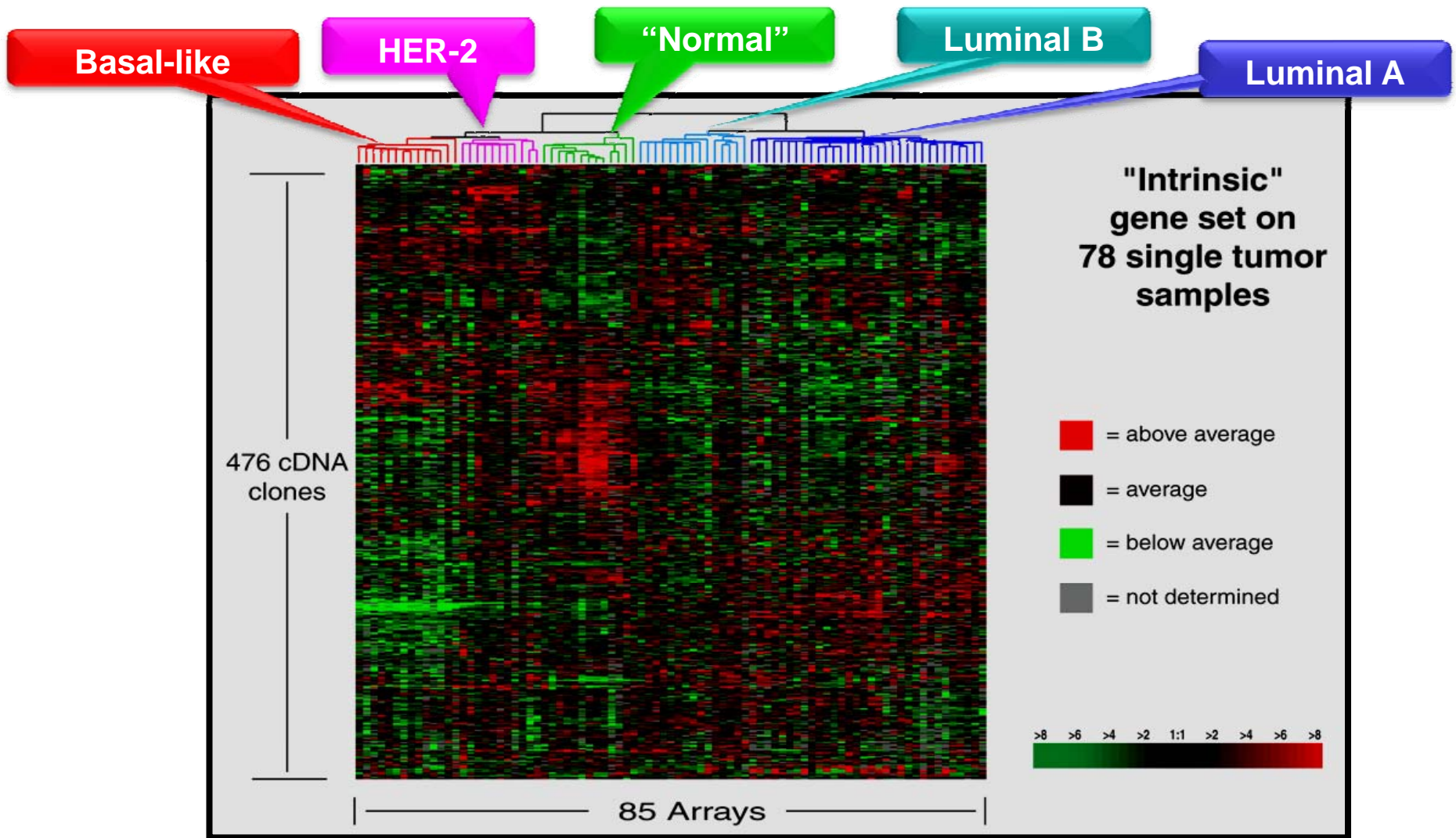


# **Triple Negative Breast Cancer: What is the optimal adjuvant therapy?**

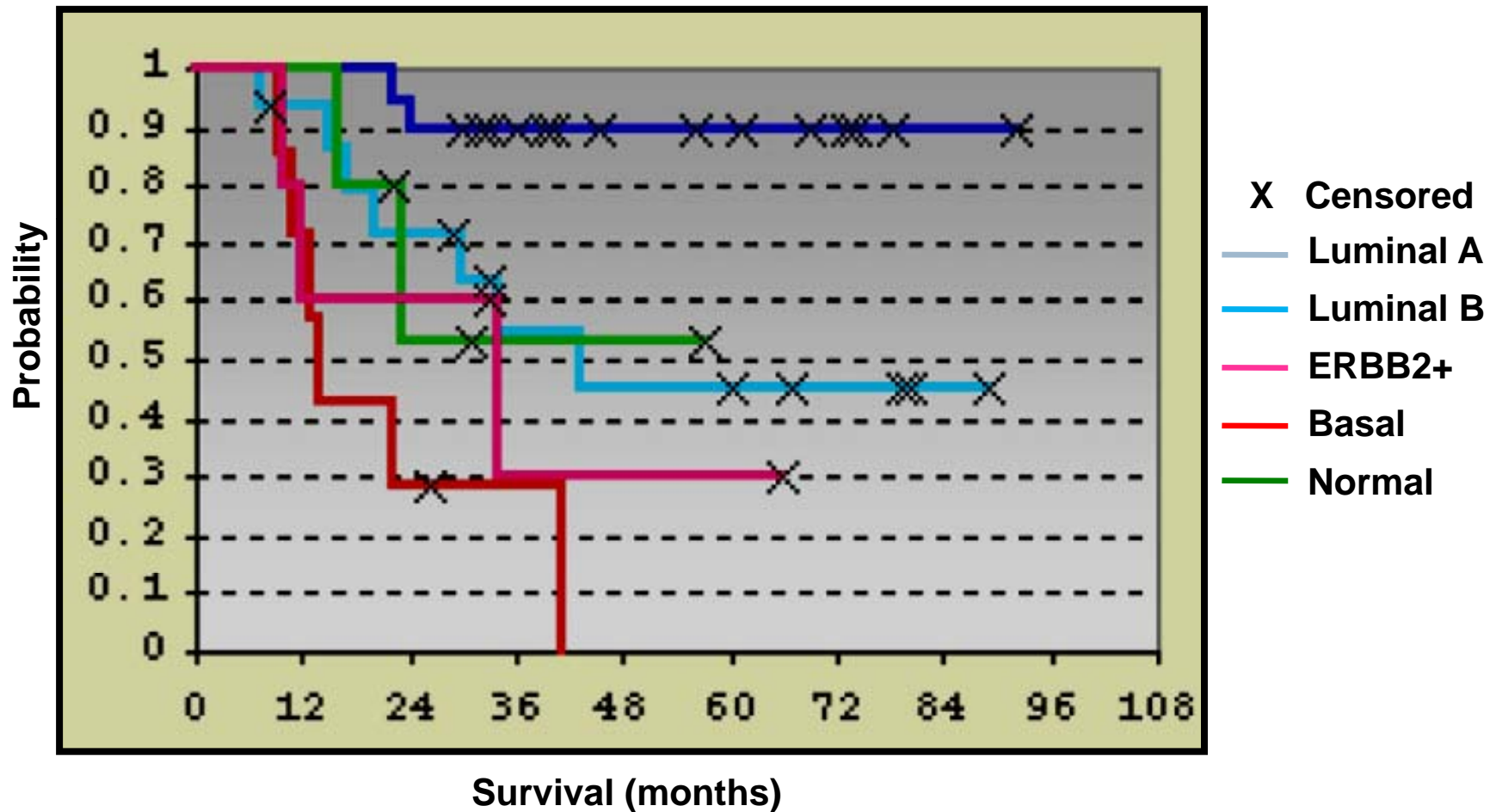
**Dr Kei-Siong KHOO  
Parkway Cancer Centre  
Gleneagles Hospital  
Singapore**

# Classifications by Biologic Subtypes: Molecular Portrait of Breast Cancers



# Biologic Subtypes Predict Clinical Outcome

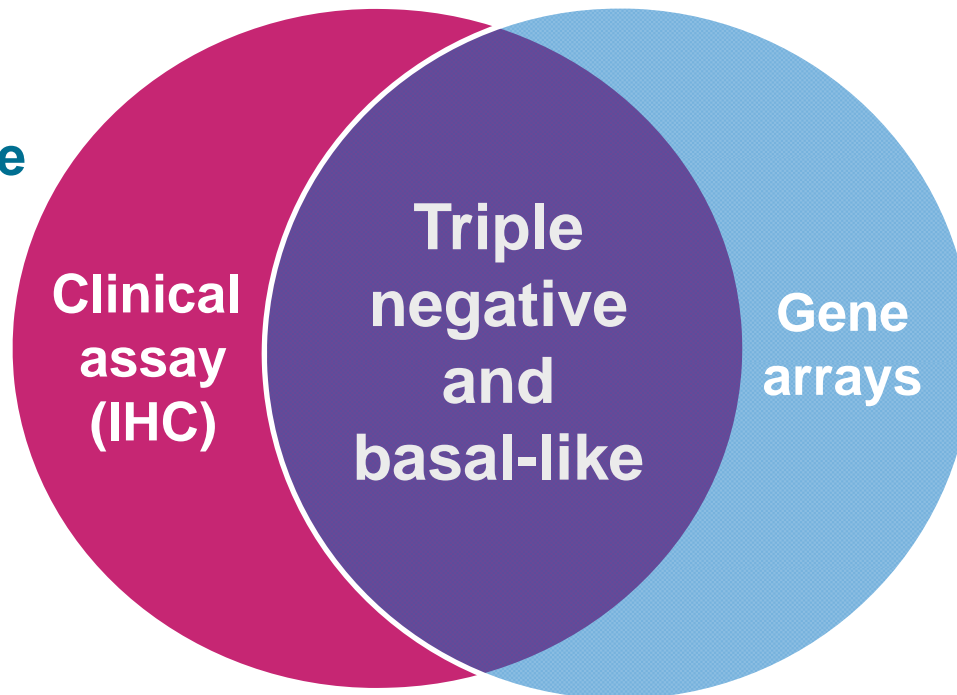
Local Treatment Only



# Triple Negative: Definition

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

- **Triple negative** but not basal
- 10-30%



- **Basal** but not triple negative
- 15-40% are ER+, PR+ or HER2+

# The Triple Negative “Hierarchy”

## Metastatic Breast Cancer

### Triple-negative (ER- / PgR- / HER2-)

15% of BCs

Poorly differentiated

Express  
cytokeratins  
5/6, 17

### Basal-like

Usually TN (low ER and HER2 cluster explosion)

High basal cluster (basal, cytokeratins, EGFR, c-kit, others)

### BRCA-1

~5% of BCs  
Most BRCA-1 carriers get basal-like BC  
Most basal-like BCs are not in BRCA-1 carriers

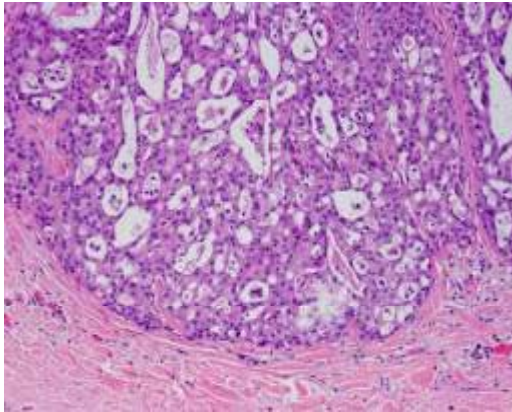
# TNBC: Range of Histology

**Basal-like and Triple Negative Breast Cancers**

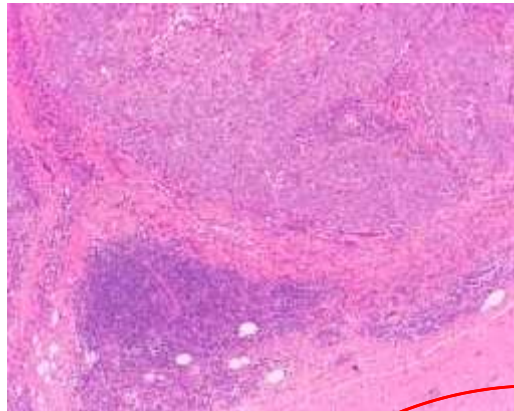
Low grade tumours

High grade tumours

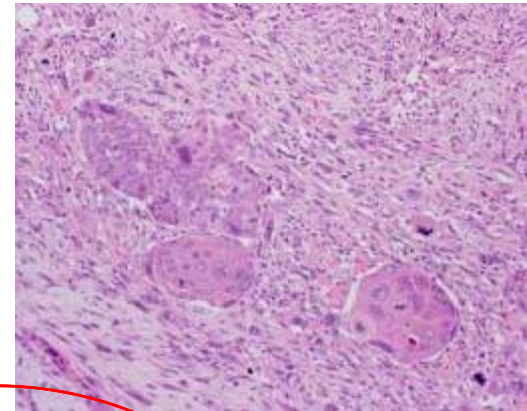
Secretory carcinoma



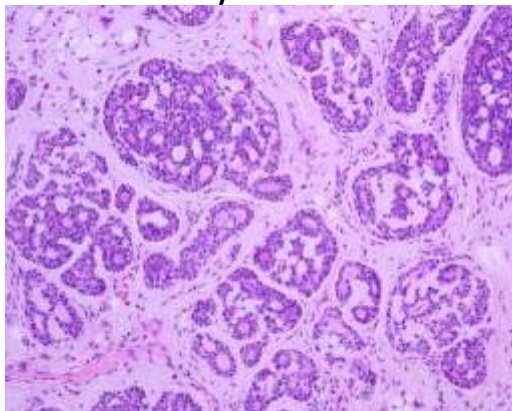
Medullary breast cancer



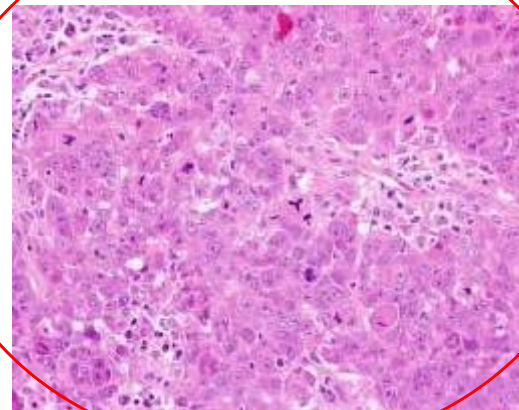
Metaplastic breast cancer



Adenoid cystic carcinoma



Grade 3 – IDC-NST



## Risk Factors for Basal-like May Be Different from Non-basal-like and Potentially Modifiable

Population-based Study N=1424	Adjusted OR cases v. controls	
	Luminal A N=796	Basal-like N=225
Menarche < 13	1.1 (0.9-1.3)	1.4 (1.1-1.9)
Waist:hip $\geq$ 0.84	1.5 (1.1-1.9)	2.3 (1.4-3.6)
$\geq$ 3 children	0.7 (0.5-0.9)	1.9 (1.1-3.3)
First birth < 26	0.7 (0.5-0.9)	1.9 (1.2-3.2)
Breastfeeding $\geq$ 4m	0.9 (0.7-1.1)	0.7 (0.4-0.9)
BMI $\geq$ 30	0.8 (0.6-1.0)	0.8 (0.6-1.2)

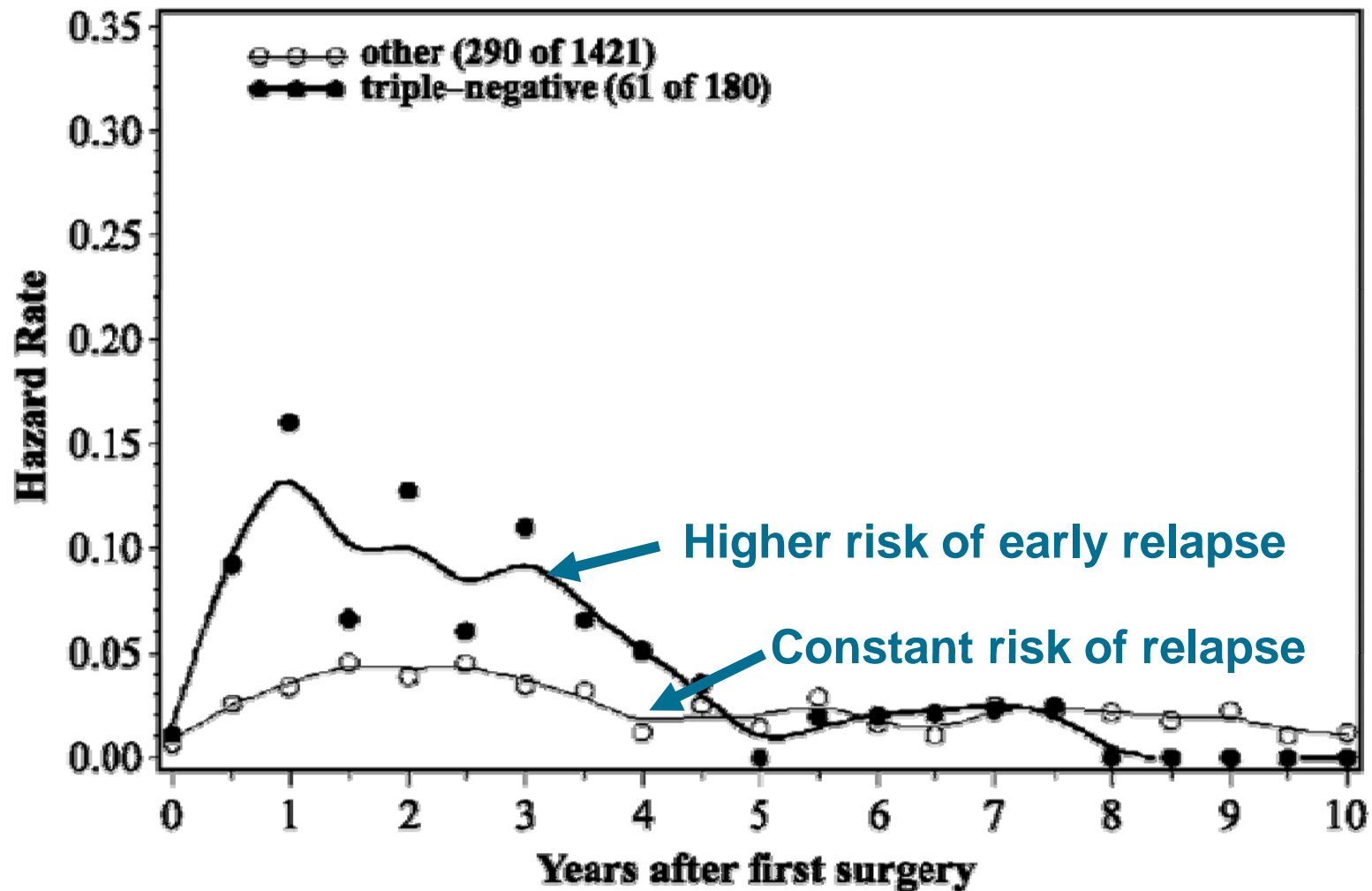
Magnitude  
of effect

Direction  
of effect

# **Triple negative breast cancer: Clinicopathological characteristics**

- **Young patients**
- **Diagnosis between screenings**
- **Poor correlation between size and nodal status**
- **Rapid rise in risk of recurrence following diagnosis**
  - **Peak risk of recurrence at 1–3 years**
  - **Increased risk of brain metastases**
- **Rapid progression from distant recurrence to death**

# TNBC: Frequent and Early Relapse

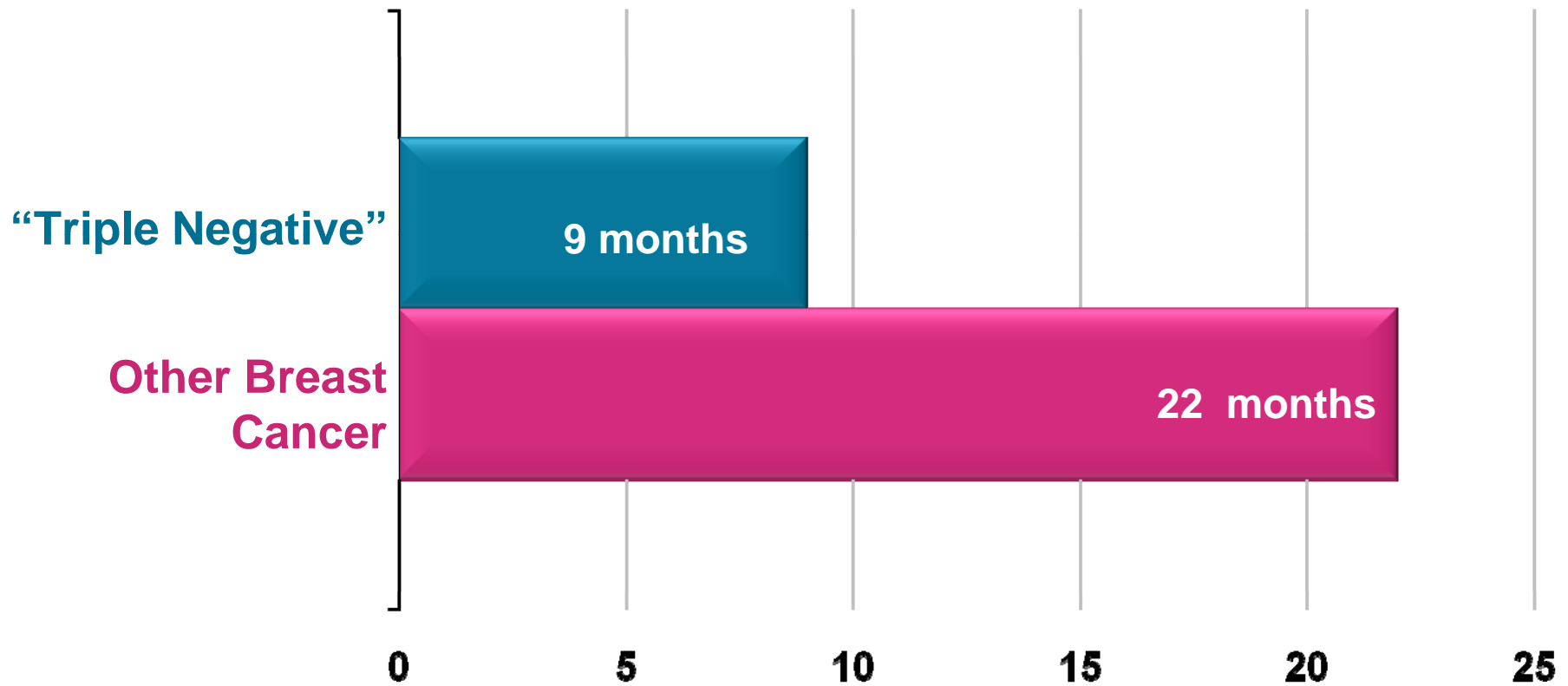


## Metastatic TNBC tends to involve viscera and CNS

<b>MDACC (1<sup>st</sup> site)</b>	<b>N</b>	<b>Bone</b>	<b>Soft Tissue</b>	<b>Viscera</b>
<b>TNBC</b>	<b>79</b>	<b>13%</b>	<b>13%</b>	<b>74%</b>
<b>ER+</b>	<b>123</b>	<b>39%</b>	<b>7%</b>	<b>54%</b>
<b>HER2+</b>	<b>78</b>	<b>7%</b>	<b>12%</b>	<b>81%</b>

<b>DFCI (over time)</b>	<b>N</b>	<b>Bone</b>	<b>Soft Tissue</b>	<b>Lung</b>	<b>Liver</b>	<b>CNS</b>
<b>TNBC</b>	<b>116</b>	<b>42%</b>	<b>32%</b>	<b>64%</b>	<b>50%</b>	<b>46%</b>

# TNBC: Shorter Median Time from Distant Relapse to Death



Dent R, Trudeau M, Pritchard K, Hana W, Narod S. et al.  
*Clinical Cancer Res* 2007

# TNBC in Asia

- **Incidence**

- Singapore<sup>1</sup>            11%
- Korea<sup>2</sup>                20%
- Malaysia<sup>3</sup>            18%
- Japan<sup>4</sup>                15%
- China<sup>5</sup>                19%

- **Characteristics**

- Larger tumour size
- Higher grade
- More nodal involvement
- Higher relapse rate

1. Thike AA et al. *Modern Pathology* (2009), 1–11. 2. Rhee J, et al. *BMC Cancer* 2008;8:307.  
3. Tan et al. *Asian Pacific J Cancer Prev*, 2009 (10) 395-398. 4. Iwase H et al. *Breast Cancer* 2009, May 23. 5. Yin et al. *Breast Cancer Res Treat* (2009) 115:325–333

# Survival of TNBC in Asia

- **1991-2003**
- **N=1993 pts**
  - ER+/HER2- 49%
  - ER-/HER2+ 32%
  - Triple neg 19%
- **Median FU 2.8 yr**
- **Adjuvant Tx**
  - Chemo 85%
  - Hormone 50%

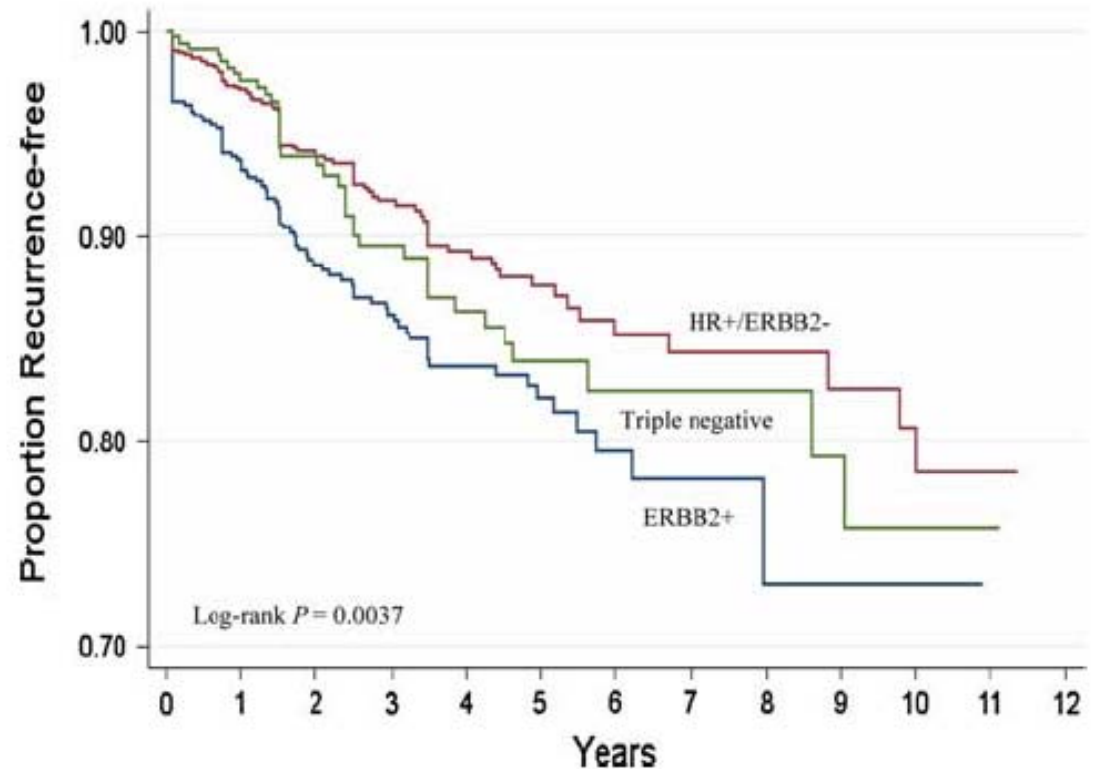


Fig. 1 Kaplan–Meier curves for recurrence-free survival in 1993 breast cancer patients by different subgroups

# TNBC: Current Treatment

- **TNBC paradox:**
  - chemosensitive, but
  - relapse more aggressive with worse OS
- **Not amenable to hormonal therapy or anti-HER2 agents**
- **Manage same as other BCs with same grade & stage**
- **Limited data available from prospective trials in this population**

# TNBC is Chemosensitive

## Data from Neoadjuvant Therapy

pCR	T-FAC (N=82)*	AC-T (n=107)*
Luminal A/B	7%	7%
HER2+/ER-	45%	36%
Triple negative	45%	26%

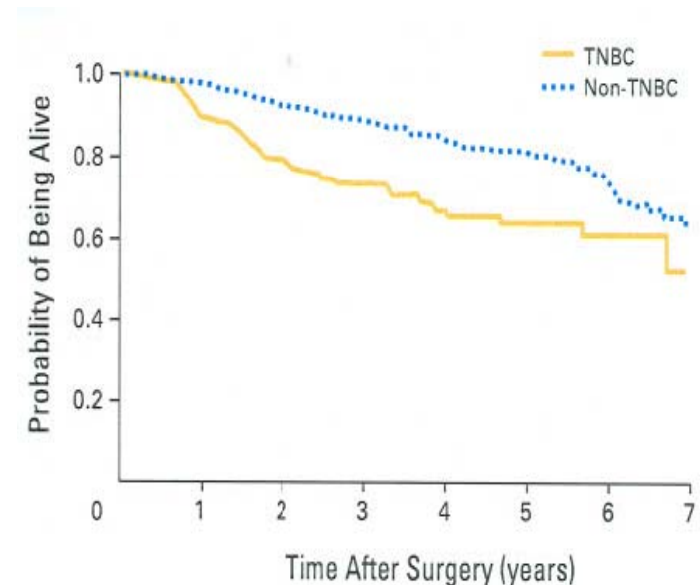
- Compared with ER+ luminal disease, TNBC and HER2+/ER- BC pts had:
  - Decreased DFS (p=0.04)
  - Decreased OS (p=0.02)

# TNBC is Chemosensitive

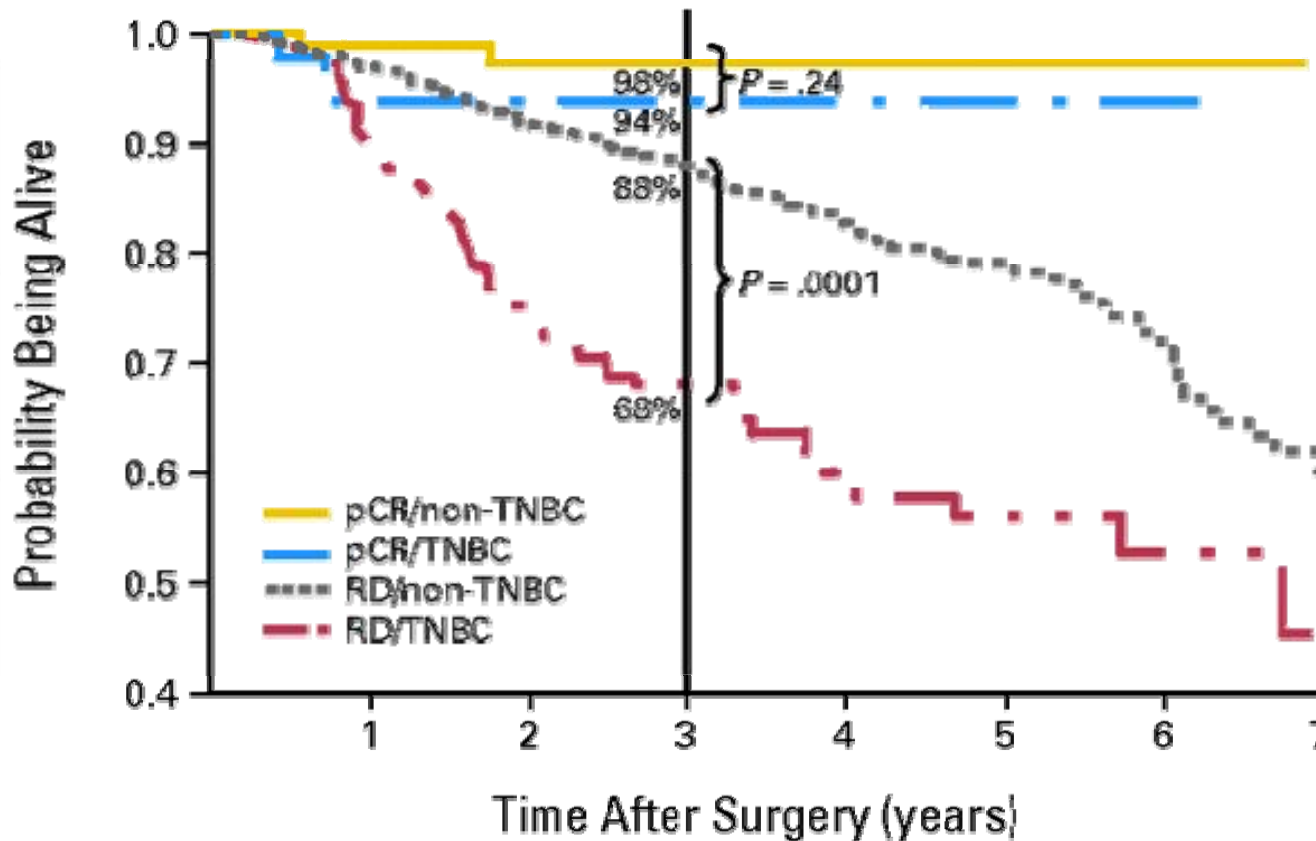
## Data from Neoadjuvant Therapy

- 1118 pts received T-FAC
- Note Paradox: Despite increase in pCR rate, TNBC had worse outcome (OS)

	TNBC	Non-TNBC	P Value
Pts, no (%)	265 (23)	863 (77)	
pCR, %	22	11	0.034
PFS (3-y), %	63	76	<0.0001
OS (3-y), %	74	89	<0.0001



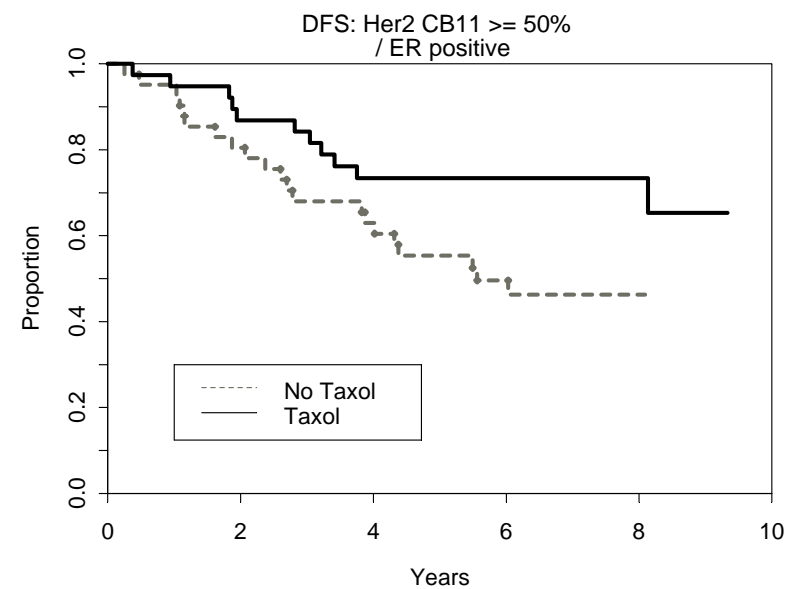
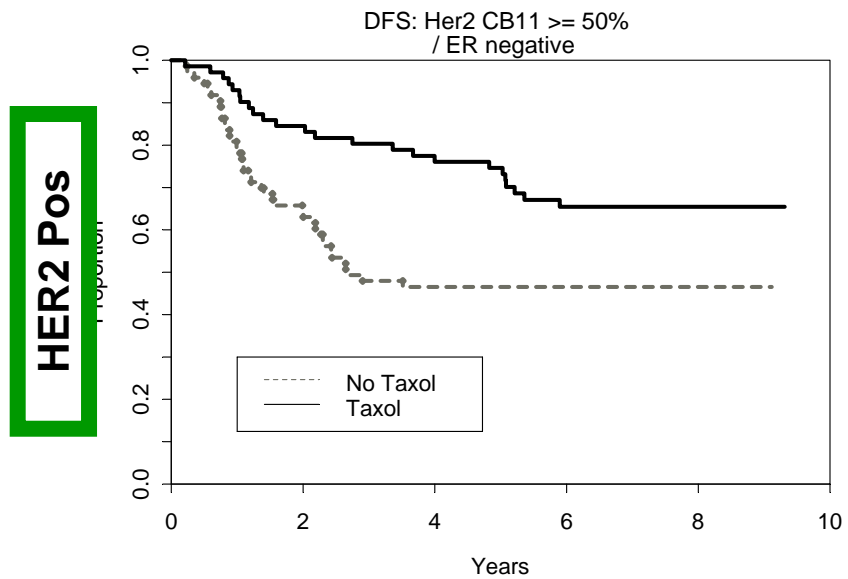
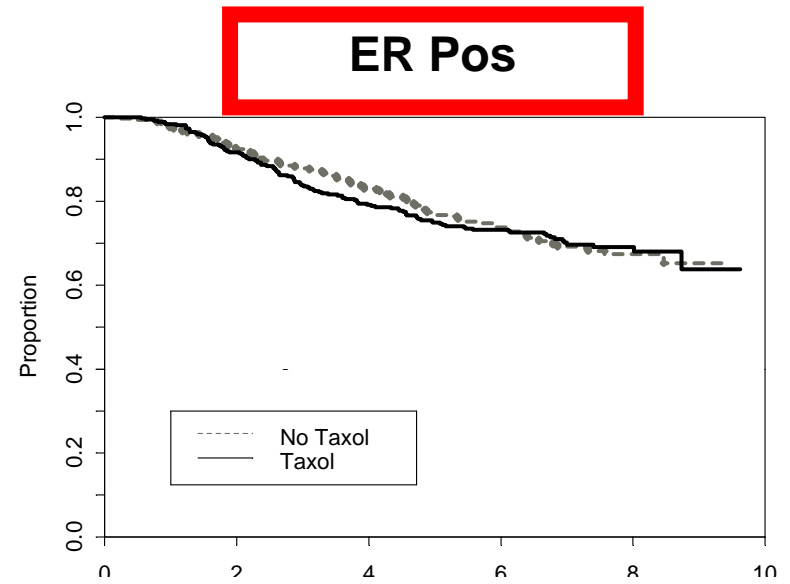
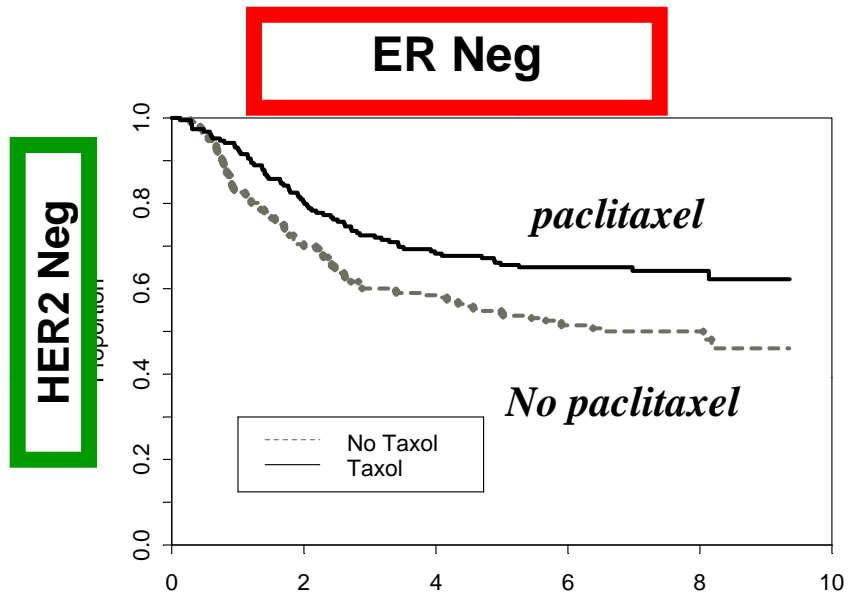
# Prognosis of TNBC Is Dependent Upon Responsiveness to Chemotherapy



pCR do well, regardless of subtype

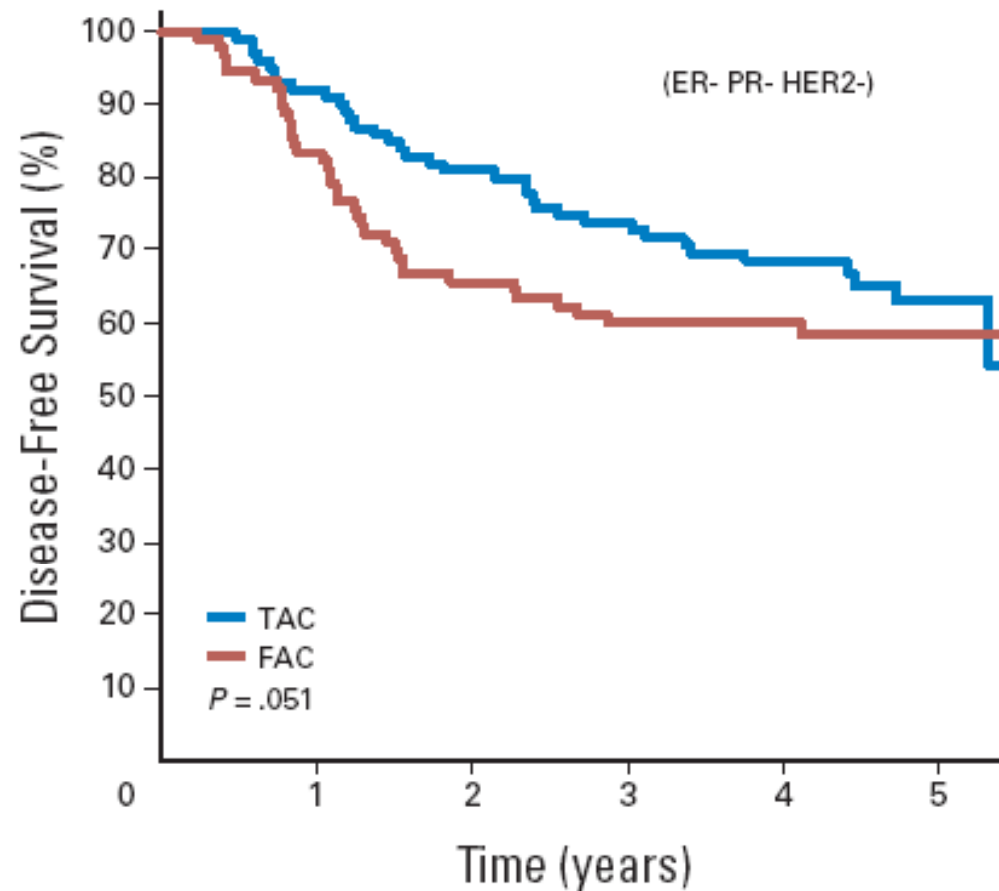
Non-pCR do not do well, especially if triple negative

# C9344 Disease-Free Survival for Paclitaxel By ER and HER2 Status



# TNBC: Adjuvant Therapy with Anthracycline plus Taxane

## BCIRG 001: TAC vs FAC (n=192)

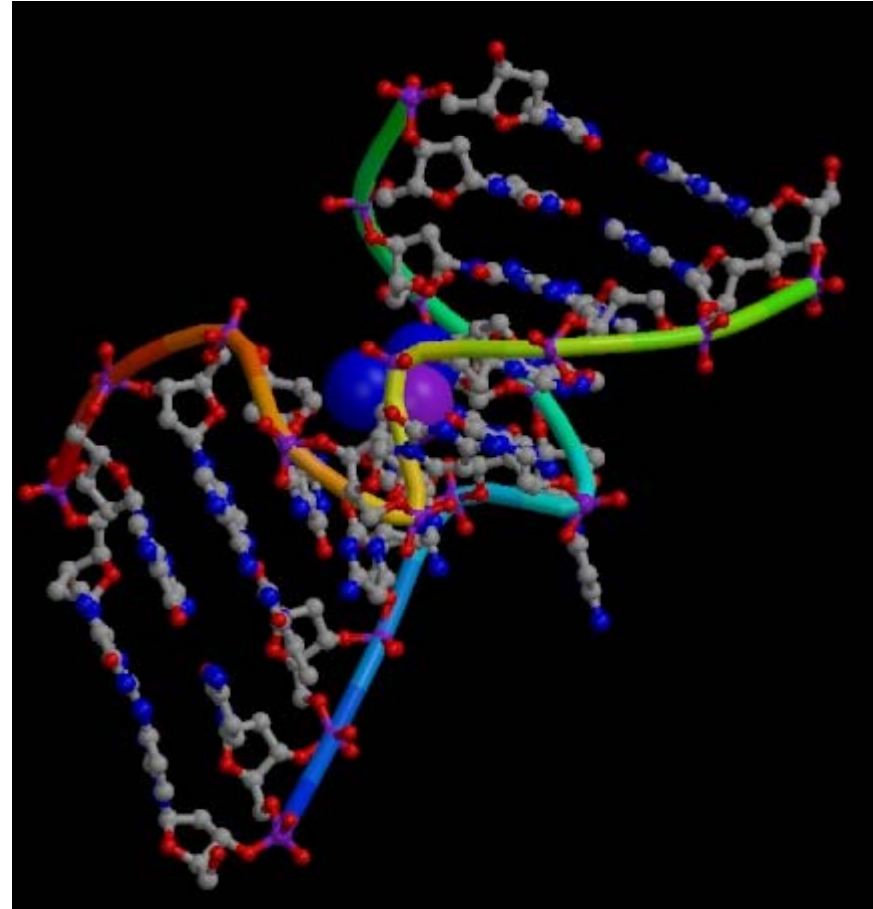


Hugh et al. J Clin Oncol. 2009;27:1168-1176.

**What is there beyond anthracycline  
and taxane?**

# Platinum Complexes Bind and Cause Cross-link DNA Triggering Programmed Cell Death

**Crystal structure of a double-stranded DNA decamer containing a cisplatin  $[\text{Pt}(\text{NH}_3)_2]$  interstrand cross-link adduct**

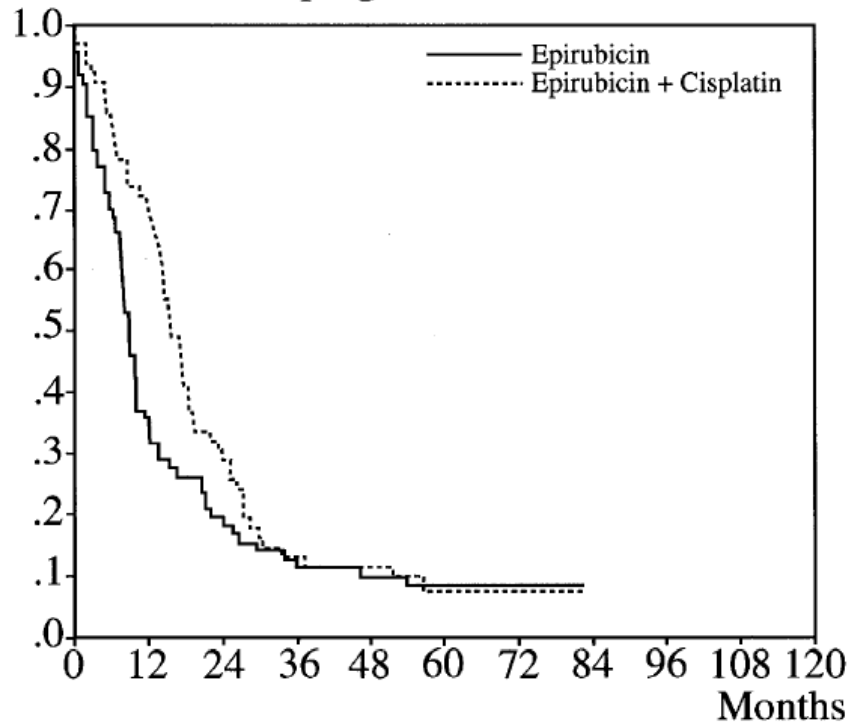


F. Coste, J. M. Malinge, L. Serre, W. Shepard, M. Roth, M. Leng and C. Zelwer, "Crystal structure of a double-stranded DNA containing a cisplatin interstrand cross-link at 1.63 Å resolution: hydration at the platinated site", *Nucleic Acids Res*, 1999, 27, 1837.

[http://images.google.com/imgres?imgurl=http://www.jonathanpmiller.com/intercalation/DNA\\_CISPLATIN.jpg&imgrefurl=http://www.jonathanpmiller.com/intercalation/&usq=\\_\\_uWCV\\_9owVHxyXYQ1EqG31VrXAp8=&h=500&w=500&sz=44&hl=en&start=2&tbnid=K8g56lBPaeT6iM:&tbnh=130&tbnw=130&prev=/images%3Fq%3DCisplatin%26gbv%3D2%26hl%3Den](http://images.google.com/imgres?imgurl=http://www.jonathanpmiller.com/intercalation/DNA_CISPLATIN.jpg&imgrefurl=http://www.jonathanpmiller.com/intercalation/&usq=__uWCV_9owVHxyXYQ1EqG31VrXAp8=&h=500&w=500&sz=44&hl=en&start=2&tbnid=K8g56lBPaeT6iM:&tbnh=130&tbnw=130&prev=/images%3Fq%3DCisplatin%26gbv%3D2%26hl%3Den)

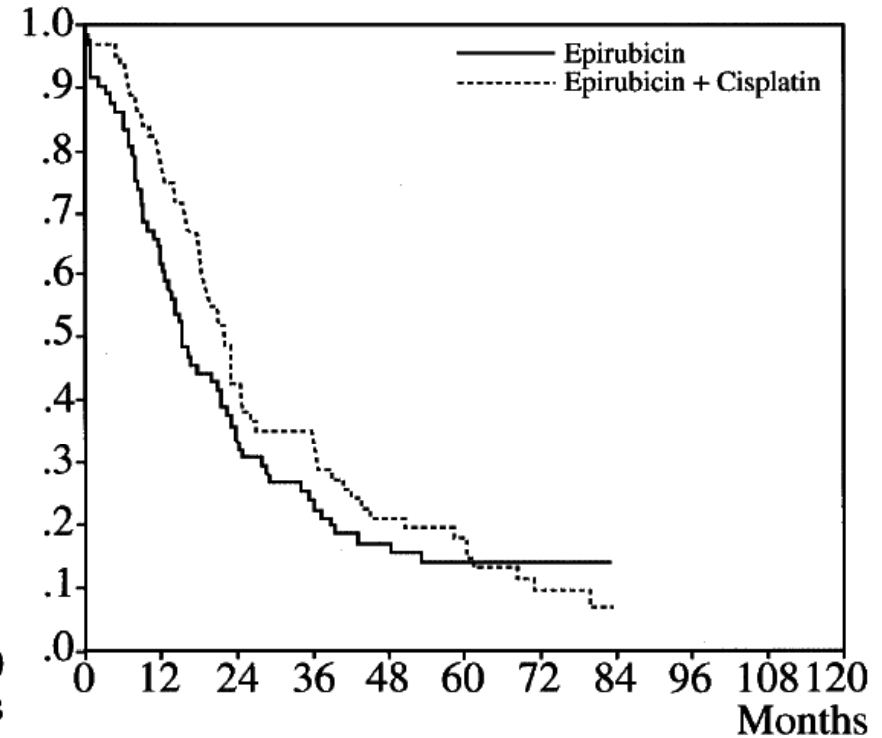
# Epi vs Epi/CDDP (n = 139)

Fraction without progression



p = 0.045

Fraction still alive



p = 0.41

# Platinum Agents for TNBC

Trial	Phase / No. of TNBC pts	Setting	Regimen	Outcome in TNBC
Sikov (2009)	II (n=12)	Neoadjuvant	Carbo-P vs carbo-P-H	pCR=67%
Torrise (2008)	II (n=30)	Neoadjuvant TNBC	E-Cis-F→P	pCR=40%; ORR=86%
Silver (2010)	II (n=28)	Neoadjuvant TNBC	Cis	pCR=22%
Leone (2009)	Retro (n=125)	Neoadjuvant TNBC	Platinum + D	pCR=34%
Uhm (2009)	II (n=36)	Metastatic	Carbo-P or Cis-P	ORR 37.5%

Carbo=carboplatin; Cis=cisplatin; D=docetaxel; E=epirubicin; F=5-FU; H=trastuzumab; P=paclitaxel; Retro=retrospective.

# Ixabepilone for TNBC

<b>Trial</b>	<b>Phase</b>	<b>Setting</b>	<b>Regimen</b>	<b>Outcome in TNBC</b>
<b>Pivot (2009)</b>	<b>III (n=187)</b>	<b>MBC resistant to anthra or taxane</b>	<b>Ixabepilone + cape vs cape alone</b>	<b>Improved ORR (27% vs 9%) and PFS (4.1 vs 2.1 mo)</b>
<b>Baselga (2009)</b>	<b>II (n=161)</b>	<b>Neoadjuvant</b>	<b>Ixabepilone</b>	<b>pCR=26%</b>

**Anthra=anthracycline; cape=capecitabine.**

# Bevacizumab for TNBC

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

## No survival data in TNBC

\*Median PFS vs non-TNBC subgroup.

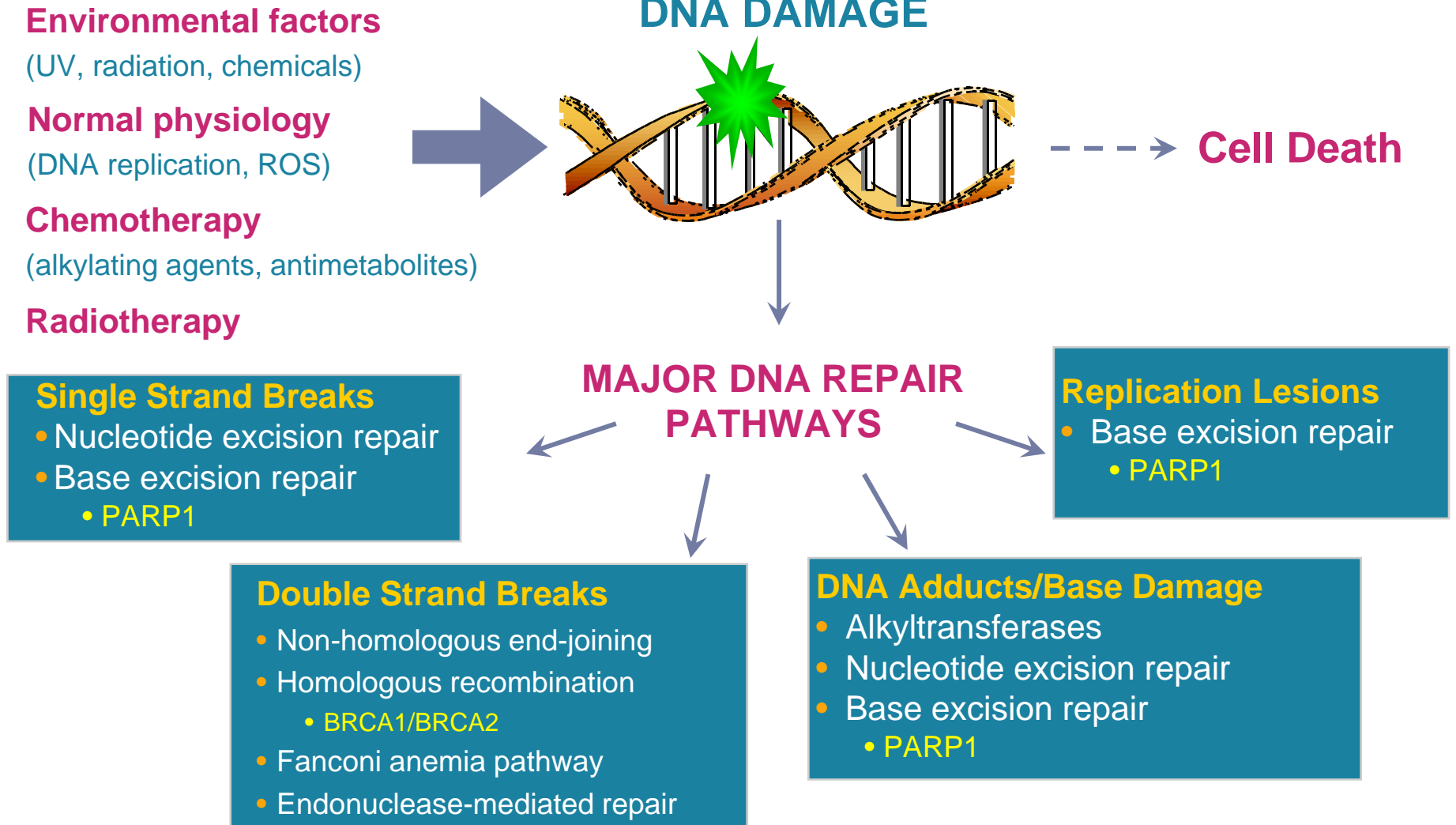
Thomssen, et al. SABCS 2009. Abstract 6093. O'Shaughnessy J, et al. SABCS 2009. Abstract 207.

# Other Targets for TNBC

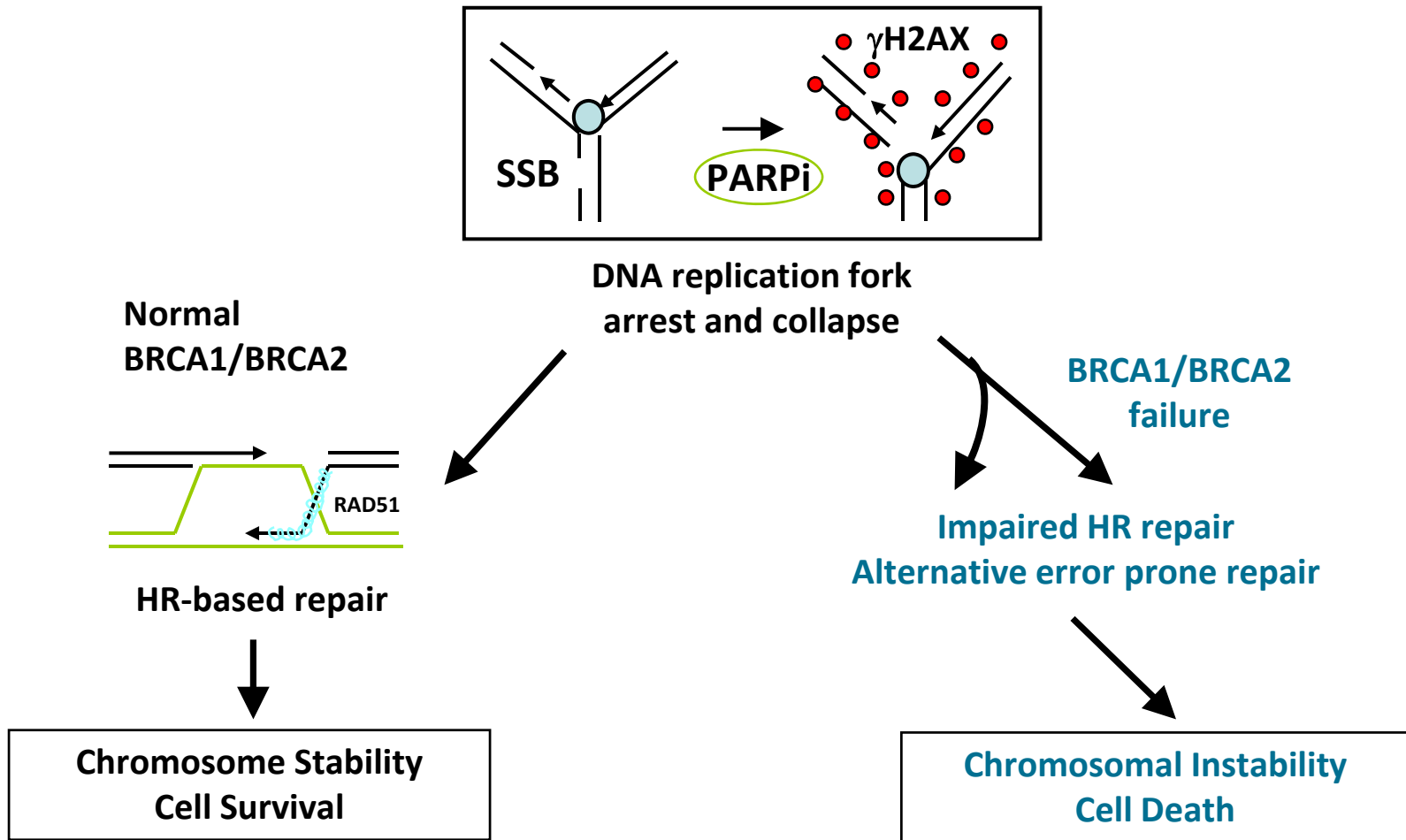
Target	Agent/Approach	Initial Outcomes
DNA repair pathways	PARP inhibitors (BSI-201, olaparib, AG014699, ABT-888), trabectedin	
VEGFR	Sunitinib	ORR=15% (Burstein 2008)
Angiogenesis	Endo TAG-1, metronomic chemotherapy	
Src kinase	Dasatinib	CBR=9.3% (Finn 2009)
Checkpoint kinase 1	UCN-01	
mTOR	RAD001, everolimus, temsirolimus	
Androgen receptor	Bicalutamide	
TRAIL	Lexatumumab	
TGF-beta	GC1008, AP 12009, LY2157299	
PDGFR, c-KIT	Imatinib	

Adapted from Tan and Swain. Cancer Journal. 2008;14.

# Mechanisms of DNA Repair

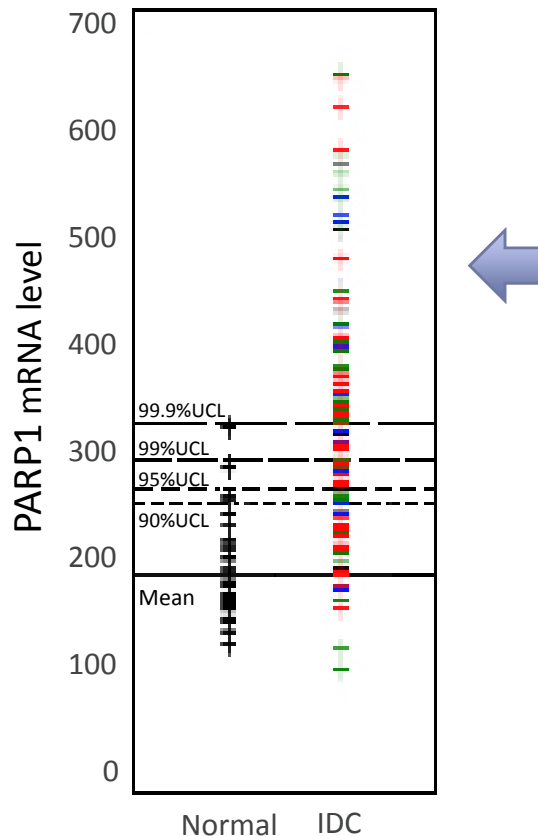


# PARP Inhibition in BRCA1 Deficient Cells



# PARP1 in Breast Cancer

- IDC shows statistically significant PARP1 upregulation in comparison with normal breast tissues
- PARP1 is upregulated in TNBC



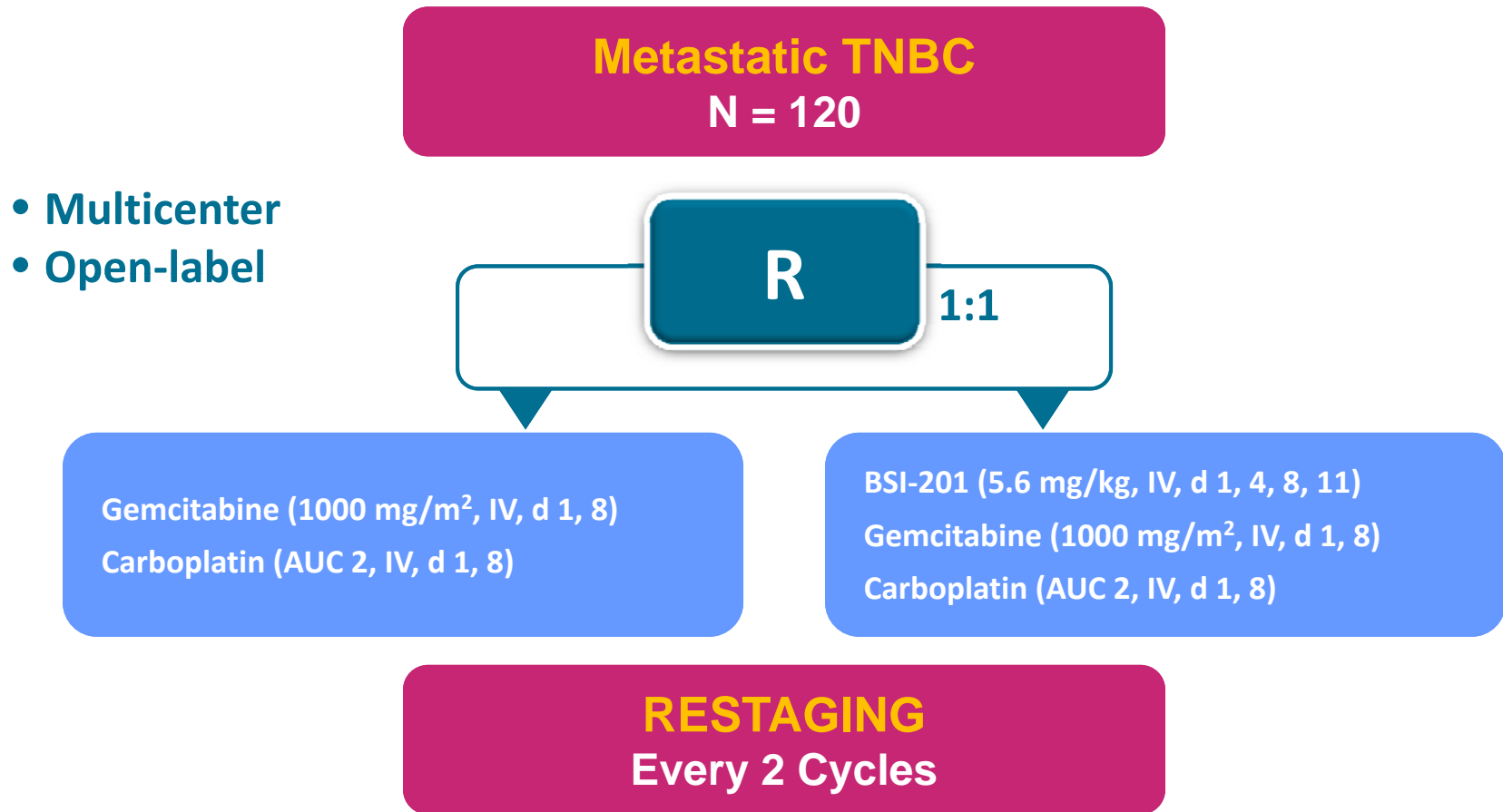
IDC Subtype	% PARP1 upregulation
Normal	2.9%
IDC	30.2%
ER+	22.9%
ER-	55.6%
PR+	23.1%
PR-	45.0%
HER2+	29.2%
HER2-	70.0%
ER+/PR+/HER2+	20.0%
ER-/PR-/HER2-	80.0%

\*defined by percentage of samples exceeding the 95% UCL of normal tissue distribution

# BSI-201

- **Small molecule**
- **Competitive inhibitor of NAD<sup>+</sup> enzyme binding**
- **Inhibits PARP1 and DNA Repair**
- **Administration: IV**
- **Potentiates activity of DNA damaging agents,  $\gamma$ -irradiation**
- **Penetrates blood-brain barrier**

# Phase II Trial of BSI-201 in TNBC: Study Design



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

O'Shaughnessy J, et al. ASCO 2009. Abstract 3; SABCS 2009. Abstract 3122.

## Phase II Trial of BSI-201: Preliminary Efficacy Results\* (Data through Mar.'09)

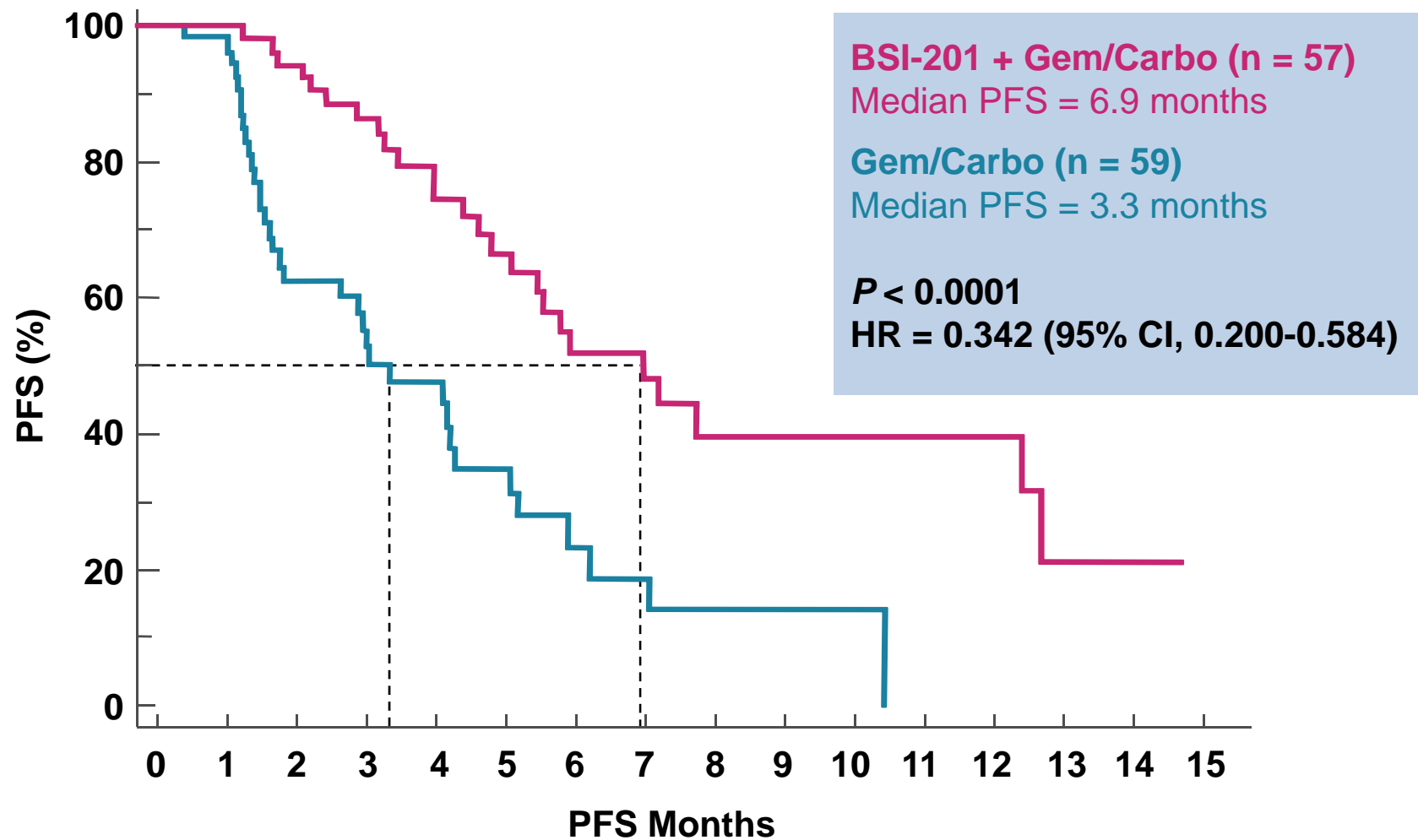
	Gem/Carbo (n = 44)	BSI-201 + Gem/Carbo (n = 42)	<i>P</i> -value
<b>Objective Response Rate n (%)</b>	<b>7 (16%)</b>	<b>20 (48%)</b>	<b>0.002</b>
<b>**Clinical Benefit Rate n (%)</b>	<b>9 (21%)</b>	<b>26 (62%)</b>	<b>0.0002</b>

\*Includes patients enrolled before September 30, 2008 and patients who had a confirmed response or disease progression

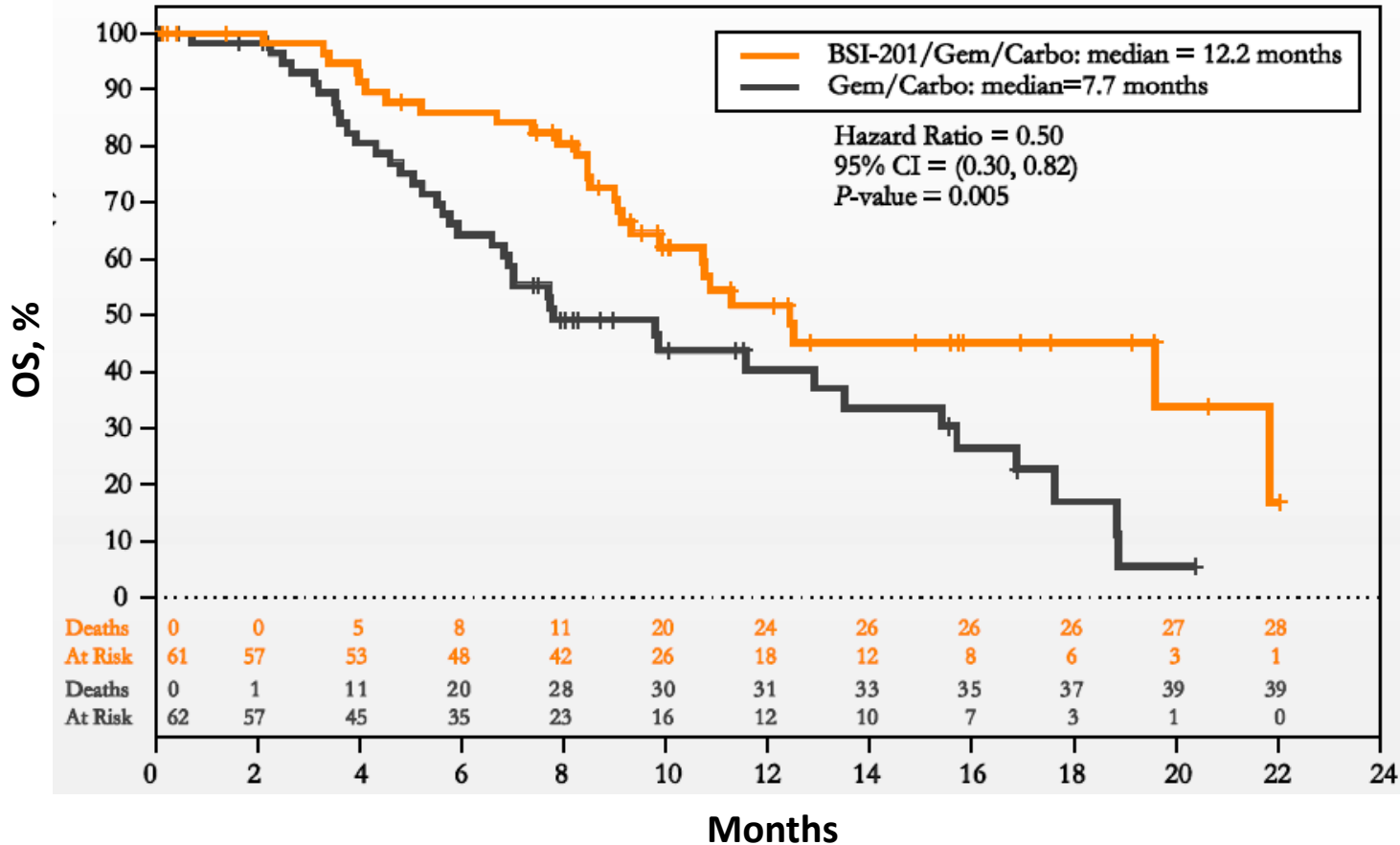
\*\*Clinical Benefit Rate = CR + PR + SD  $\geq$  6 months

O'Shaughnessy J, et al. ASCO 2009. Abstract 3; SABCS 2009. Abstract 3122.

# Phase II Trial of BSI-201: PFS (Data through Mar.'09)



# Phase II Trial of BSI-201: Overall Survival, ITT (Data through Nov.'09)



# Phase II Trial of BSI-201: Safety

Hematologic, n (%)	Gem/Carbo (n=59)			BSI-201 + Gem/Carbo (n=57)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
<b>Hematologic</b>						
Anemia	23 (39)	8 (14)	1 (2)	27 (47)	12 (21)	0
Thrombocytopenia	8 (14)	10 (17)	6 (10)	5 (9)	8 (14)	9 (16)
Neutropenia	7 (12)	19 (32)	14 (24)	5 (9)	21 (37)	12 (21)
Febrile neutropenia	0	3 (5)	1 (2)	0	0	0
RBC transfusion	8 (14)	7 (12)	5 (8)	5 (9)	6 (11)	3 (5)
G-CSF use	9 (15)	8 (14)	5 (8)	7 (12)	6 (11)	1 (2)
<b>Non-Hematologic</b>						
Nausea	13 (22)	2 (3)	0	10 (18)	0	0
Vomiting	9 (15)	0	0	4 (7)	1 (2)	0
Fatigue	12 (20)	13 (22)	1 (2)	11 (19)	4 (7)	0
Neuropathy	2 (3)	0	0	1 (2)	0	0
Diarrhea	6 (10)	2 (3)	0	2 (4)	2 (4)	0

# Phase III Trial of BSI in mTNBC: Study Design

## Patient Population:

- MBC
- ER-, PR-, and HER2-non-overexpressing (IHC 0,1 or FISH)
- 0-2 prior chemo for metastatic TNBC

## Stratification:

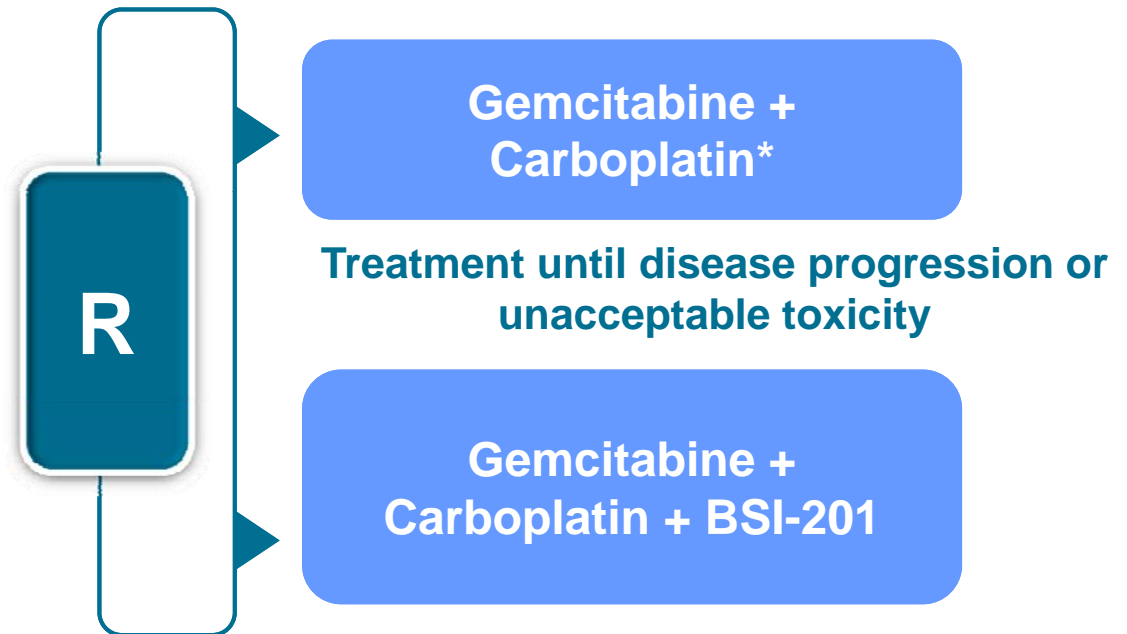
- No prior chemo vs 1-2 prior chemo for mTNBC

## Endpoints:

**Primary: OS, PFS**

**Secondary: ORR, safety**

N= 420



\*Upon progressive disease, allowed to crossover to receive gemcitabine-carboplatin + BSI-201

>100 sites in US; FPI July '09

# Adjuvant therapy for TNBC

What do the consensus statements or clinical practice guidelines say?

- **St. Gallen (brief mention)**
- **NCCN (not specific)**
- **ASCO (no)**
- **ESMO (no)**

# TNBC Ongoing Trials

Trial	Phase	No. Pts	Primary endpoint	Question
<b>Adjuvant</b>				
PACS08	III	2500	5y DFS	Does CT work? Sequential ixabepilone vs taxane post anthracycline
TITAN	III	1800	5y DFS	
BEATRICE	III	2530	Invasive DFS	Does biologic therapy work? (std chemo + bev)
<b>Metastatic</b>				
TNT	III	400	ORR	Does CT work? docetaxel vs carboplatin
<b>Neoadjuvant</b>				
CALGB 40603	II	362	pCR	Does biologic therapy work? Paclitaxel +/- carbo and/or bev→AC
MD Anderson	II	96	Molecular changes	Does biologic therapy work? Pacli + everolimus→FEC

# TNBC: Summary

- **TNBC is a distinct subtype of BC**
  - ER, PgR, HER2-negative by IHC
  - Surrogate of basal-like BC
  - Sub-subtypes likely
  - More aggressive
- **Evolving treatment strategies**
  - Antracycline and taxane work (but not very well...)
  - Platinum-based chemotherapy emerging as backbone of new treatments
  - Molecular pathways that control tumor development could determine treatment
  - Novel agents like PARPi showing promise