3
Nausea	3	2
Mucositis	2.3	2
Arthralgia	3	0

\*Defined as the time from onset of worst grade to baseline or grade 1; NA: neuropathy not seen

Adapted from Thomas ES, et al. *J Clin Oncol.* 2007;25(33):5210-5217.

# Eribulin as a Novel Antimicrotubule Cytotoxic Agent

- Eribulin is a synthetic analogue of the marine natural product halichondrin B
- Eribulin is a microtubule dynamics inhibitor with a novel mechanism of action (it suppresses microtubule growth and it sequesters tubulin into nonfunctional aggregates)
- Phase I studies have shown that neutropenia is the dose-limiting toxicity (DLT). Other side effects include alopecia, fatigue, and nausea

# Phase II Trials with Eribulin in Patients with Advanced Breast Cancer Previously Treated With Anthracyclines And Taxanes

	Vahdat et al* <i>J Clin Oncol</i> 2009 <sup>1</sup>	Vahdat et al** <i>ASCO</i> 2008 <sup>2</sup>
Number of patients	103	269
Median number of prior chemotherapy regimens for M+ disease	4	4
Eribulin dose	1.4 mg/m <sup>2</sup> IV bolus d 1 + 8 q 21 days	1.4 mg/m <sup>2</sup> IV bolus d 1 + 8 q 21 days
ORR, % (95% CI)	16 (10-25)	9 (6-13)
FN/G3 fatigue/G3 neurotox, %	4/5/5	5/10/5

\*70/103 patients received d 1 + 8 +15 q 28 days; \*\*previously treated with A, T, and capecitabine

# ***Nab*-Paclitaxel in Breast Cancer**

- ***Nab*-paclitaxel is albumin-bound, polyethoxylated castor oil-free paclitaxel → no steroids premedication and short duration infusion**
- **Previous study testing *nab*-paclitaxel in taxane pretreated advanced breast cancer patients (N = 181 patients; ORR 31%)\***

# Two Trials Comparing *Nab*-Paclitaxel to Either Paclitaxel or Docetaxel in Patients with Advanced Breast Cancer

	<i>Nab</i> -Paclitaxel (nTx) vs Docetaxel (TxT)	<i>Nab</i> -Paclitaxel (nTx) vs Paclitaxel (Tx)
No. patients	300	454
Arms	<u>nTx</u> 300 mg/m <sup>2</sup> q3w vs <u>nTx</u> 100 mg/m <sup>2</sup> w vs <u>nTx</u> 150 mg/m <sup>2</sup> vs <u>TxT</u> 100 mg/m <sup>2</sup> q3w	<u>nTx</u> 300 mg/m <sup>2</sup> q3w vs <u>Tx</u> q3w 175 mg/m <sup>2</sup> q3w
ORR	37% 45% 49% 35%	33% 19%
Median PFS	11.0 months 12.8 months 12.9 months 7.5 months	23.0 weeks 16.9 weeks
Toxicity	Less fatigue and neutropenic fever with nTx; similar rates of neurotoxicity	More neurotoxicity with nTx; similar rates of neutropenic fever

# Conclusions on Ixabepilone, Eribulin, and *Nab*-Paclitaxel in Patients with Advanced Breast Cancer

- Evidence of activity in anthracycline and taxane pretreated patients with advanced breast cancer
- Toxicity profile similar to taxanes: Neutropenia, fatigue, alopecia, neurotoxicity → no ideal compounds in heavily pretreated patients where quality of life is an important treatment endpoint
- Potential future indication: As a replacement for taxanes. Data available only for *nab*-paclitaxel, suggesting that replacement might be advantageous