TRIPLE NEGATIVE BREAST CANCER

Finding the Positives in Triple-Negative Breast Cancer: A Three-Part Live CME Webcast Series

Seminar II: Thursday, March 11, 2010, 8:00 PM - 9:00 PM EST

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Disclosures for Moderator Neil Love, MD

Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Abraxis BioScience, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Centocor Ortho Biotech Services LLC, Cephalon Inc, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, Genzyme Corporation, GlaxoSmithKline, ImClone Systems Incorporated, Lilly USA LLC, Millennium Pharmaceuticals Inc, Monogram BioSciences Inc, Novartis Pharmaceuticals Corporation, OSI Oncology, Roche Laboratories Inc, Sanofi-Aventis and Spectrum Pharmaceuticals Inc.

Agenda

Case Presentation from Dr Chang

Module 3 – Dr Chang

- Major mechanisms of DNA repair: Recombinational repair, nucleotide excision repair, base excision repair, mismatch repair, direct reversal
- Mechanism of action of PARP inhibitors
- BRCA mutations and DNA repair
- “Synthetic lethality”

Panel Discussion

Response to Audience Questions/Cases

Agenda

Case Presentation from Dr O'Shaughnessy

Module 4 – Dr O'Shaughnessy

- PARP inhibitors:
  - Method of administration
  - Tolerability alone and with chemotherapy
- Clinical trials of PARP inhibitors in TNBC
- Updated results of the Phase II randomized trial of carboplatin/gemcitabine alone or with BSI-201

Panel Discussion

Response to Audience Questions/Cases

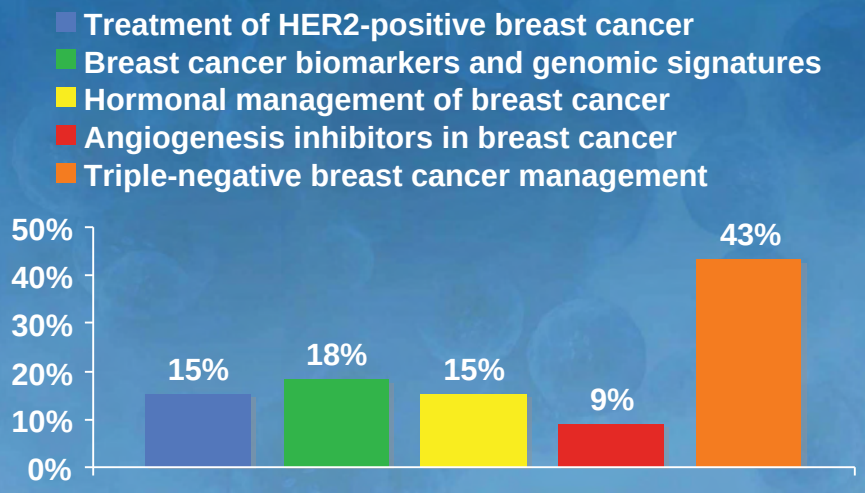
Submit a Challenging Case or Question

- Use the text box at the bottom-left of the screen to type in a case or question. You may also submit a case or question by phone at (866) 447-3623.
- You may include your full name, city and state of practice or you may choose to remain anonymous.
- Select entries will be discussed and reviewed by our esteemed faculty during the hour-long segment.

Seminar Overview

- This is the second of three unique online, integrated educational courses. The next seminar will take place on March 16, from 8:00 PM — 9:00 PM EST.
- An archive of these webcasts will also be available on **www.ResearchToPractice.com** within three days of the broadcast.
- Please remember to complete your CME evaluation. A link will be provided at the conclusion of each seminar.

Which topic tonight is of greatest interest to you?



SABCS 09 Live CME meeting audience poll

CASE PRESENTATION
Dr Chang

42-year-old woman

10-2002

- Left lumpectomy, ALND
- 1.8-cm, node-neg TNBC
- Adjuvant RT, no chemo

10-2008

- Right inflammatory TNBC (9 by 9 cm)
- BRCA 1 germline mutation-positive
- Disease progression (12 by 12 cm) after 2 cycles docetaxel
- AC resulted in clinical CR
- MRM: path CR

42-year-old woman developed primary breast cancer in right breast. Diagnosed as triple-negative invasive ductal carcinoma, treated with mastectomy and dose-dense AC/paclitaxel. After 2 years, she developed left breast invasive ductal carcinoma similar in histology to the first breast cancer: triple negative and same histology. S/P mastectomy, what chemo I should use? She is a healthy lady.

– Dr Rifat Elkhatib

TRIPLE NEGATIVE BREAST CANCER

Current Management of Triple Negative Breast Cancer

Jenny C Chang, MD
Dan L Duncan Professor
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Disclosures for Jenny C Chang, MD

Research Support/PI	N/A
Employee	N/A
Consultant	Boehringer Ingelheim Pharmaceuticals Inc
Major Stockholder	N/A
Speakers' Bureau	GlaxoSmithKline
Scientific Advisory Board	N/A

N/A = Not Applicable

Background

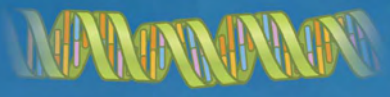
- Germline BRCA1 mutations account for 20% of breast cancers that appear to be inherited, which is only <2% of all breast cancers.
- Tumors from BRCA1 carriers have somatic inactivation of their second wild-type allele

BRCA1 Function

- Sensor for DNA damage
- **Double-strand DNA break repair**
  - RAD51 and Fanconi's anemia protein
- Cell cycle checkpoint control
- Apoptosis in response to DNA damage
- Transcription factor involved in hormone receptor regulated gene expression

Brody LC. *N Engl J Med* 2005;353(9):949-50.

BRAC1 and BRCA2 Maintain Specialized DNA Repair

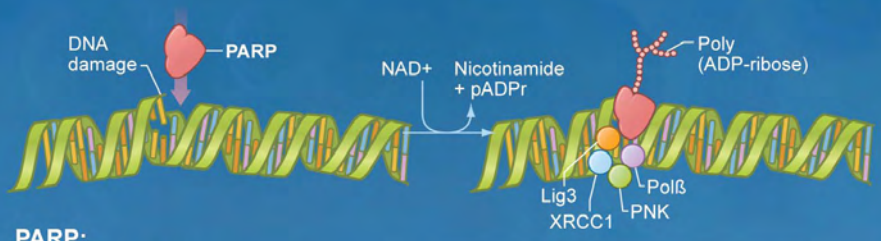


Cancer cells in BRCA1 or BRCA2 carrier	Healthy cells in BRCA1 or BRCA2 carrier
BRCA1/BRCA2 gene is lost	A normal BRCA gene remains
Specialized DNA repair is lost	Specialized DNA repair continues

Types of DNA Damage and Repair

Type of damage	Single-strand breaks (SSBs)	Double-strand breaks (DSBs)	Bulky adducts	Insertions deletions	06-alkylguanine
Repair pathway	Base excision repair	Recombinational repair	Nucleotide excision repair	Mismatch repair	Direct reversal
Repair enzymes	PARP	HR → ATM; NHEJ → DNA-PK	XP, polymerases	MSH2 MLH1	AGT

Poly (ADP-ribose) Polymerase (PARP)

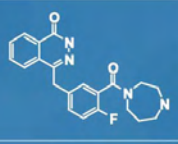


PARP:

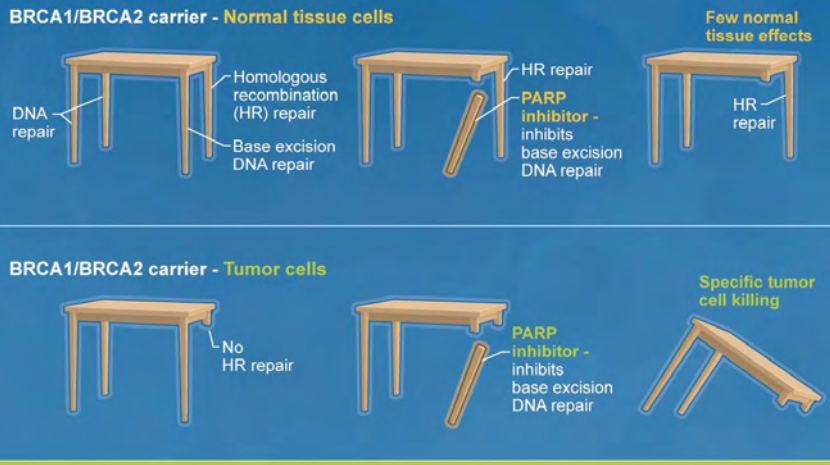
- Involved in DNA base-excision repair
- Binds directly to DNA damage
- Produces large branched chains of poly(ADP-ribose)

PARP Inhibitors

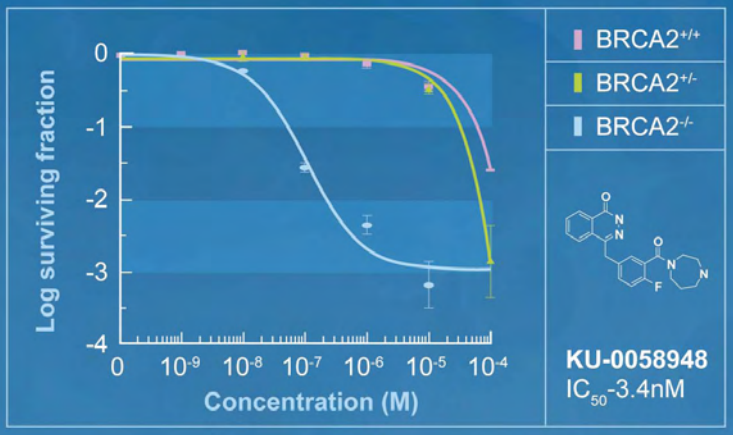
KU-0058948
IC_{50}-3.4nM



Targeting a Weakness in Tumor DNA Repair

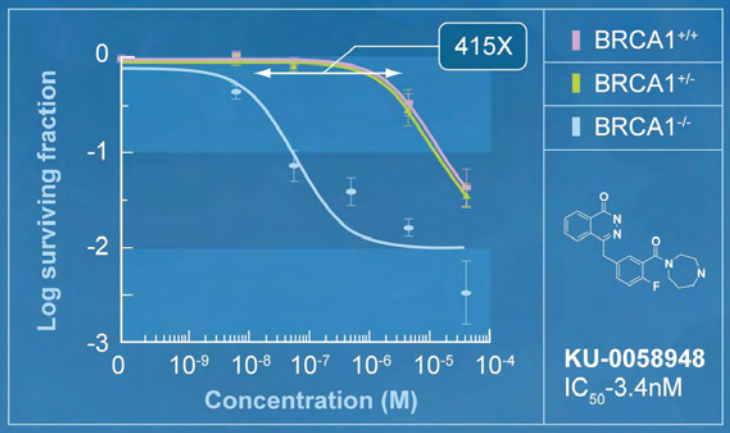


Extreme Sensitivity of BRCA2-Deficient Cells to PARP Inhibition



Farmer H et al. *Nature* 2005;434(7035):917-21.

BRCA1-Deficient Cells are also Extremely Sensitive to PARP Inhibition



Farmer H et al. *Nature* 2005;434(7035):917-21.

Olaparib, PARP1 Inhibitor

- 54 patients with BRCA1/2 advanced breast cancer
- Refractory to chemotherapy
- 26 patients with evaluable disease
  - ORR: 11/26 42%
  - 1 complete response

Tutt A et al. ASCO 2009;Abstract CRA501.

Key Observations from Phase I Trial of AZD2281

- Well tolerated and not associated with the typical toxicities of chemotherapy
- Clear evidence of beneficial tumor response in BRCA mutated ovarian cancer patients
  - 53% response rate (RECIST or GCIG CA125)
  - 7% meaningful disease stabilization
  - Total clinical benefit rate of 60%

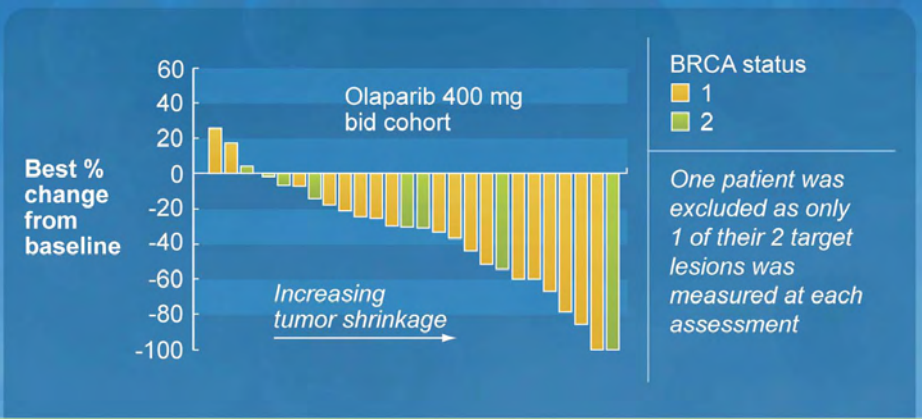
Fong PC et al. *N Engl J Med* 2009;361(2):123-34.

Key Observations from Phase I Trial of AZD2281 (continued)

- **Responses also in breast (including male) and prostate cancer**
- Ongoing randomized phase II trial in BRCA ovarian cancer pts with platinum-free interval of 0-12 months
  - AZD2281 vs pegylated liposomal doxorubicin

Fong PC et al. *N Engl J Med* 2009;361(2):123-34.

Best Percentage Change From Baseline in Target Lesions by Genotype - Breast Cancer

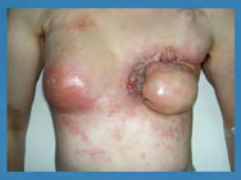


Tutt A et al. ASCO 2009;Abstract CRA501.

Response in a Heavily Pretreated Breast Cancer Patient

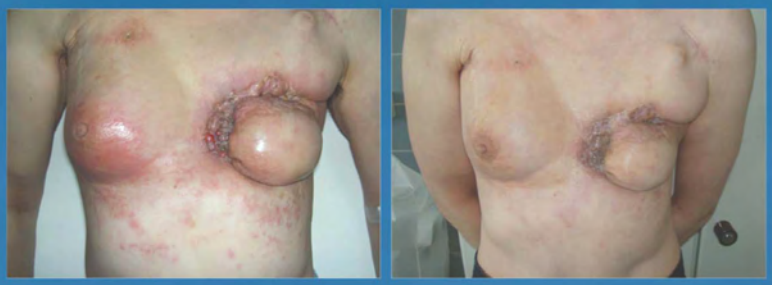
46 year old patient,
BRCA1 mutation carrier (c4154delA)

1. BC right. 1991 (29y): pT1, pN0, M0, Histopathol.: Invasive ductal, HR neg.
2. BCT +radiation right
3. BC left. 1993 (31 y): pT1, pN0, M0, Histopathol.:Invasive ductal, HR neg., Her2neg.
4. BCT + radiation left.
5. Local recurrence left, 1994: HR pos.
6. Hormone-therapy
7. Lung metastasis 1995 (33 y)
8. Lung surgery (R0)
9. Chemotherapy 1995
10. PBSO 2006 (44 y)
11. Inflammatory recurrence le. 2006
12. Before surgery. FEC>Doc, Ablatio le. + TRAM
13. Cutan. metastasis chest both sides, 2007
14. Chemotherapy Progressive disease



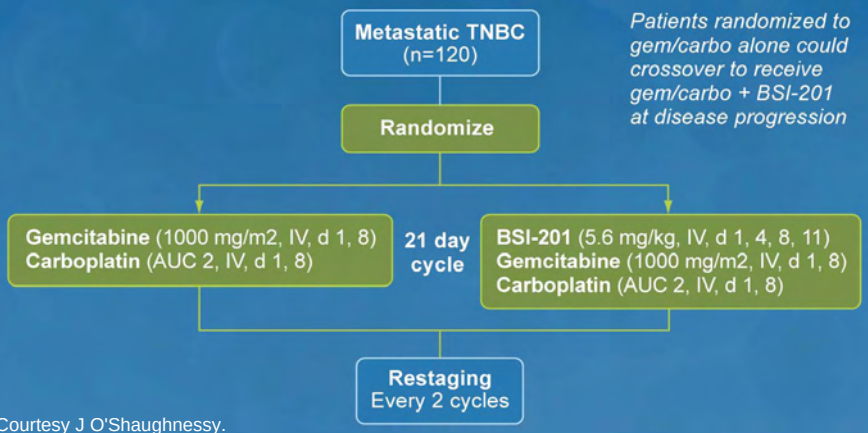
Clinical Response to PARP Inhibitor: Olaparib (AZD2281)

9 Weeks PARPi (associated with only minimal toxicity)



Courtesy of Monika Graesser and Rita Schmutzler, Cologne

Phase II TNBC Study of PARPi BSI-201



Courtesy J O'Shaughnessy.

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

Preliminary Efficacy Results*

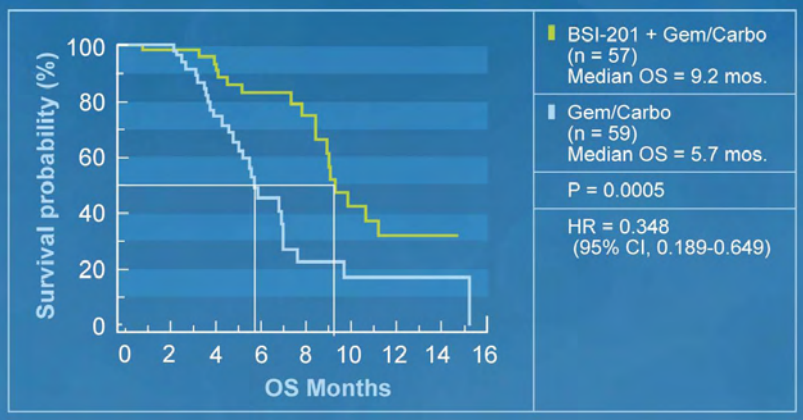
	Gem/Carbo (n = 44)	BSI-201 + Gem/Carbo (n = 42)	P-value
Objective Response Rate n (%)	7 (16%)	20 (48%)	0.002
****Clinical Benefit Rate n (%)**	9 (21%)	26 (62%)	0.0002

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

** *Clinical Benefit Rate = CR + PR + SD ≥ 6 months*

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

Overall Survival



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

PARPi – Who Has What

- KuDOS/AZ - Olaparib Ph1 single agent
  Ph2 single agent
  Various combos
- BiPAR.Sanofi-Aventis BSI-201
  - Ph2 with Gem-platinum
- Pfizer (iv) Ph2 ??? Development strategy
- Abbott (selectivity?)
- Merck - Ph1
- Inotek - Genentech
- Cephalon - cancer strategy?

Objectives

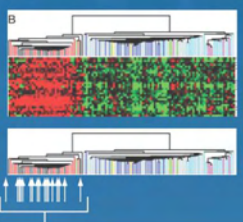
- To identify a molecular signature that differentiates between two subsets of sporadic triple negative breast cancer
  - Defective DNA repair: Sensitivity to DNA damaging agents, such as anthracyclines, platinums, or PARP inhibitors.
  - Effective DNA repair: Sensitive to taxanes but not to DNA damaging agents

Classic BRCA1 Phenotype

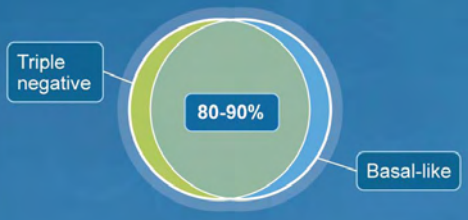
- Negative hormonal receptor status
- Negative HER-2/neu status
- Histological grade 3
- High proliferation rate
- Pushing margins
- Lymphocytic infiltrate
- CK5/6+ and/or EGFR+, p53+

Phillips KA. *J Clin Oncol* 2000;18(21S):107s-12s;
Foulkes WD et al. *J Natl Cancer Inst* 2003;95(19):1482-5.

BRCA1 Genotype



80% of BRCA1 mutation-associated cancers sort with the "basal-like" group of ER(-) breast cancers



Sorlie T et al. *Proc Natl Acad Sci* 2003;100(14):8418-23.

Outstanding Issues

- Can we identify sporadic triple negative breast cancers with BRCA1 deficiency?
- If so, should we stratify patients with BRCA1 deficiency in therapeutic trials?

Biochimica et Biophysica Acta 1796 (2009) 266–280

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journal homepage: www.elsevier.com/locate/bbacan

Review

Therapeutic options for triple-negative breast cancers with defective homologous recombination

Janneke E. Jaspers, Sven Rottenberg *, Jos Jonkers *

Division of Molecular Biology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

"Van't Veer et al. used gene expression profiling for classification of ER-negative sporadic and BRCA1-related tumors [238]. Because one sporadic tumor that was classified as BRCA1-related showed strong BRCA1 promoter methylation (presumably resulting in BRCA1 silencing), ***one could speculate that this signature might also be predictive for BRCA1-like sporadic tumors.***

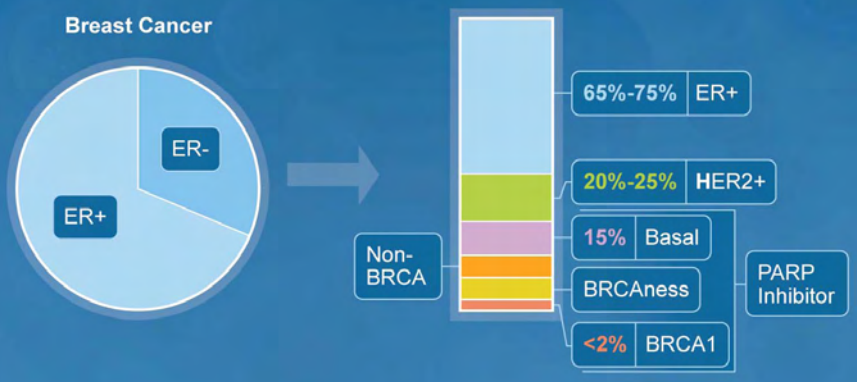
In principle it might also be possible to identify HR deficiency by ***quantitative expression profiling*** *and mutational analysis* ***of genes known to be involve in DNA repair****."*

Sporadic Triple Negative Tumors May Have BRCAness

- BRCA1 familial cancers show:
  1. Phenotypic similarities to sporadic triple negative breast cancers
  2. Gene expression similarities to sporadic triple negative breast cancers
- These two observations suggest there may be an underlying defect in BRCA1-related pathways in a subset of sporadic triple negative breast cancers.

Foulkes et al. 2003; Sorlie et al. 2003; Lakhani et al. 2005.

Redirecting Therapies In Triple Negative Breast Cancer

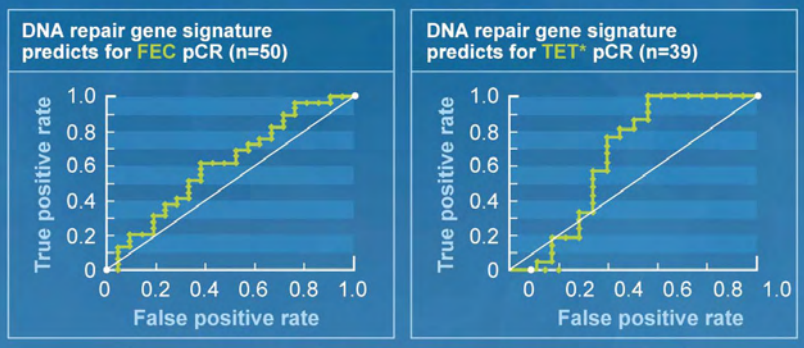


BRCA1 Tumors Are More Sensitive To Anthracyclines Than Sporadic Triple Negatives

	BRCA1 mutated FEC regimen	Controls FEC Regimen
N	19	73
Median Age (years)	37 (25-48)	49 (29-66)
Median T (mm)	55 (32-90)	50 (30-120)
% ER-	84%	100%
% grade 3	83%	86%
Median NBR cycles	4 (3-6)	4 (3-6)
PCR rate	47%	22% (p=0.03)
pN+	16%	40%

Delaloge S et al. ASCO 2008;Abstract 574.

Receiver Operating Characteristics (ROC) Curve

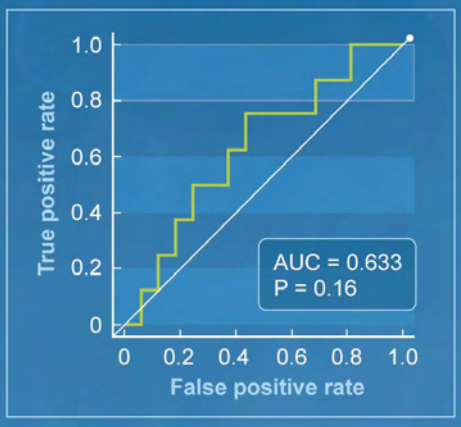


	pCR FEC (%)	pCR TET* (%)
BRCA1-like	13/24 (54.2)	7/23 (30.4)
NonBRCA1-like	8/26 (30.8)	11/18 (68.8)

* Taxane-based chemotherapy

Rodriguez A et al. San Antonio Breast Cancer Symposium 2009;Abstract 110.

ROC Curve For DNA Repair Gene Structure and Cisplatin Sensitivity (n = 24, MP 0,1,2,3 vs 4,5)



Summary

- PARPi exploit defective DNA repair mechanism present in BRCA mutated cancers
- A subset of sporadic TN cancers may share similar defective DNA repair mechanism
- We have identified and validated a set of genes by microarray analysis and RTQPCR that can identify sporadic triple negative breast cancer with “BRCAness”
- May be useful to predict which patients will respond to anthracyclines, PARP inhibitors, or other DNA-damaging drugs.

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TRIPLE NEGATIVE BREAST CANCER

Finding the Positives in Triple-Negative Breast Cancer: A Three-Part Live CME Webcast Series

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Loss of PTEN may sensitize breast cancer cells to the lethality of PARP inhibitors, so has there been any interest in looking at the combination of PARP inhibitors with mTOR inhibiting agents or other agents that target that pathway?

– Dr Karen Tedesco

Should one obtain BRCA 1 & 2 on all triple negatives regardless of age and lack of family history?

– Dr Raji McKenna

CASE PRESENTATION
Dr O'Shaughnessy

57-year-old woman

- TNBC with 6+ nodes
- LMRM
- TAC adjuvant chemo
- Postmastectomy RT

One year later

- Painful supraclavicular and cervical lymphadenopathy
- Mediastinal adenopathy
- Node biopsy: Recurrent TNBC

CASE PRESENTATION: FOLLOW-UP
Dr O'Shaughnessy

Enrolled phase II trial: gem/carbon + BSI 201

- Stable for 15 months
- Thrombocytopenia: dose reduction gem/carbo

Disease progression

- Vinorelbine/bevacizumab
- Rapid PR after cycle 1
- Progression at 6 months: pleural effusions CNS mets

TRIPLE NEGATIVE BREAST CANCER

PARP Inhibitors in Breast Cancer

Joyce O'Shaughnessy, MD
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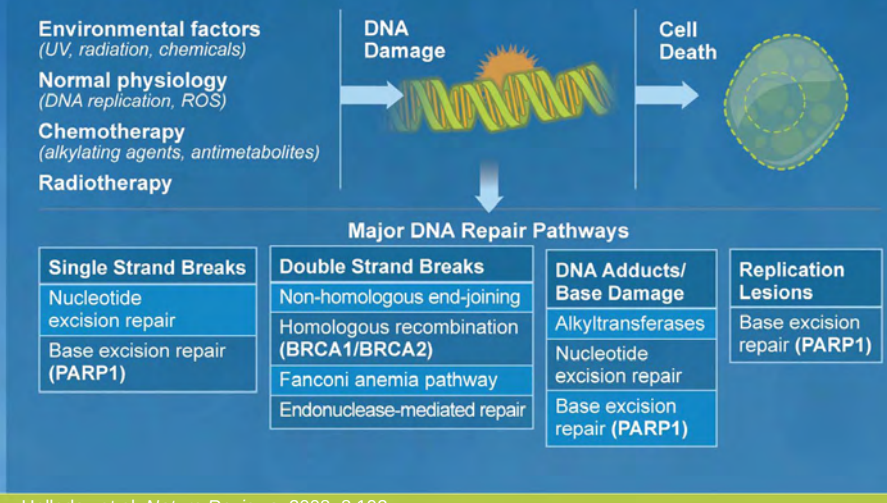
Baylor-Charles A Sammons Cancer Center
Texas Oncology, PA
US Oncology
Dallas, Texas

Disclosures for Joyce O'Shaughnessy, MD

Research Support/PI	N/A
Employee	N/A
Consultant	N/A
Major Stockholder	N/A
Advisory Committee	Genentech BioOncology
Speakers' Bureau	Abraxis BioScience, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Genentech BioOncology, Lilly USA LLC, Sanofi-Aventis

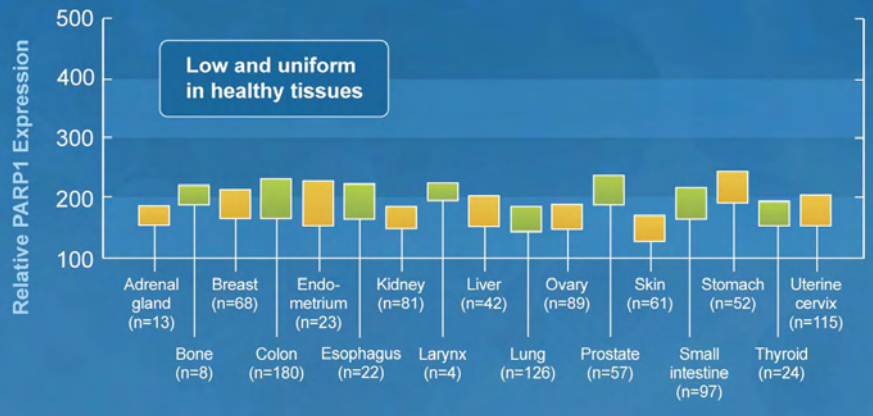
N/A = Not Applicable

Mechanisms of DNA Repair



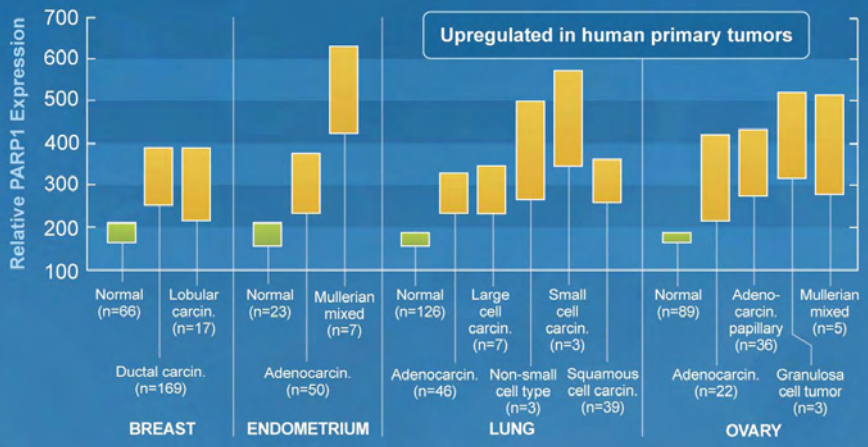
Helleday et al. *Nature Reviews*. 2008; 8:193
BiPar Sciences, unpublished data.

PARP1 Expression



BiPar Sciences, unpublished data.

PARP1 Expression



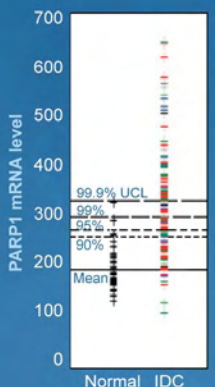
BiPar Sciences, unpublished data.

PARP1 in Breast Cancer

Infiltrating ductal carcinoma (IDC) is a highly invasive tumor, accounting for 70-80% of all breast malignancies

IDC shows statistically significant PARP1 upregulation in comparison with normal breast tissues: p = 2x10-27

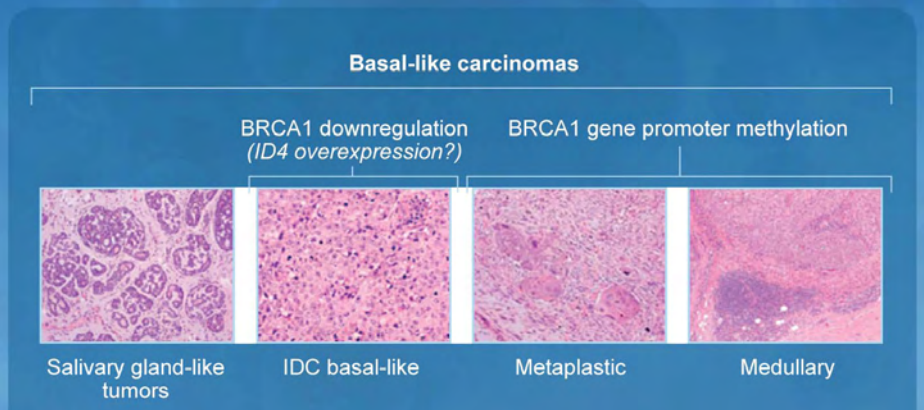
PARP1 is upregulated in TNBC



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%**

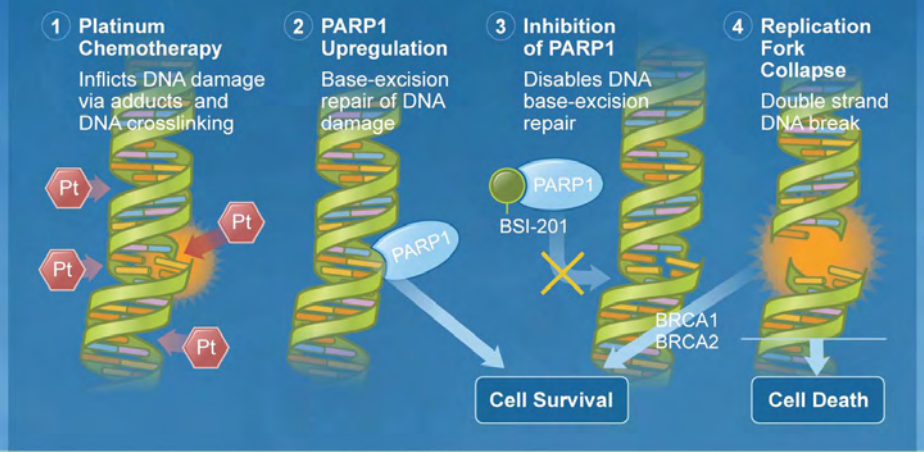
Defined by percentage of samples exceeding the 95% UCL of normal tissue distribution

Basal-Like Breast Cancer and BRCA1



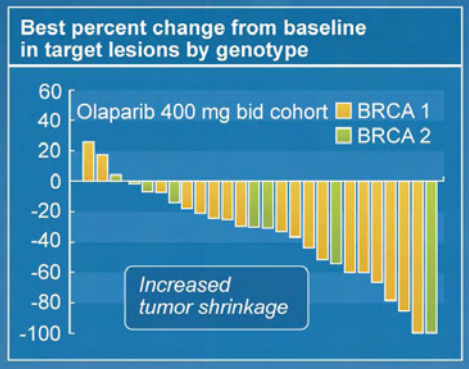
Rakha, EA et al. *J Clin Oncol* 26:2568-2581

PARP Inhibitor Mechanism of Action



Oral PARP Inhibitor Olaparib in BRCA-deficient Metastatic Breast Cancer Patients

ITT cohort	400 mg BID (n = 27)	100 mg BID (n = 27)
ORR	11 (41%)	6 (22%)
CR	1 (4%)	0
PR	10 (37%)	6 (22%)
Median PFS	5.7 mo (4.6-7.4)	3.8 mo (1.9 – 5.5)



Tutt A et al. *J Clin Oncol* 2009;27(18S):803s (abstr CRA501)

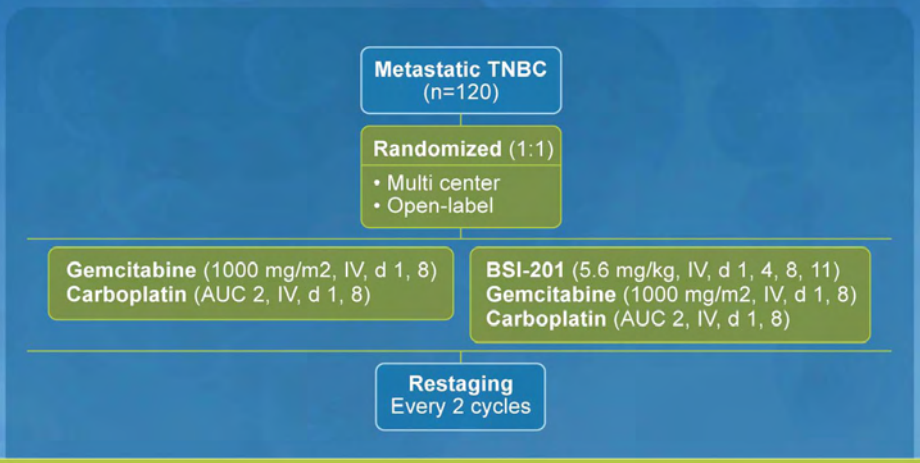
BSI-201

- Small molecule
- Competitive inhibitor of NAD+ enzyme binding
- Inhibits PARP1 and DNA Repair
- Administration: IV
- Potentiates activity of DNA damaging agents, γ-irradiation
- Penetrates blood-brain barrier

BSI-201 for TNBC: Rationale

- PARP1 is upregulated in majority of triple-negative human breast cancers
- TNBC known to have defects in homologous DNA repair
- BSI-201 potentiates effects of chemotherapy-induced DNA damage
  - Marked and prolonged PARP inhibition in PMBCs
- No dose-limiting toxicities in phase I/Ib studies of BSI-201 alone or in combination with chemotherapy

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



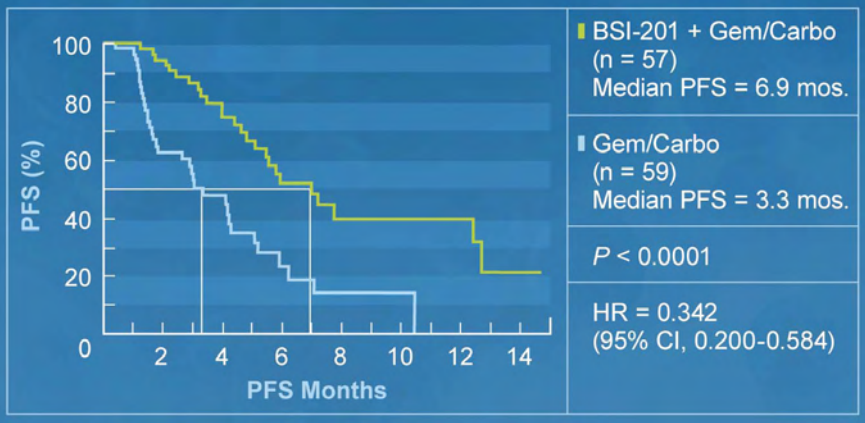
Phase II Trial of BSI-201: Preliminary* Efficacy Results (Data Through March 2009)

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

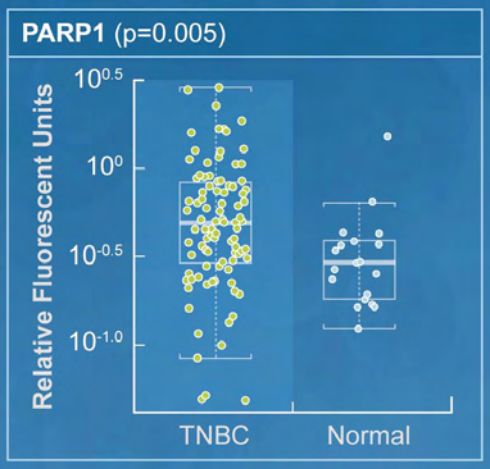
* *Includes patients enrolled before September 30, 2008 and patients who had a confirmed response or disease progression*

** *Clinical Benefit Rate = CR + PR + SD ≥ 6 months*

Phase II Trial of BSI-201: PFS
(Data Through March 2009)

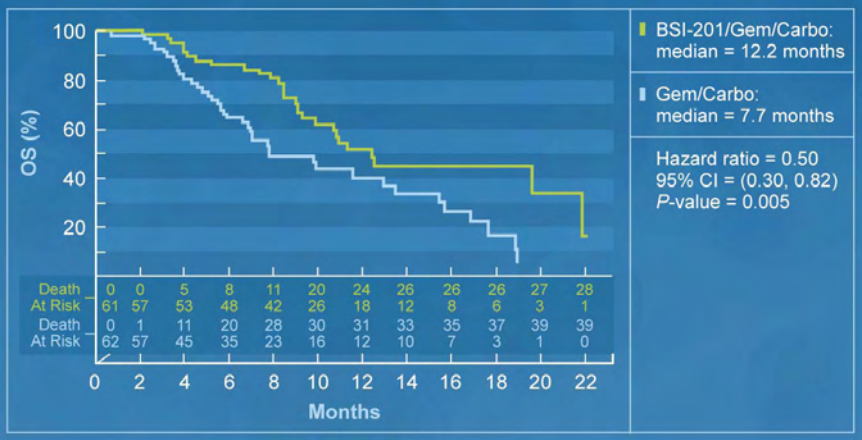


Phase II Trial of BSI-201: Upregulation of PARP



O'Shaughnessy J et al. SABCS *2009*;Abstract 3122.

Phase II Trial of BSI-201: Overall Survival, ITT
(Data Through November 2009)



O'Shaughnessy J et al. SABCS *2009*;Abstract 3122.

Phase II Trial of BSI-201: Safety

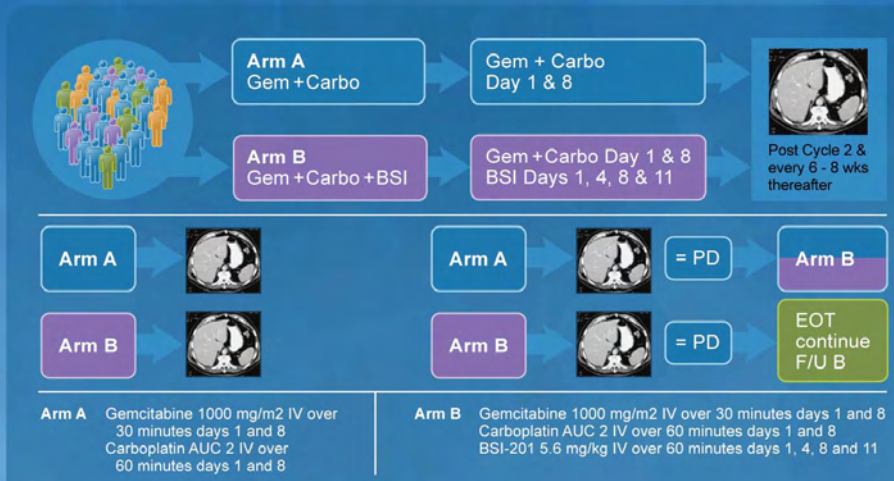
Hematologic, n (%)	Gem/Carbo (n=59)			BSI-201 + Gem/Carbo (n=57)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Hematologic						
Anemia	23 (39)	8 (14)	1 (2)	27 (47)	12 (21)	0
Thrombocytopenia	8 (14)	10 (17)	6 (10)	5 (9)	8 (14)	9 (16)
Neutropenia	7 (12)	19 (32)	14 (24)	5 (9)	21 (37)	12 (21)
Febrile 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)
Non-Hematologic						
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

O'Shaughnessy J et al. SABCS *2009*;Abstract 3122.

Conclusions

- BSI-201 improved patients' clinical outcomes
  - Data through March 2009:
    - Clinical Benefit Rate (62% vs 21%; *P* = 0.0002)
    - ORR (48% vs 16%; P = 0.002)
    - Median PFS (6.9 months vs 3.3 months; *P* < 0.0001)
  - Data through November 2009:
    - Median OS (12.2 months vs 7.7 months; *P* = 0.005)
- BSI-201 + gemcitabine/carboplatin was well tolerated and did not potentiate chemotherapy-related toxicities
- **Phase III study initiated July '09 based on promising Phase II safety and efficacy data**

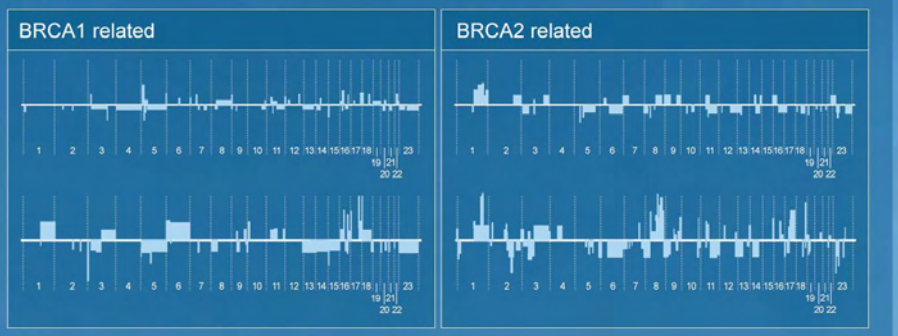
Phase III Trial of BSI-201 in MBC: Study Design



BSI-201: Key Questions in Breast Cancer

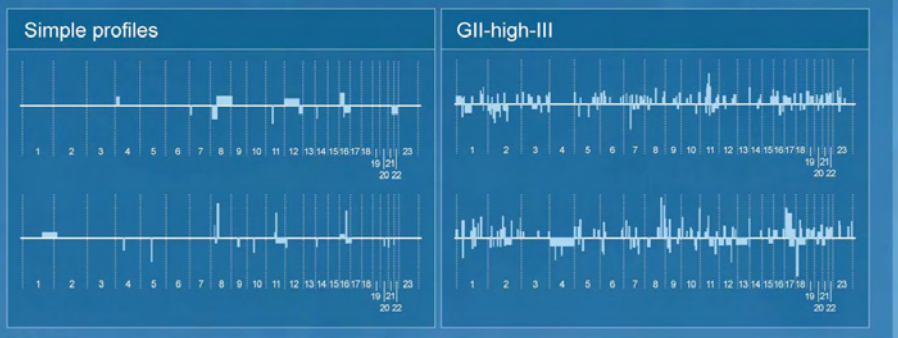
- What is the optimal delivery schedule?
- Can BSI-201 potentiate the activity of other DNA damaging agents?
- Does BSI-201 potentiate the activity of non-DNA damaging chemotherapy and/or radiation therapy?
- Is BSI-201 active in breast cancer subtypes beyond TNBC?

Target of PARP Inhibition?



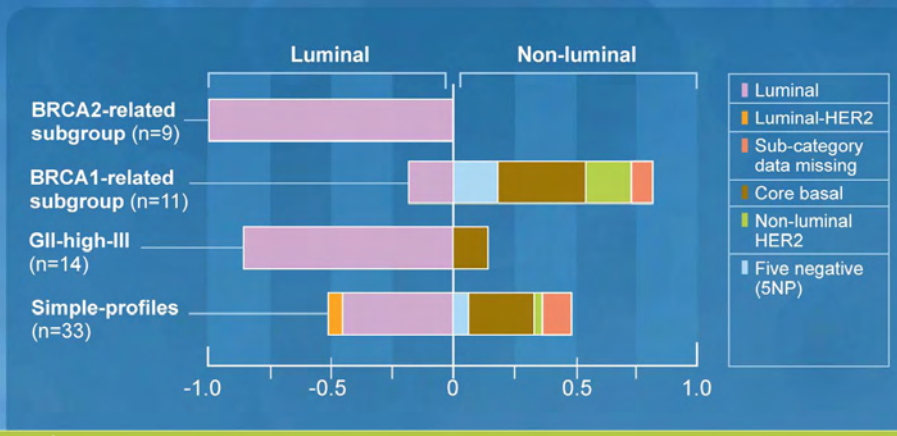
Stefansson OA. *Breast Cancer Res* 2009;11:R47.

Target of PARP Inhibition?



Stefansson OA. *Breast Cancer Res* 2009;11:R47.

Breast Cancer Genomic Instability: Target of PARP Inhibition?



Stefansson OA. *Breast Cancer Res* 2009;11:R47.

TNBC | TRIPLE NEGATIVE BREAST CANCER

Finding the Positives in Triple-Negative Breast Cancer: A Three-Part Live CME Webcast Series

Seminar II: Thursday, March 11, 2010, 8:00 PM - 9:00 PM EST

- Why is it that when BRCA1+ women have breast cancer, it is overwhelmingly TNBC?
- Are we any closer to a 'compassionate use' PARP inhibitor trial?

– Steve
Los Angeles, CA

- How infrequent are late recurrences in triple-negative breast cancer?
- Are there other promising PARP inhibitors besides BSI-201? Are any being studied as single agents without chemotherapy?
- Is there a difference between BRCA1 triple-negative breast cancer and those that are BRCA negative?

– Dr Bill Harwin

- Are there any data on the incorporation of platinum agents into the adjuvant setting in triple-negative disease?
- Despite the utility of gemcitabine in the metastatic setting, it has not been incorporated into traditional adjuvant regimens.

– Dr Raji McKenna

TNBC | TRIPLE NEGATIVE BREAST CANCER

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