

Recurrent Breast Cancer v. New Primary

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Case #2

- 49 year old, peri-menopausal woman presents with a self-detected left breast mass. History is notable for an earlier diagnosis of left breast cancer 5 years earlier at which time a 2 cm, SLN – negative tumor was removed with lumpectomy. The tumor was ER-/PR-/HER2-. She received 4 cycles of AC and RT. The patient has been compliant with follow-up and mammograms.

Case #2 (continued)

- Evaluation of the current breast mass revealed a ~1 cm indurated area at the distal end and deep to the previous lumpectomy scar as well as a suspicious pea-sized left axillary node. A mammogram and MRI of the left breast showed a ~1.1 cm mass without any other suspicious areas. Bx revealed IDC with characteristics similar to prior cancer.

Management of Recurrent Breast Cancer After Initial Lumpectomy, Sentinel Node Biopsy, and Whole Breast Radiation Therapy

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Recurrence after Lumpectomy

- New primary versus recurrence often determined through biopsy of new lesion- info on tumor characteristics can be important for adjuvant systemic therapy options
- Majority (~97%) of in-breast recurrences occur within region of previous lumpectomy site

Kuerer et al. Ann Surg 2004

- After 20 years, B-06 local recurrence rate of 14.3% for patients who underwent lumpectomy with radiation versus 39.2% lumpectomy alone
- Timing of recurrence: lumpectomy alone- 73% in the first 5 years versus lumpectomy with radiation- 39.7%

Fisher et al, NEJM, October 2002

- Oxford review of 10 European and US trials showed 5-year risk of recurrence at 7% for radiated versus 26% unirradiated

Early Breast Cancer Trialists' Collaborative Group, Lancet, December 2005

- Recent pooled analysis 5 NSABP trials looking at node negative patients showed 11% incidence of LRF for irradiated patients

Anderson et al, JCO, May 2009

Risk Factors for Recurrence

- Node positive
- Positive margins
- Larger tumor size
- LVI
- Multifocality
- Invasive disease versus DCIS

T1 - T2 lesions

- Young age
- Grade III pathology
- ER-
- Node positive

Impact of Recurrence

- Local recurrence can be a harbinger of distant disease
- Collective review of the NSABP studies: node negative and positive patients, LRF associated with significantly worse OS and DDFI

Wapnir et al, JCO, May 2006; Anderson et al, JCO, May 2009

- Oxford Review: Differences in local treatment that substantially affect local recurrence rates would avoid ~1 breast cancer death over the next 15 years for every 4 local recurrences avoided, and should reduce 15-year overall mortality

Early Breast Cancer Trialists' Collaborative Group, Lancet, December 2005

Management Issues

- Metastatic work-up
- If distant disease detected- systemic therapy
- Mastectomy versus repeat lumpectomy?
- Whole breast re-irradiation generally not recommended- significant skin toxicity, fibrosis, telegectasia, poor wound healing, organ injury, brachial plexopathy, lymphedema
- Mastectomy typically primary option; skin sparing technique may result in some flap loss
- Repeat SLNB versus completion axillary dissection?

Repeat Lumpectomy

- At initial consultation this option desirable for many patients
- For patients without prior radiation history, may be considered
- 1988-2004 SEER data: 5-year survival 67% for lumpectomy versus 78% for mastectomy

2009

Martinez et al, American J of Surgery, Sept

- Selected study of patients with localized recurrence, tumor size < 3 cm, no skin or LV invasion, < or = 3 positive nodes showed no significant survival difference (65.7% - Mastectomy versus 58% - Lumpectomy) at 10 years follow-up

Alpert et al, Int J Radiat Oncol Biol Phys, Nov 2005

- 1998 – 2008: 26 previously irradiated patients with recurrent DCIS or T1 lesions offered APBI; at median follow-up 38 months 1 local and 2 distant recurrences, cosmesis good overall

Trombetta et al, Am J Clin Oncol, May, 2009

Partial Breast Irradiation

- Additional small studies have demonstrated feasibility repeat lumpectomy and brachytherapy for local recurrence after BCS and whole breast irradiation
- Cosmesis deemed acceptable
- Longer follow-up and larger patient studies necessary to determine safety and efficacy as an alternative to completion mastectomy

Chadha et al, Brachytherapy, Jan-March 2008

Trombetta et al, Brachytherapy Jan-March 2008

Axillary Recurrence After SLNB

- Axillary recurrence is a rare event, regardless of initial nodal status and management

Jeruss et al, Annals of Surgical Oncology, September 2004

- Microscopic nodal metastasis at initial presentation: completion ALND does not appear to improve outcomes; trend toward better outcomes for ALND with initial macroscopic LN disease

Bilimoria et al, JCO, June 2009

- Patients with T1-T2 disease and 1+ positive node have higher local and regional recurrence risk and may benefit from RT to regional nodes as well as whole breast XRT

Truong et al, Int J Radiation Oncology Biol Phys, April 2008

- Suspicious recurrent lymph nodes can be assessed using FNA or core needle biopsy with ultrasound guidance; negative result not conclusive

Sentinel Node Biopsy for Local Recurrence

- Area of active investigation
- Small studies indicate feasibility of technique after breast conservation, SNB or axillary dissection, and adjuvant irradiation
- Higher incidence of success when fewer than 10 nodes removed at initial procedure
- Radioisotope and blue dye used in conjunction
- Alternative drainage patterns and longer tracer migration time noted
- Lymphoscintigraphy

Port et al, J Am Coll Surg, August 2002

Taback et al, Annals of Surgical Oncology, June 2006

Boughey et al, Clin Breast Cancer, August 2006

BRCA Patients

- Recent small study: 54 BRCA mutation carriers treated with BCS and whole breast XRT
- 10 year LR: 27% for mutation carriers and 4% for sporadic controls
- 10 year incidence CBC 25% for mutation carriers, 1% for sporadic controls
- Oophorectomy has shown to reduce risk of LR in mutation carriers and can be considered simultaneously if BCS is planned
- Overall mutation carriers need to be carefully counseled regarding high risk of LR and CBC if considering BCS

Garcia-Etienne et al, Ann Surg Oncol, March 2009

Inflammatory Recurrence

- Local-regional recurrence of this nature rare and consistently associated with distant metastasis and death
- Initial systemic therapy and high dose re-irradiation considered post-mastectomy

Conclusions

- Local recurrence can be harbinger of distant disease
- Majority of data points towards better outcomes for patients treated with mastectomy
- APBI may expand options though prospective data and long-term follow-up needed
- Repeat SLNB possible with aid of lymphoscintigraphy
- Plan of care must be handled on individual basis using multidisciplinary approach

Locally Recurrent Breast Cancer after Breast Conserving Therapy- The Role of Radiotherapy

William Small Jr., MD

Professor of Radiation Oncology

The Robert H. Lurie Comprehensive cancer Center
of Northwestern University

Current Patient

- Original T2 N0 treat with lumpectomy, sentinel node and RT.
- Assume she received standard whole breast radiotherapy.
- Now with a probably local recurrence and a small axillary lymph node.

The Local Control Issues

- Can a repeat lumpectomy be performed alone – or is mastectomy necessary ?
- If a repeat lumpectomy is performed – should re-irradiation be accomplished?
- What should be done about the regional nodal basins?
- If a mastectomy is performed – should the chest wall be re-irradiated ?

The Local Control Issues

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Local Recurrence After Mastectomy – Selected Series

Author	N	Percentage Chest Wall Recurrence
Doyle	112	3%
Huang	118	18% (True Local Recurrences)
Cajucom	25	32%

Local Recurrence After Conservative Surgery Alone – Selected Series

Author	N	Percentage Chest Wall Recurrence
Abdner	39	31 %
Voogd	16	52%
Salvadori	57	19%

The Local Control Issues

- Can a repeat lumpectomy be performed alone – or is mastectomy necessary ?
- If a repeat lumpectomy is performed – should re-irradiation be accomplished?
- What should be done about the regional nodal basins?
- If a mastectomy is performed – should the chest wall be re-irradiated ?

Local Recurrence After Conservative Surgery and Re-irradiation – Selected Series

Author	N	Technique	Local Recurrence	Major Complication
Maulard	15	Interstitial	26%	30%
Deutsh	39	External (Tumor Bed)	21%	0
Resch	17	Interstitial +/- Whole Breast Radiotherapy	24%	0
Hannoun-Levi	69	Interstitial	16%	10%

The Local Control Issues

- Can a repeat lumpectomy be performed alone – or is mastectomy necessary ?
- If a repeat lumpectomy is performed – should re-irradiation be accomplished?
- What should be done about the regional nodal basins?
- If a mastectomy is performed – should the chest wall be re-irradiated ?

Radiotherapy Nodal Treatment

- Virtually no data
- Probably should treat as would be treated with a primary presentation.

The Local Control Issues

- Can a repeat lumpectomy be performed alone – or is mastectomy necessary ?
- If a repeat lumpectomy is performed – should re-irradiation be accomplished?
- What should be done about the regional nodal basins?
- If a mastectomy is performed – should the chest wall be re-irradiated ?

A Multi-Institutional Review of Chest Wall and Breast Re-Irradiation for Recurrent Breast Cancer

*American Society for Therapeutic Radiation and Oncology,
48th Annual Meeting, November 4-9, 2006, Philadelphia, PA.*

A.O. Wahl, A. Rademaker, K.D. Kiel, E.L. Jones, L.B. Marks, V. Croog,
B.M. McCormick, A. Hirsch, A. Karkar, S.B. Motwani, W. Tereffe, T.K.
Yu, J. Silverstein, L.A. Kachnic, C. Kesslering, G.M. Freedman, W.
Small Jr.

Background

- Locoregional recurrences occur in approximately 5-15% of patients despite adjuvant RT
- In postmastectomy patients, a second local failure following excision of local recurrences occurs in 60-70% of patients
 - The addition of RT to excision improves local failure rate to 25-50%
- Second local failure rates following salvage mastectomy for in-breast recurrence are 3-32%

Purpose

- To conduct multi-institutional review of patients who received two separate courses of external beam RT to breast or chest wall to determine:
 - Acute and late toxicity
 - Response rates and local control

Methods

- Eight collaborating institutions identified 81 patients
 - All patients had prior whole breast RT or chest wall RT
 - Excluded those patients who received partial breast radiation therapy as the initial course of RT or brachytherapy as part of their second course of RT

Methods – Initial Diagnosis

- Breast conserving surgery performed in 69% of patients
- Mastectomy performed in 31% of patients[§]

Characteristic	
Median Age	48 (26-70)
Race	
Caucasian	80%
African American	14%
Other	6%
Nodal Status*	
Positive	36%
Negative	64%
Axillary Dissection†	
Yes	88%
No	12%

§ Data missing on 4 patients

† Data missing on 8 patients

* Data missing on 14 patients

Methods – Initial RT Course

Characteristic	
Median dose to breast or chest wall	48 Gy (14-72 Gy)
Boost	78%
Median dose of boost	14 Gy (4-30.5 Gy)*
Median total dose of initial RT course	60 Gy (19.6-82)
Supraclavicular RT	44%
Median dose of supraclavicular RT	50 Gy (5-50.4)
Axillary RT	24%

* Brachytherapy boost in 2 patient

Methods – Second RT Course

- 72% had gross disease at time of second RT course
- 30% had metastatic disease at time of second RT course
- 19% had lymphedema at start of 2nd RT course†

Characteristic	
Recurrence Site	
Chest wall only	69%
Breast only	14%
Chest wall and reg. nodal	10%
Regional nodal	5%
Breast and regional nodal	3%
Concurrent hyperthermia	54%
Concurrent chemotherapy	54%

† Data missing in 13 patients

Methods – Second RT Course

Median dose	48 (26-70)
Median cumulative dose	106 Gy (74.4-137.5)
Modality	
Photons only	80%
Electrons only	14%
Both	6%
RT given twice daily*	20%
RT Fields	
Whole chest wall	55%
Whole chest wall and supraclavicular LN	21%
Partial chest wall	14%
Partial chest wall and supraclavicular LN	8%
Whole Breast	2%

* Data missing in 5 patients

Methods – Toxicity

- Local disease free survival defined as date of initiation of 2nd RT course to local disease or death
- A complete response (CR) was scored only for patients with gross disease and was defined as the absence of local disease following re-irradiation.
- Toxicity assessed according to CTC version 3.0
 - Dermatitis
 - Burns
 - Induration/Fibrosis
 - Skin Infection
 - Lymphedema
 - Soft tissue necrosis
 - Osteonecrosis
 - Fracture
 - Brachial plexopathy
 - Pneumonitis
 - Pericarditis

Late Toxicity

- In the 26 patients with follow-up greater than 20 months, there was no grade 3-4 late toxicity.
- Three late grade 3 toxicities were noted: one induration, skin infection and lymphedema
- One grade 4 dermatitis toxicity was noted
- Late follow-up was not available in 11 patients due to death or short follow-up.

Local Disease Free Survival

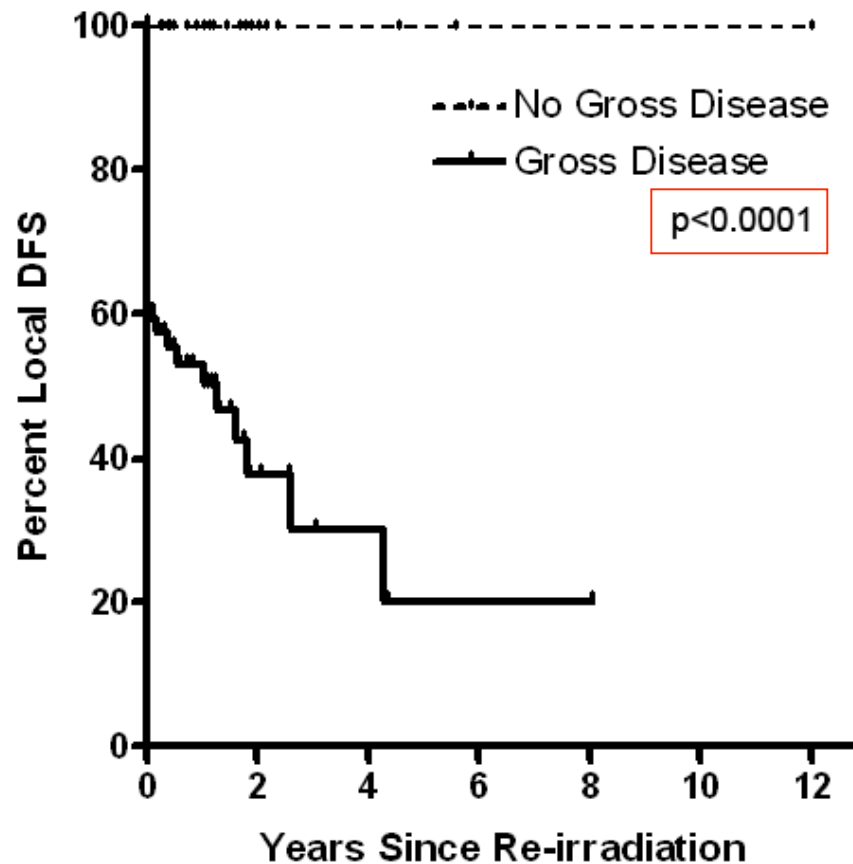


Figure 2- Local DFS, gross disease vs. no gross disease

Re-Irradiation - Conclusions

- Acute and late toxicity rates are acceptable, with major late toxicities occurring in 5-10% of patients.
- Re-irradiation of the chest-wall or breast was associated with an acceptable complete response rate.

Conclusion

- For a local recurrence after breast conserving therapy – mastectomy continues to be the treatment of choice.
- In patients that refuse mastectomy, lumpectomy and re-irradiation is a consideration
- Regional nodal radiotherapy should be considered based on risk and previous radiotherapy
- If mastectomy is performed, post-mastectomy radiotherapy should be considered based on risk factors for recurrence

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Medical Oncology Issues

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Regardless of whether this is a
recurrence or a new
primary.....

What would be the role of
chemotherapy ??

Neoadjuvant Cisplatin in BRCA1-deficient and Triple Negative Breast Cancer

Patient Population	Stage	Regimen	Pathological Complete Response, n (%)
BRCA1 mutation ¹ (n = 25)	I – III*	Cisplatin 75 mg/m ² q3w X4	18 (72%)
Triple negative ² (n = 28)	II - III	Cisplatin 75 mg/m ² q3w X4	6 (22%)**
Triple negative ³ (n = 51)	II - III	Cisplatin 75 mg/m ² q3w X4 + bevacizumab 15 mg/kg X3	8 (16%)
Triple negative ⁴ (n = 78)	II - III	Multiple cisplatin - based***	NA (32%)

¹Gronwald et al. *J Clin Oncol* 2009; 27(suppl):7s (abstract 502)

²Garber et al. *Breast Cancer Res Treat* 2006; 105(suppl1):S149 (abstract 3074)

³Ryan et al. *J Clin Oncol* 2009; 27(suppl):18s (abstract 551)

Leone et al. *J Clin Oncol* 2009; 27(suppl):37s (abstract 625)

DF/HCC NeoAdjuvant Platinum in Triple Negative Breast Cancer

> 2cm, Stage II/ III
ER/PR/Her Neg
Breast Cancer on
Core Biopsy

Cis Platinum
75mg/m² q3wks
x 12 weeks*

Standard
Adjuvant
Therapy
per MD

Tissue:

5q, 8q LOH

IHC: BRCA1, CK5/6

Microarrays: cDNA, SNP

FANCF methylation

Radiation damage assay

Blood:

BRCA1

Imaging

Mammo

US

MRI

* Additional MRI and Core bx after 1 dose of CDDP: radiation damage assay

Neoadjuvant Cisplatin (CDDP) in Triple-Negative Breast Cancer

- N = 28 \geq 2-cm stage II/III triple negative
- Single-agent cisplatin 75 mg/m² q3w x 4 cycles prior to surgery

Grade 4

↑ LFT 1 pt

Grade 3

Neutropenia 2 pts

Tinnitus 1 pt

Nausea 1 pt

Fatigue 1 pt

Hyperkalemia 1 pt

↑ LFT 1 pt

Pathologic CR 6 (22%)

Clinical CR 4 (14%)

Clinical PR 10 (36%)

Stable Disease 5 (17%)

- **Age associated with pCR (P < .04)**
Both women with BRCA1 mutations had Path Complete Response

Efficacy of BSI-201, a poly (ADP-ribose) polymerase-1 (PARP1) inhibitor, in combination with gemcitabine/carboplatin in patients with metastatic triple-negative breast cancer: Results of a randomized phase II trial.

J. O'Shaughnessy, C. Osborne, J. Pippin, M. Yoffe, D. Patt, G. Monaghan, C. Rocha, V. Ossovskaya, B. Sherman, C. Bradley; Baylor Sammons, Texas Oncology, US Oncology, Dallas, TX; Cancer Centers of North Carolina/US Oncology, Raleigh, NC; Texas Oncology Cancer Center, US Oncology, Austin, TX; Kansas City Cancer Center, US Oncology, Kansas City, MO; BiPar Sciences, Inc., Brisbane, CA

Abstract 3

Phase II TNBC Study: Treatment Schema

Metastatic TNBC
N = 120

RANDOMIZE

Gemcitabine 1000mg/m² IV D1, 8
Carboplatin AUC 2 IV D1, 8

21-Day
Cycle

BSI-201 5.6mg/kg IV D1, 4, 8, 11
Gemcitabine 1000mg/m² IV D1, 8
Carboplatin AUC 2 IV D1, 8

RESTAGING
Every 2 Cycles

Mostly first-line,
20 to 30% second-line
BRCA status not reported
Majority had upregulated levels of PARP

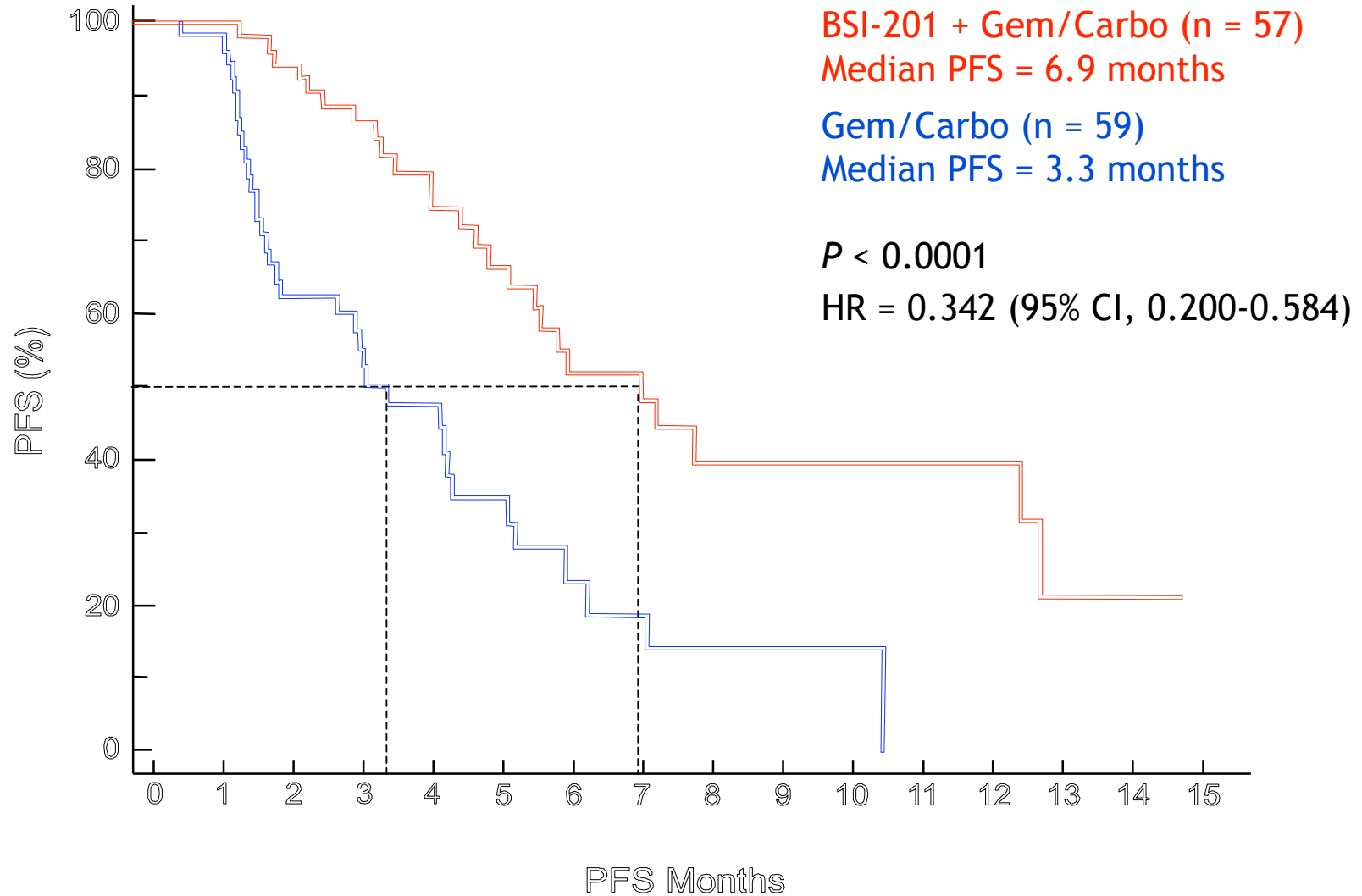
* Patients randomized to gem/carbo alone could crossover to receive gem/carbo + BSI-201 at disease progression

Preliminary Efficacy Results*

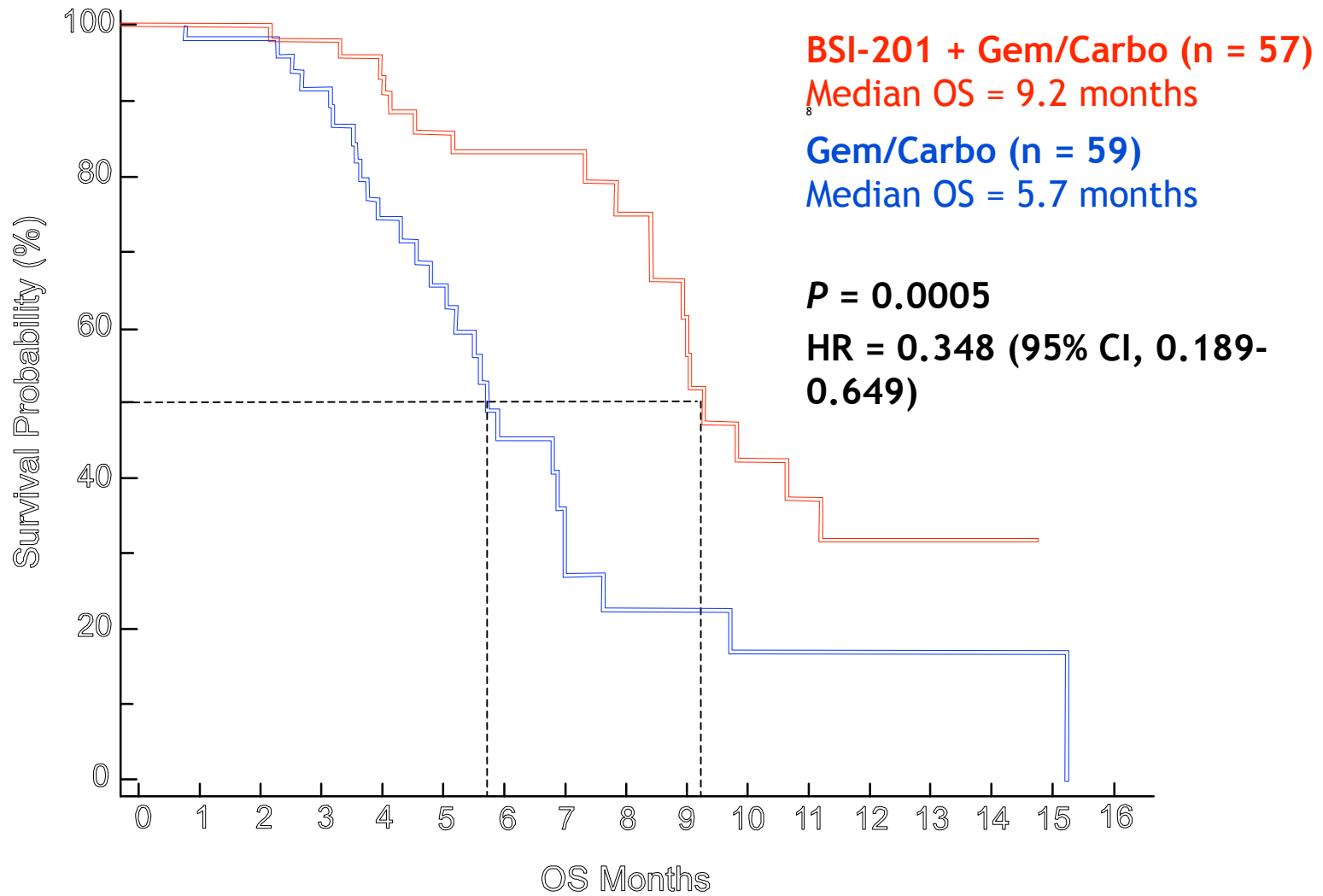
	Gem/Carbo (n = 44)	BSI-201 + Gem/Carbo (n = 42)	<i>P</i> -value
Objective Response Rate n (%)	7 (16%)	20 (48%)	0.002
**Clinical Benefit Rate n (%)	9 (21%)	26 (62%)	0.0002

No increase in chemotherapy-related toxicity with the use of the PARPi

Progression-Free Survival



Overall Survival



Gemcitabine/carboplatin ± BSI-201: Hematologic Toxicity

	Gem/Carbo (n = 59)			BSI-201 + Gem/Carbo (n = 57)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Anemia, n (%)	12 (20.3%)	7 (11.9%)	0 (0.0%)	15 (26.3%)	7 (12.3%)	0 (0.0%)
Thrombocytopenia, n (%)	7 (11.9%)	6 (10.2%)	6 (10.2%)	4 (7.0%)	6 (10.5%)	7 (12.3%)
Neutropenia, n (%)	7 (11.9%)	18 (30.5%)	13 (22.0%)	7 (12.3%)	18 (31.6%)	7 (12.3%)
Febrile neutropenia, n (%)	0 (0.0%)	3 (5.1%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
RBC treatment*, n (%)	5 (8.5%)	5 (8.5%)	2 (3.4%)	3 (5.3%)	5 (8.8%)	2 (3.5%)
G-CSF Use, n (%)	6 (10.2%)	6 (10.2%)	3 (5.1%)	4 (7.0%)	5 (8.8%)	1 (1.8%)

*Transfusion and/or EPO use

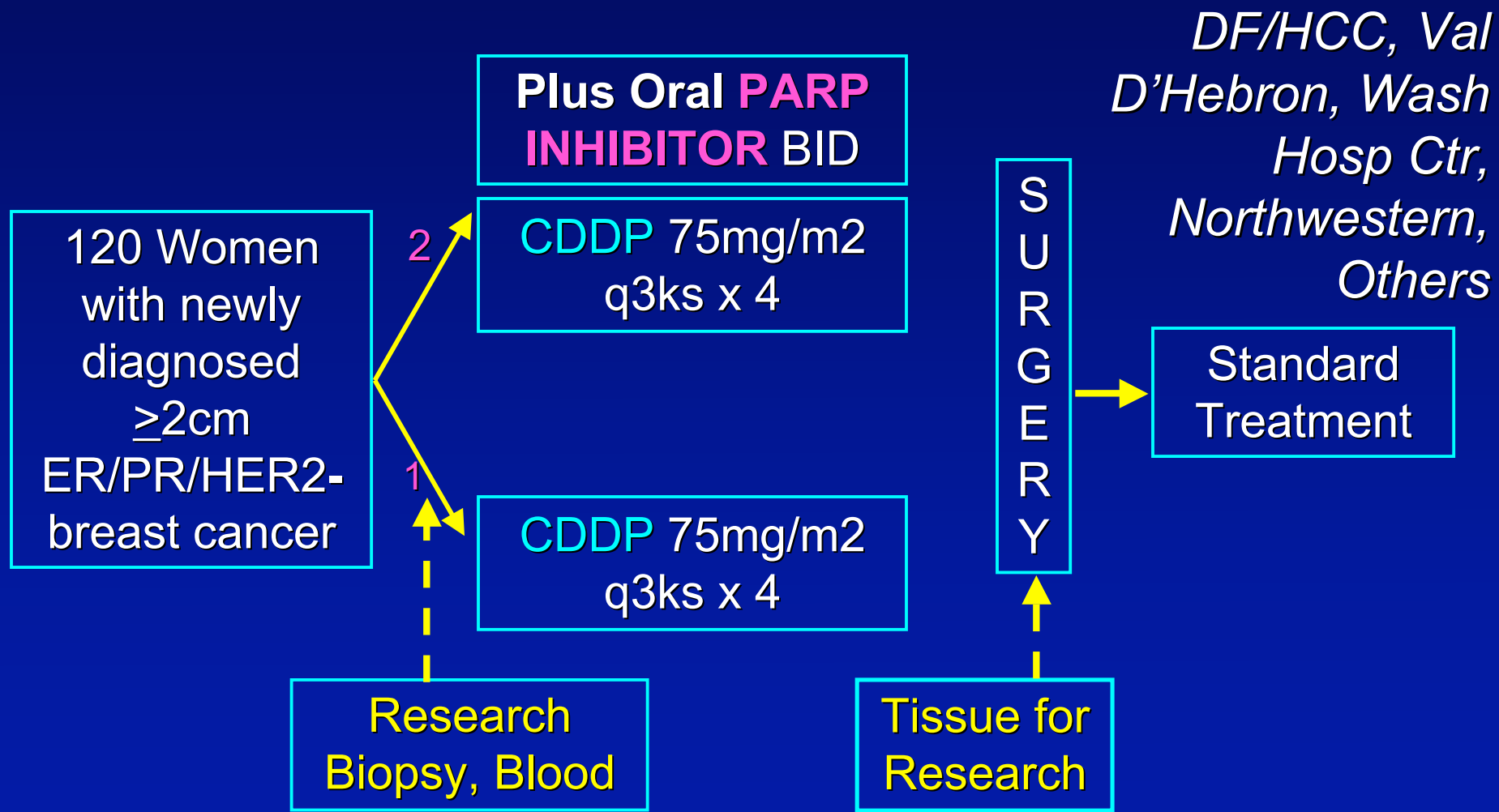
Gemcitabine/carboplatin ± BSI-201: Non-Hematologic Toxicity

	Gem/Carbo (n = 59)			BSI-201 + Gem/Carbo (n = 57)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Nausea, n (%)	10 (16.9%)	2 (3.4%)	0 (0.0%)	7 (12.3%)	0 (0.0%)	0 (0.0%)
Vomiting, n (%)	9 (15.3%)	0 (0.0%)	0 (0.0%)	4 (7.0%)	1 (1.8%)	0 (0.0%)
Fatigue, n (%)	10 (16.9%)	6 (10.2%)	0 (0.0%)	10 (17.5%)	1 (1.8%)	0 (0.0%)
Neuropathy, n (%)	2 (3.4%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
Diarrhea, n (%)	6 (10.2%)	1 (1.7%)	0 (0.0%)	1 (1.8%)	1 (1.8%)	0 (0.0%)

Conclusion

- Potential treatment recommendations:
 - Taxane (TC)
 - Platinum
 - ? Addition of targeted agent
- From the above data I would either give the patient a platinum-containing regimen or enroll her on a clinical trial.

Pre-Surgical CDDP_±AZD2281 in Triple Negative Breast Cancer



Courtesy of Dr J Garber

NSABP B-37

IBCSG 27-02, BIG 1.2

Isolated Local and/or Regional
Recurrence of **Invasive** Breast
Cancer after Mastectomy or Breast
Conserving Surgery

Observation
+/- XRT

Chemotherapy
+/- XRT

Hormone therapy for ER or PR + tumors
Trastuzumab or **other anti-HER therapy allowed**

Courtesy of Dr Mamounas

NSABP B-37

IBCSG 27-02, BIG 1.2

Protocol Changes

- **Sample Size**
 - Lowering of sample size from 900 to 265
 - » Previous assumptions were modest
 - Original 5 yr DFS HR 0.74
 - Overview, B-20 and Intergr 0100 show HR of 0.5 to 0.6
 - e.g. B-20 : 35% Risk reduction CMFT vs TAM
- **Any anti-HER2 therapy**
 - Trastuzumab, lapatinib, pertuzumab
- **QOL component discontinued**

Accrual
3 patients per month
to complete
by 2012

149 ~ 56.2%