Breast Cancer Update
Oncology Highlights
New York July 11th 2009

Ruth M. O'Regan, MD
Associate Professor of Hematology and Oncology
Director Translational Breast Cancer Research Program

EMORY

WINSHIP CANCER INSTITUTE

Breast cancer abstracts

- Triple negative breast cancer (Abstracts 3, 501, 502)
- HER2-targeted agents in trastuzumab-resistant MBC (Abstracts 1004,1017)
- Bevazicumab-based chemotherapy for MBC (Abstracts 1005, 1006)
- Local-regional therapy (Abstracts 506, 507)
- CYP2D6 inhibitors with tamoxifen (Abstracts 508, 509)

BRCA, Platinums and Triple negative breast cancers

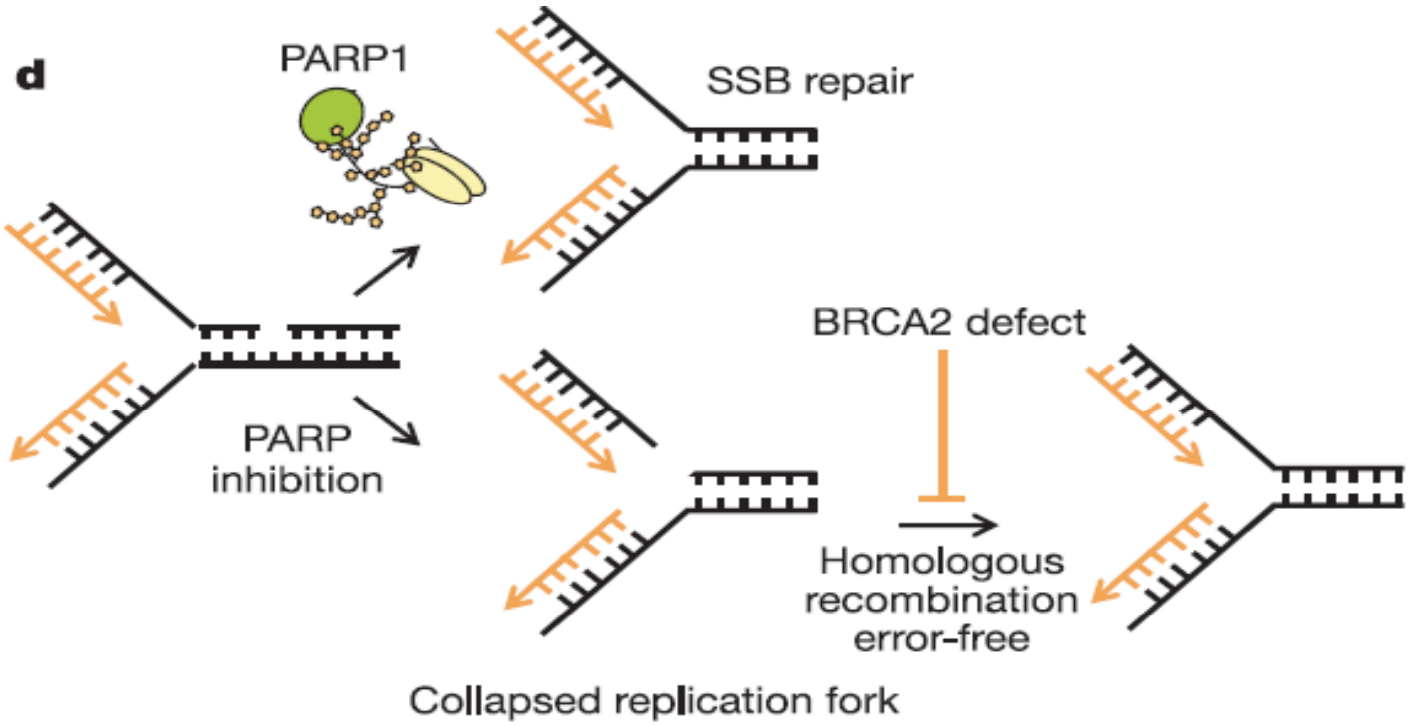
- BRCA1 mutation carriers develop basal-like (triple negative) breast cancers almost exclusively
- BRCA plays a role in pathogenesis of a subset (as yet undefined) of triple negative breast cancers
- Preclinical models have demonstrated differential sensitivity of BRCA mutant cells to platinums rather than taxanes

Sorlie et al *PNAS* 2003, Quinn Cancer Res 2003

PARP inhibition is especially effective in BRCA deficient cancers

PARP (Poly (ADP-ribose) Polymerase)

- A key regulator of DNA damage repair processes
- Involved in DNA base-excision repair (BER)
- Binds directly to DNA damage



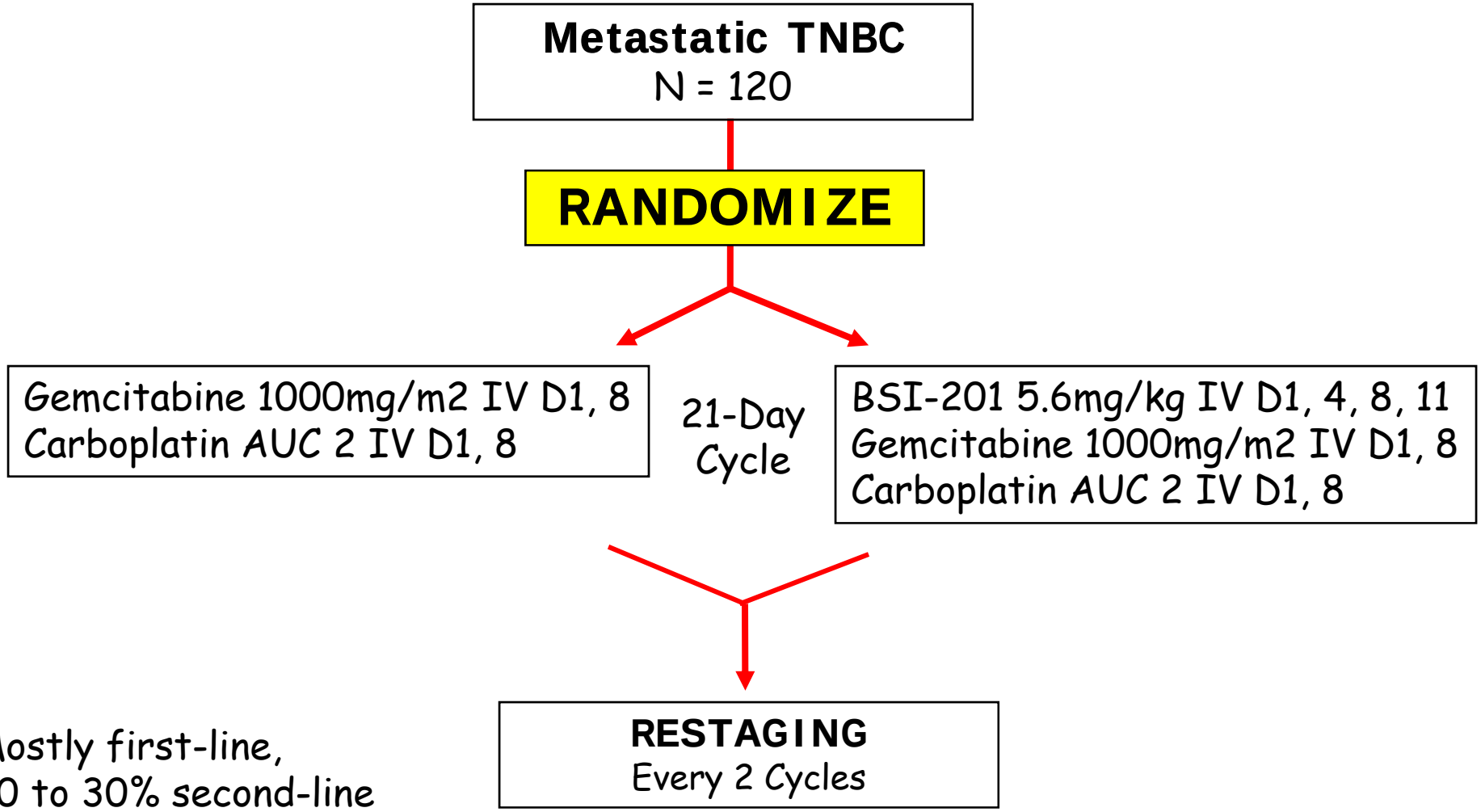
NATURE | VOL 434 | 14 APRIL 2005 | www.nature.com/nature

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. Pippen, 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



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

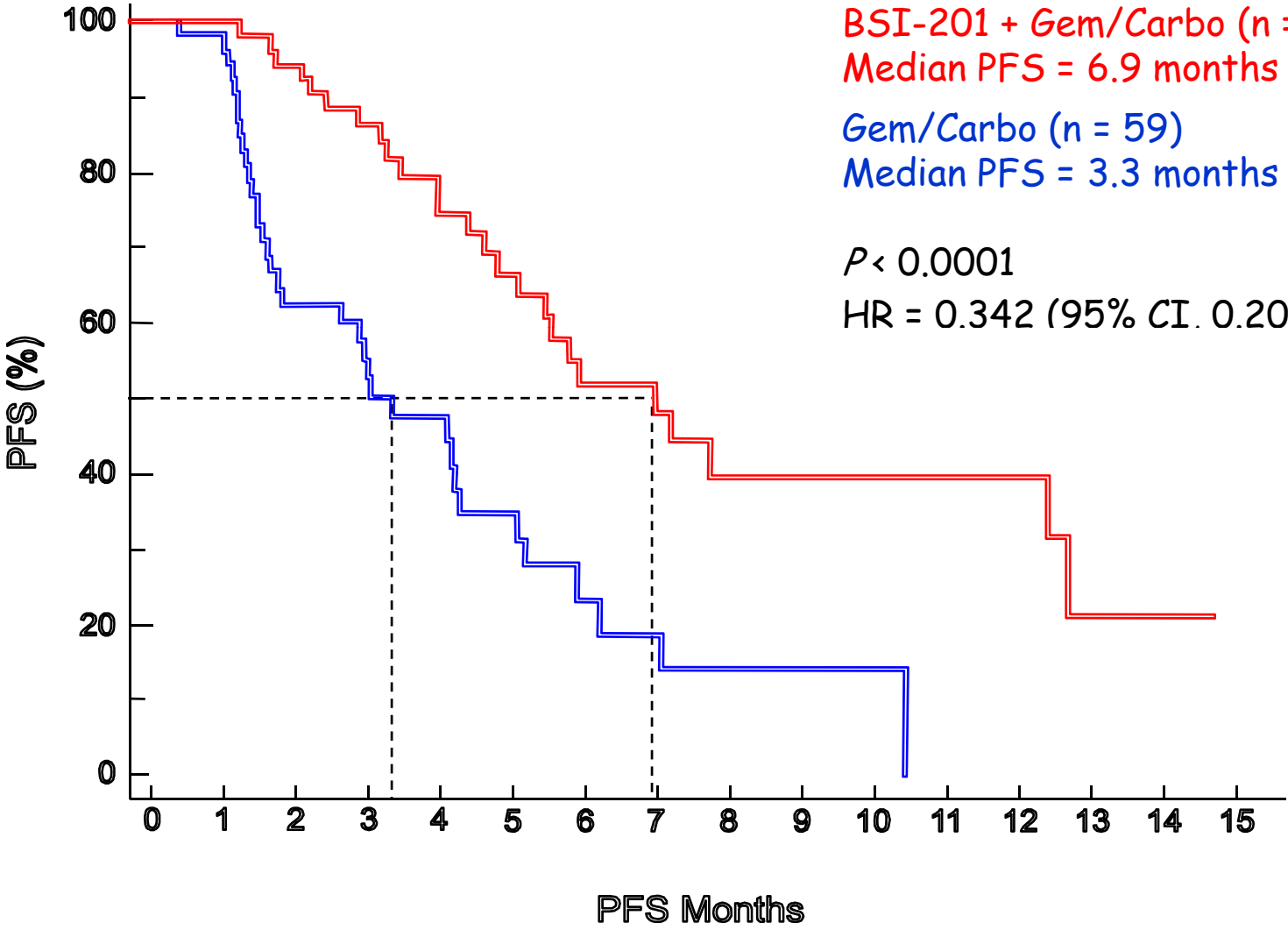
* Patients randomized to gem/carbo alone could crossover to receive gem/carbo + BSI-201 at disease progression

Preliminary Efficacy Results*

	Gem/Carbo (n = 44)	BSI-201 + Gem/Carbo (n = 42)	*P*-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



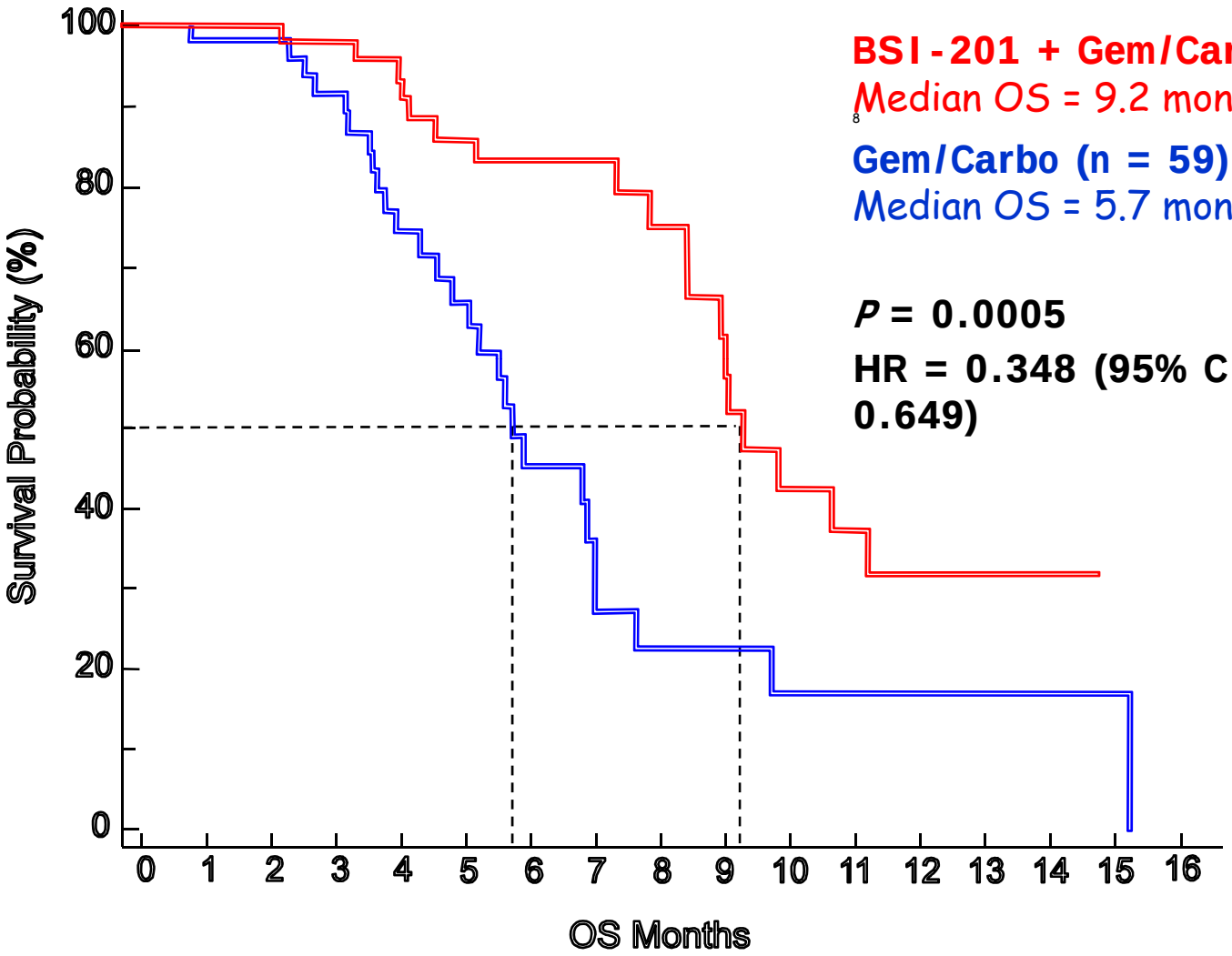
BSI-201 + Gem/Carbo (n = 57)
Median PFS = 6.9 months

Gem/Carbo (n = 59)
Median PFS = 3.3 months

P < 0.0001

HR = 0.342 (95% CI. 0.200-0.584)

Overall Survival



BSI-201 + Gem/Carbo (n = 57)
Median OS = 9.2 months

Gem/Carbo (n = 59)
Median OS = 5.7 months

***P* = 0.0005**

HR = 0.348 (95% CI, 0.189-0.649)

Phase II trial of the oral PARP inhibitor olaparib in BRCA-deficient advanced breast cancer

A. Tutt, M. Robson, J. E. Garber, S. Domchek, M. W. Audeh, J. N. Weitzel, M. Friedlander, J. Carmichael; Breakthrough Breast Cancer Research Unit, Kings College London School of Medicine, Guy's Hospital, London, United Kingdom; Memorial Sloan-Kettering Cancer Center, New York, NY; Dana-Farber Cancer Institute, Boston, MA; University of Pennsylvania, Philadelphia, PA; Cedars-Sinai Outpatient Cancer Center, Los Angeles, CA; City of Hope Comprehensive Cancer Center, Duarte, CA; Prince of Wales Cancer Centre, Sydney, Australia; AstraZeneca, Macclesfield, United Kingdom

Abstract CRA 501

Phase II Study of Olaparib in BRCA-deficient Advanced Breast Cancer

- **Patient population**
  - Stage IIIB/IIIC/IV
  - Failure of ≥ 1 prior chemotherapy for advanced disease
  - *BRCA1* or *BRCA2* mutation
- **Single arm, sequential cohort trial design**
  - Cohort 1 (n = 27): olaparib 400 mg po bid 28 day cycle (50% TN)
  - Cohort 2 (n = 27): olaparib 100 mg po bid 28 day cycle (64% TN)
- **Primary endpoint: ORR by RECIST**
- **Secondary endpoints included: PFS and safety**

Tutt et al. *J Clin Oncol* 2009; 27(suppl):803s (CRA501).

Phase II Study of Olaparib in BRCA-deficient Breast Cancer: Efficacy and Safety

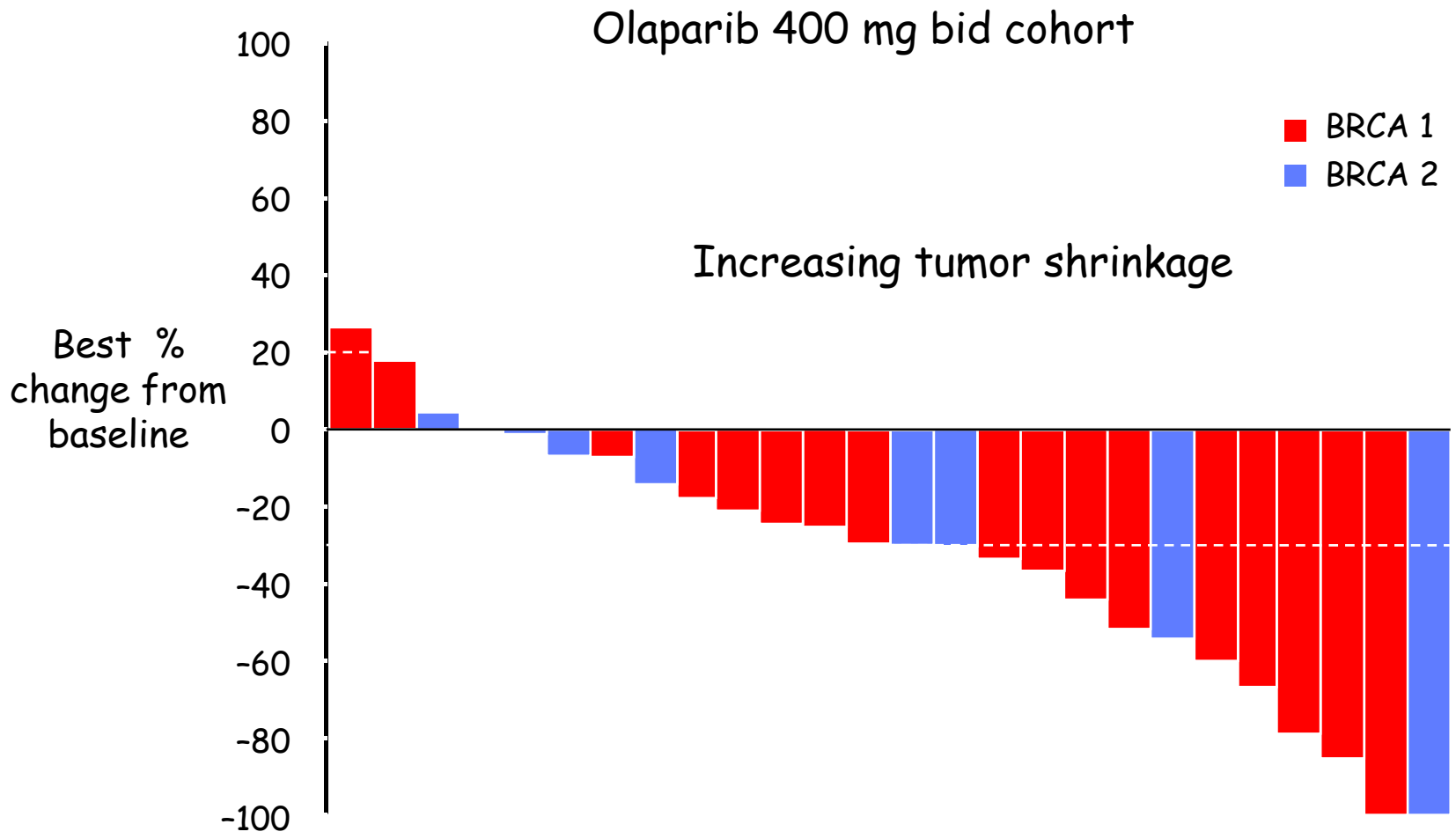
Efficacy	Olaparib 400 mg bid (n = 27)	Olaparib 100 mg bid (n = 27)
ORR	11 (41%)*	6 (22%)
CR	1 (4%)	0
PR	10 (37%)	6 (22%)
PFS	5.7 months	3.8 months

*Includes 5 patients that received prior anthracycline, taxane, and capecitabine

Grade 3 AE	Olaparib 400 mg bid (n = 27)	Olaparib 100 mg bid (n = 27)
Fatigue	4 (15%)	2 (7%)
Nausea	5 (19%)	0
Vomiting	3 (11%)	0

Tutt et al. *J Clin Oncol* 2009; 27(suppl):803s (CRA501)

Best % change from baseline in target lesions by genotype



One patient was excluded as only 1 of their 2 target lesions was measured at each assessment

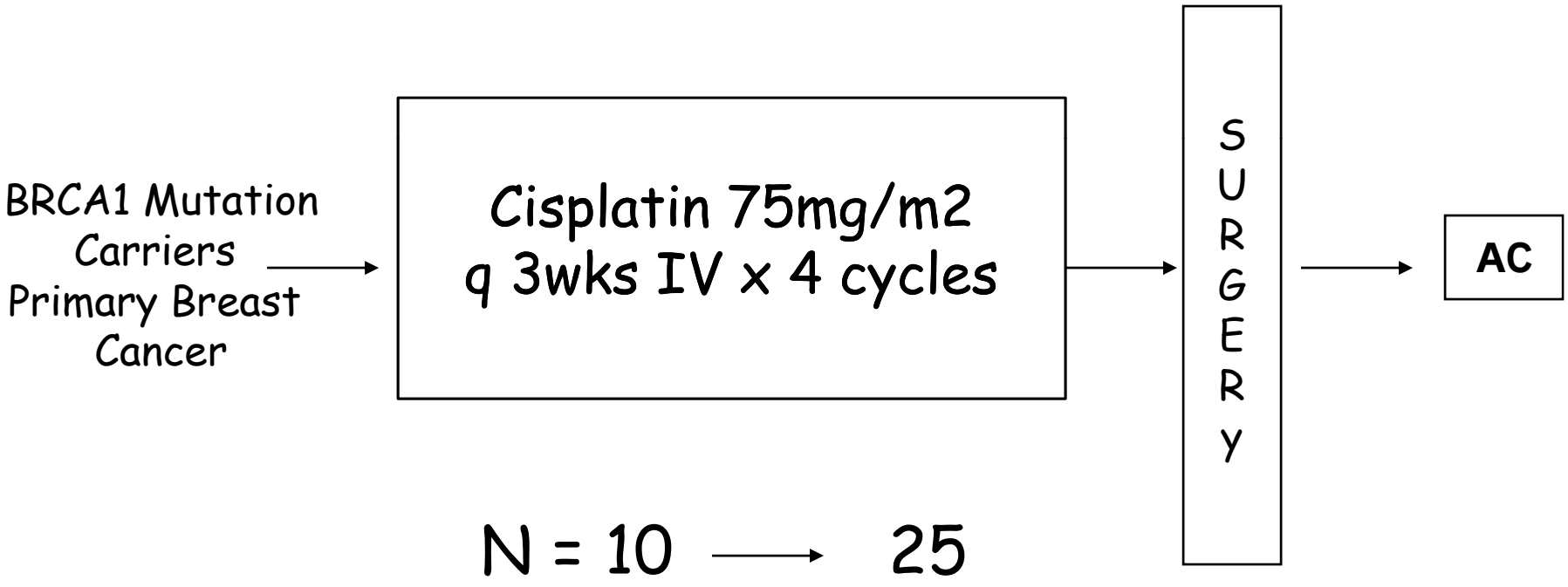
Tutt et al. *J Clin Oncol* 27:15s, 2009 (suppl; abstr 5500)

Neoadjuvant therapy with cisplatin in BRCA1-positive breast cancer patients

J. Gronwald, T. Byrski, T. Huzarski, R. Dent, V. Bielicka, D. Zuziak, R. Wisniowski, J. Lubinski, S. Narod; Pomeranian Medical University, Szczecin, Poland; Sunnybrook Odette Cancer Centre, Toronto, ON, Canada; Regional Oncology Center, Bielsko-Biala, Poland; Women's College Research Institute, Toronto, ON, Canada

Abstract 502

Phase 2 trial of pre-operative cisplatin in BRCA1 mutations carriers



Primary Endpoint: pCR (in breast and axilla, DCIS permitted)

Response to treatment

Response	No.	%
Clinical response		
Complete response	18	72
Partial response	7	28
No change	0	0
Progressive disease	0	0
Pathologic response		
Complete pathologic response	18	72
Partial reseponse	7	28
No response	0	0
Residual disease in breast		
None	19	76
<1 cm	0	0
1 – 5 cm	6	24
>5 cm	0	0
Number of lymph nodes positive		
0	21	84
1 – 3	4	16
4 – 9	0	0
>9	0	0

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%)

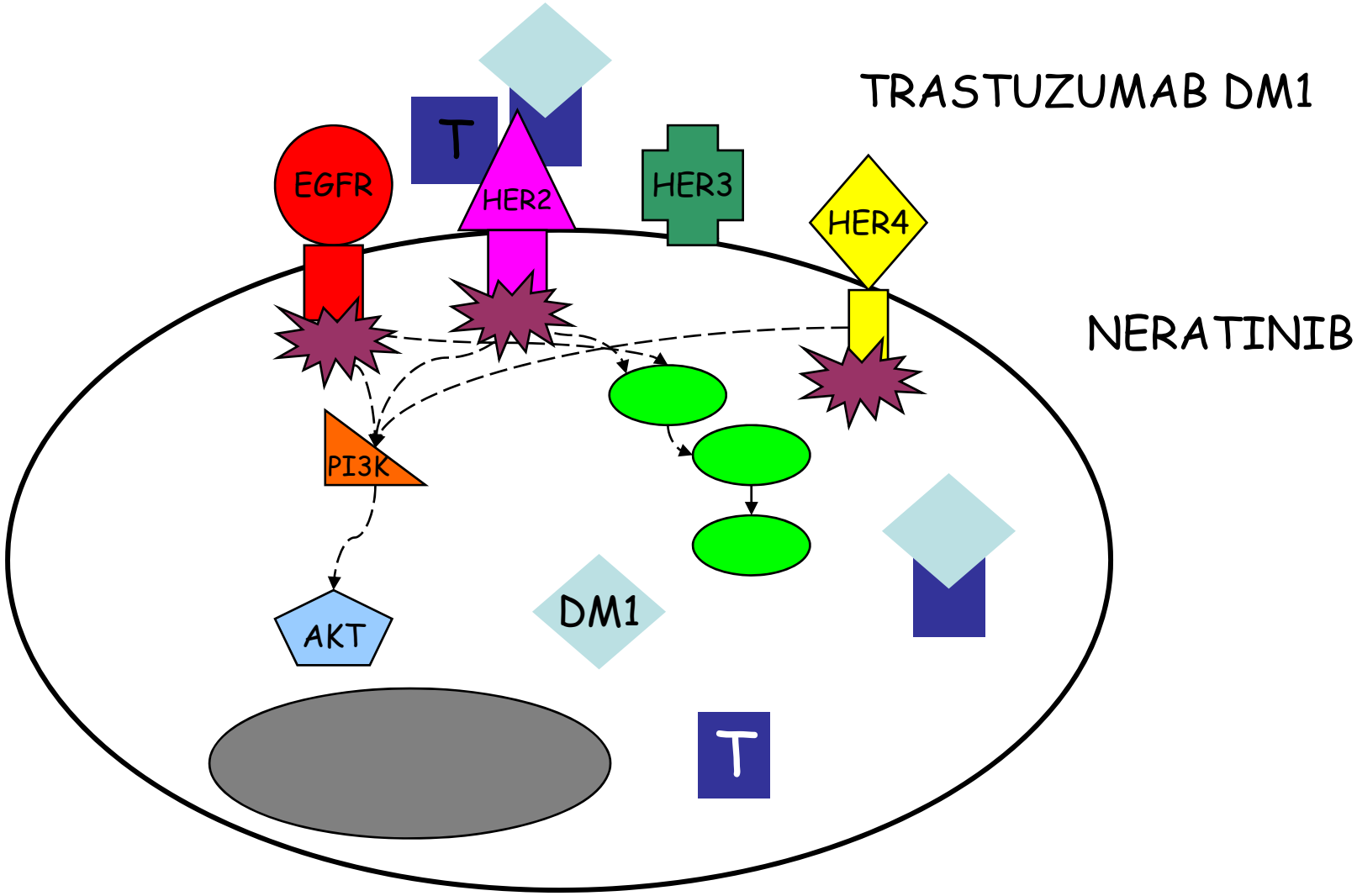
*Includes T1 (n = 10) and N0 (n = 18)
**Including both patients with identified BRCA1 mutations
***Retrospective study subgroup analysis

[1]Gronwald et al. *J Clin Oncol* 2009; 27(suppl):7s (abstract 502)
[2]Garber et al. *Breast Cancer Res Treat* 2006; 105(suppl1):S149 (abstract 3074)
[3]Ryan et al. *J Clin Oncol* 2009; 27(suppl):18s (abstract 551)
Leone et al. *J Clin Oncol* 2009; 27(suppl):37s (abstract 625)

These trials are proof of concept

- Single agent PARPi active in BRCA-related breast cancers
- Single agent platinum effective in BRCA1-related TN breast cancers
- PARPi in combination with gemcitabine and platinum significantly improves outcome for patients with TN breast cancer (BRCA status not assessed)
- PARPi well-tolerated and do not increase chemotherapy-related toxicity

HER2 directed agents in trastuzumab-resistant cancers



Neratinib in combination with trastuzumab for the treatment of advanced breast cancer: A phase I/II study

R. Swaby, K. Blackwell, Z. Jiang, Y. Sun, V. Dieras, K. Zaman, C. Zacharchuk, C. Powell, R. Abbas, M. Thakuria; Fox Chase Cancer Center, Philadelphia, PA; Duke Breast Oncology Program, Durham, NC; Hospital of the Chinese People's Liberation Army, Beijing, China; Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China; Institut Curie, Paris, France; University Hospital CHUV, Lausanne, Switzerland; Wyeth Research, Cambridge, MA; Wyeth Research, Collegeville, PA

Abstract 1004

Neratinib plus trastuzumab: efficacy in trastuzumab-exposed/resistant MBC

Investigator Assessment	NER-MTD (240 mg) + T (n=28)
Objective Response Rate*	28.6%
Clinical Benefit Rate	35.7%
Complete Response	7.1%
Partial Response	21.4%
16 week PFS	45%
Median PFS	16 weeks

Diarrhea most frequent adverse event

Swaby et al PASCO Abstract 1004

A phase II study of trastuzumab-DM1 (T-DM1), a HER2 antibody-drug conjugate (ADC), in patients (pts) with HER2+ metastatic breast cancer (MBC): Final results

C. L. Vogel, H. A. Burris, S. Limentani, R. Borson, J. O'Shaughnessy, S. Vukelja, S. Agresta, B. Klencke, M. Birkner, H. Rugo; Lynn Regional Cancer Center West, Boca Raton, FL; Sarah Cannon Cancer Center, Nashville, TN; Blumenthal Cancer Center, Charlotte, NC; St. Louis Cancer and Breast Institute, St. Louis, MO; Texas Oncology P.A. Baylor Sammons Cancer Center, Dallas, TX; Tyler Cancer Center, Tyler, TX; Genentech, Inc., South San Francisco, CA; University of California, San Francisco, San Francisco, CA

Abstract 1017

Efficacy of T-DM1 in resistant HER2+ MBC* (n = 112)

	IRF n (%)	Investigator n (%)
Best Objective Response		
CR	0	3 (2.7)
PR	28 (25.0)	40 (35.7)
SD	54 (48.2)	43 (38.4)
PD	21 (18.8)	22 (19.6)
ORR	28 (25.0)	43 (38.4)
Clinical Benefit Rate*	39 (34.8)	50 (44.6)
Median PFS	4.9 months	4.9 months

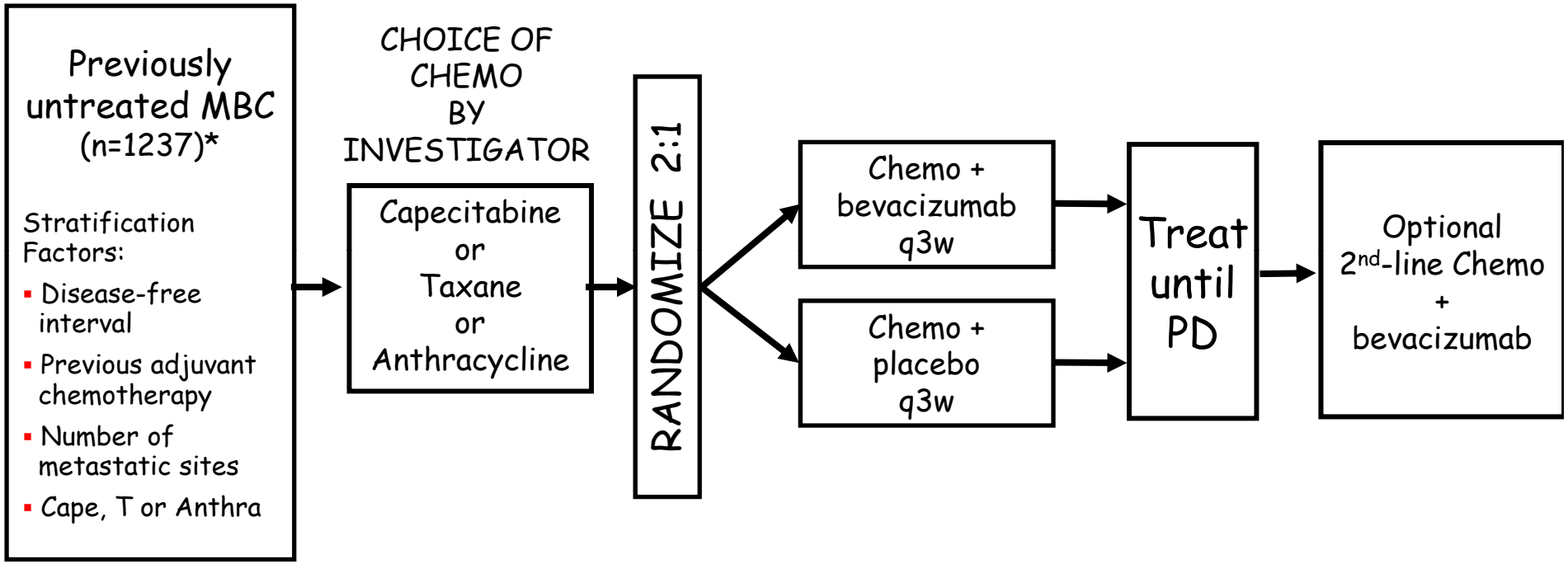
*Median number of metastatic treatments = 3
Median duration of trastuzumab = 17 months
Prior lapatinib = 60% (median duration of lapatinib 6 months)

RIBBON-1: Randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer

N. J. Robert, V. Dieras, J. Glaspy, A. Brufsky, I. Bondarenko, O. Lipatov, E. Perez, D. Yardley, X. Zhou, S. Phan; Fairfax-Northern Virginia Hematology-Oncology, Fairfax, VA; Institut Curie, Paris, France; UCLA TORI, Los Angeles, CA; University of Pittsburgh, Pittsburgh, PA; State Medical Academy, Dnipropetrovsk, Ukraine; Bashkirian Republican Clinical Oncology, Ufa, Russian Federation; Mayo Clinic, Jacksonville, FL; Sarah Cannon Cancer Center, Nashville, TN; Genentech, Inc., South San Francisco, CA

Abstract 1005

Phase III trial of Chemotherapy ± Bevacizumab



*75% ER-positive, 25% TN

- Capecitabine (1000 mg/m^2 BID x 14d)
- Taxane (docetaxel q3w or protein-bound paclitaxel q3w)
- Anthracycline-based chemotherapy (AC, EC, FAC, FEC)
- Placebo or bevacizumab (15 mg/kg q3w)

Efficacy: Chemotherapy ± Bevazicumab

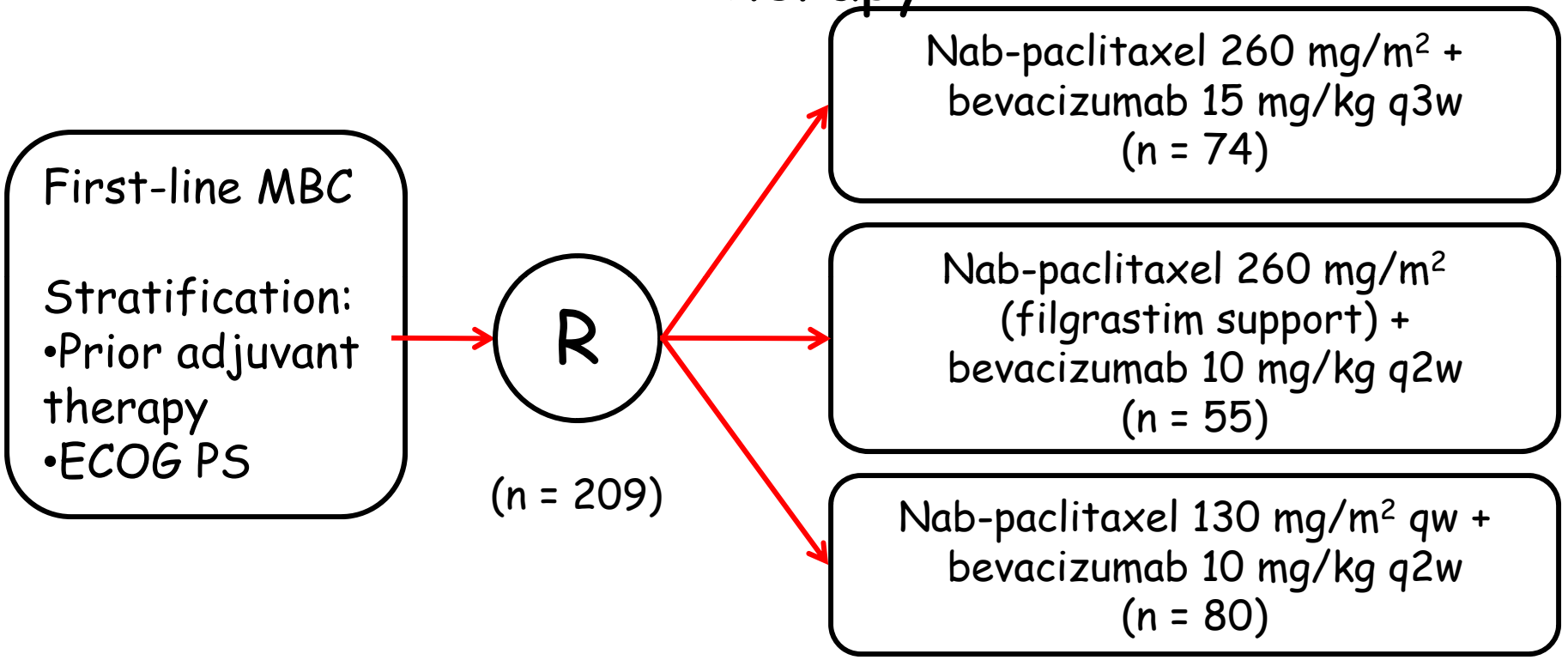
	Capecitabine		Taxane/Anthra	
	PL	BV	PL	BV
PFS	6.2 mos.	9.8 mos.	8.3 mos.	10.7 mos.
	HR 0.68 (0.54–0.86) P = .0011		HR 0.77 (0.60–0.99) P =.04	
ORR	24%	35%	38%	51%
	P =.01		P = .005	
OS	21.2 mos.	29 mos.	23.8	25.2
	0.85 (0.63–1.14) P = .27		1.03 (0.77–1.38) P =.83	

Randomized phase II trial of nanoparticle albumin-bound paclitaxel in three dosing schedules with bevacizumab as first-line therapy for HER2-negative metastatic breast cancer (MBC)

K. Conlin, C. A. Hudis, A. Bach, M. Moynahan, D. Lake, A. Forero-Torres, G. Wright, M. Hackney, A. Clawson, A. D. Seidman; Memorial Sloan-Kettering Cancer Center, New York, NY; University of Alabama at Birmingham, Birmingham, AL; Florida Cancer Institute, Hudson, FL; Virginia Commonwealth University, Richmond, VA; Abraxis BioScience, Durham, NC

Abstract 1006

Phase II Trial of Nab-paclitaxel with Bevacizumab as a First-line, HER2- MBC Therapy



- Primary endpoints: Safety, ORR
- Secondary endpoints: TTP, OS

Two weekly nab-paclitaxel + bevacizumab arm closed early due to toxicity

Conlin et al. *J Clin Oncol* 2009; 27(suppl):42s (abstract 1006)

Phase II Trial of Nab-paclitaxel with Bevacizumab as a First-line, HER2- MBC Therapy: Safety

	Nab-paclitaxel + Bevacizumab					
	Every 3 weeks* (n = 73)		Every 2 weeks* (n = 54)		Every week (n = 78)	
	G2	G3/4	G2	G3/4	G2	G3/4
Sensory neuropathy	20 (27%)	22 (30%)	8 (15%)	26 (48%)	18 (23%)	31 (40%)
Arthralgia**	9 (12%)	4 (5%)	9 (17%)	1 (2%)	1 (1%)	0
Fatigue	NR	12 (16%)	NR	18 (33%)	NR	13 (17%)
Bone pain**	6 (8%)	2 (3%)	8 (15%)	3 (6%)	2 (3%)	1 (1%)
Febrile neutropenia	NR	2 (2%)	NR	1 (2%)	NR	0

*One death deemed not related to treatment
** No grade 4 events

Conlin et al. *J Clin Oncol* 2009; 27(suppl):42s (abstract 1006)

Phase II Trial of Nab-paclitaxel with Bevacizumab as a First-line, HER2-MBC Therapy: Efficacy

	Nab-paclitaxel + Bevacizumab		
	Every 3 weeks (n = 73)	Every 2 weeks (n = 54)	Every week (n = 78)
ORR	32 (44%)	21 (39%)	36 (46%)
CR	1 (1%)	1 (2%)	1 (1%)
PR	31 (42%)	20 (37%)	35 (45%)
	n = 38	n = 28	n = 32
TTP (95% CI)	7.7 months (7.0 – 10.3)	6.3 months (5.4 – 7.9)	9.0 months (7.3 – 14.2)

ORR overall *P* = .525
TTP data are not mature

Conlin et al. *J Clin Oncol* 2009; 27(suppl):42s (abstract 1006)

Conclusions: Targeted/Biologic therapies in MBC

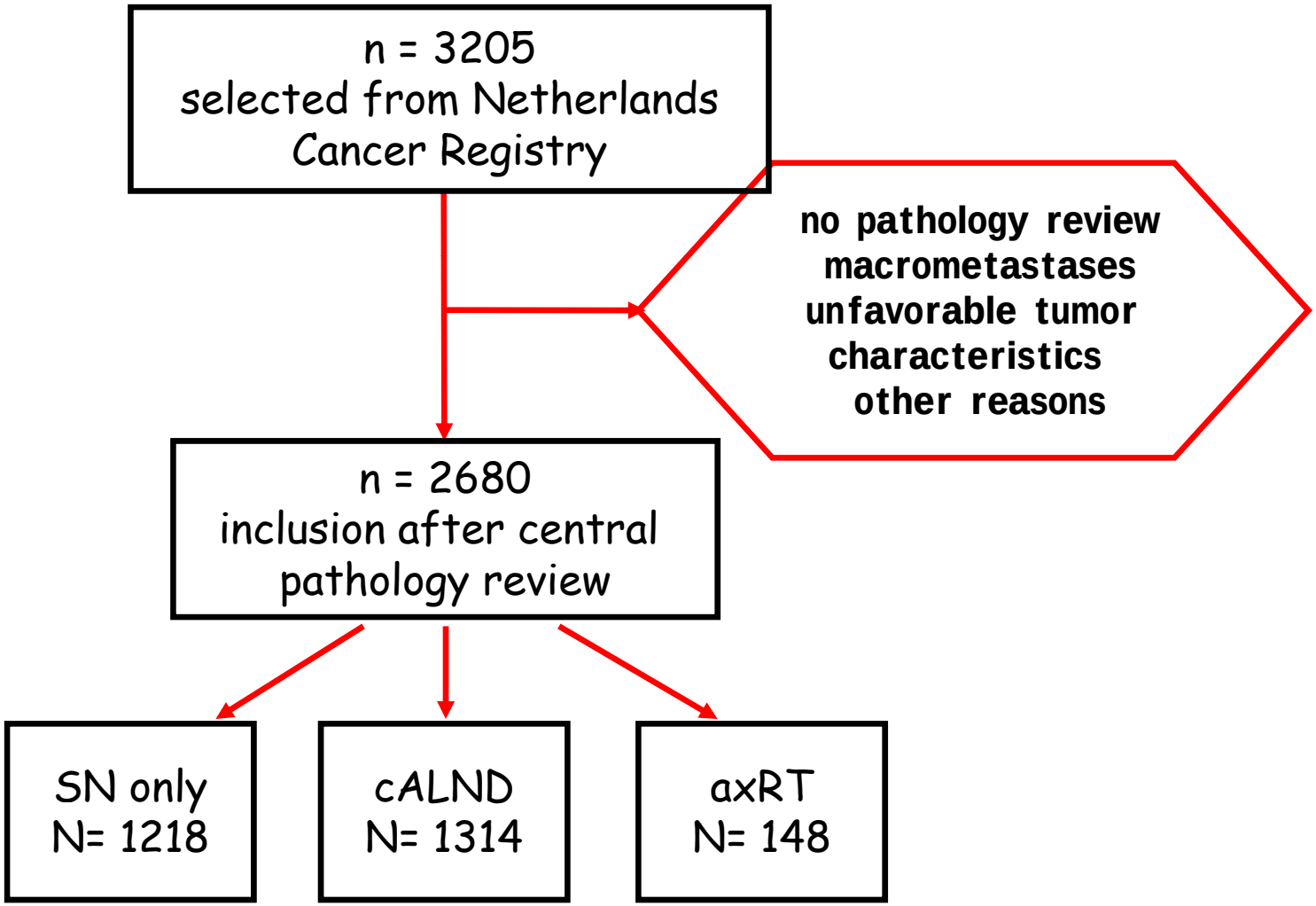
- Final results confirm potential of T DM-1 in resistant HER2 breast cancer
  - Lap/capecitabine versus T-DM1
  - T DM-1 plus pertuzumab
- Neratinib adds to exciting novel agents in trastuzumab-resistant MBC
- Bevazicumab improves outcome from chemotherapy regardless of agent used
  - BUT no survival benefit

Impact of omission of completion axillary lymph node dissection (cALND) or axillary radiotherapy (ax RT) in breast cancer patients with micrometastases (pN1mi) or isolated tumor cells (pN0[i+]) in the sentinel lymph node (SN): Results from the MIRROR study.

V. C. Tjan-Heijnen, M. J. Pepels, M. de Boer, G. F. Borm, J. A. van Dijck, C. H. van Deurzen, E. M. Adang, M. B. Menke-Pluymers, P. J. van Diest, P. Bult; Maastricht University Medical Centre, Maastricht, Netherlands; University Medical Centre St Radboud, Nijmegen, Netherlands; Comprehensive Cancer Centre East, Nijmegen, Netherlands; University Medical Centre Utrecht, Utrecht, Netherlands; Erasmus Medical Center-DDH, Rotterdam, Netherlands

Abstract CRA 506

Micrometastases and Isolated tumor cells: Relevant and Robust Or Rubbish?
A cohort study from the Netherlands in patients with ESBC who had undergone a SN procedure in 1997 – 2005



Baseline characteristics

		SN only n= 1218	cALND n= 1314	axRT n= 148	P-value SN only vs cALND / RT
SN status	pN0	60%	9%	3%	
	pN0(i+)	28%	30%	36%	<0.0001
	pN1mi	12%	61%	61%	
Tumor size	≤ 1 cm	36%	25%	24%	<0.0001
	1.1-2.0 cm	54%	58%	64%	
	2.1-3.0 cm	10%	18%	13%	
Adjuvant systemic therapy	No	87%	45%	39%	<0.0001
	Yes	13%	55%	61%	
RT breast	No	29%	35%	5%	0.09
	Yes	71%	65%	95%	

MV analysis: axillary recurrence (AR)

Variable	N	5-yrs AR	HR	95 % CI
pN0(sn) * cALND	125	1.6%	1.00	
pN0(sn) * SN only	732	2.3%	1.08	0.23-4.98
pN0(i+)(sn) * cALND/axRT	450	0.9%	1.00	
pN0(i+)(sn) * SN only	345	2.0%	2.39	0.67-8.48
pN1mi(sn) * cALND / axRT	887	1.0%	1.00	
pN1mi(sn) * SN only	141	5.0%	4.39	1.46-13.24

HR, corrected for age, tumor size, differentiation grade, hormone receptor status, adjuvant systemic therapy, radiotherapy to the breast

Efficacy of axRT

Variable	N	5-years AR
pN0(i+)(sn) * cALND	396	1.0%
pN0(i+)(sn) * axRT	54	0%
pN0(i+)(sn) * SN	345	2.0%
pN1mi(sn) * cALND	793	1.1%
pN1mi(sn) * axRT	94	0%
pN1mi(sn) * SN	141	5.0%

MV analysis: 5-yrs AR rate pN1mi(sn)

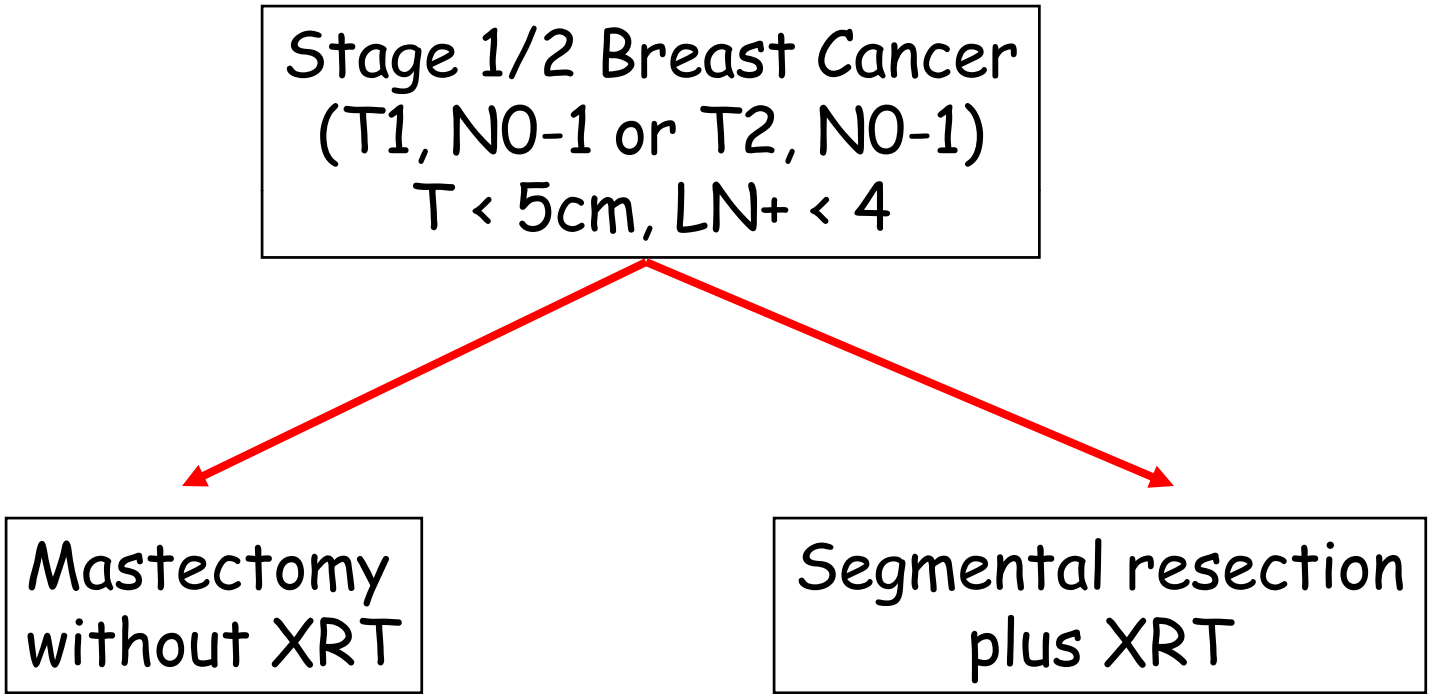
Variable	HR	95 % CI	P-value
Tumor size	8.62	1.38 – 53.84	0.021
Histological grade III	25.05	1.26 – 497.18	0.035
Negative ER / PgR status	4.96	1.48 – 16.62	0.010
No systemic therapy	1.36	0.47 – 3.99	0.572
No breast radiotherapy	1.01	0.36 – 2.88	0.979

Value of adjuvant radiation therapy in breast cancer patients with one to three positive lymph nodes undergoing a modified radical mastectomy and systemic therapy

S. Dawood, A. M. Gonzalez-Angulo, W. Woodward, F. Meric-Bernstam, K. Hunt, A. Buzdar, G. Hortobagyi, T. Buchholz; Dubai Hospital, Dubai, United Arab Emirates; UT M. D. Anderson Cancer Center, Houston, TX

Abstract CRA 507

Retrospective Analysis using MDACC Database



Patients who had mastectomy plus XRT were excluded

LRDFS (5 year estimate)

	Mast w/o XRT	Seg Mast + XRT	P value
T1NO (n=1191)	91%	92%	.93
T2N0 (n=997)	89%	91%	.99
T1N1 (n=876)	90%	91%	.65
T2N1 (n=676)	87%	91%	.009

Adjusted hazard ratio for T2N1 HR 3.0 p = .0008

DDFS (5 year estimate)

	Mast w/o XRT	Seg Mast + XRT	P value
T1NO (n=1191)	86%	87%	.11
T2N0 (n=997)	80%	85%	.38
T1N1 (n=876)	85%	90%	.004
T2N1 (n=676)	68%	77%	.0177

Adjusted hazard ratio for T2N1 HR 1.7 p = .007

Risk of breast cancer recurrence in women initiating tamoxifen with CYP2D6 inhibitors

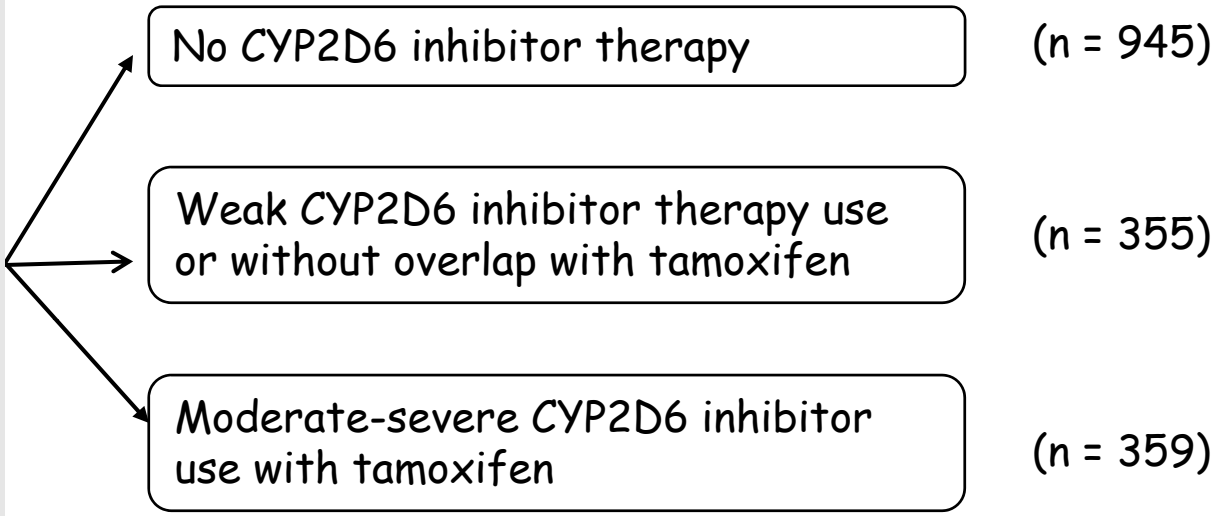
R. E. Aubert, E. J. Stanek, J. Yao, J. R. Teagarden, M. Subar, R. S. Epstein, T. C. Skaar, Z. Desta, D. A. Flockhart; Medco Health Solutions, Franklin Lakes, NJ; Indiana University School of Medicine, Indianapolis, IN

Abstract CRA 508

Risk of breast cancer recurrence in women initiating tamoxifen with CYP2D6 inhibitors

Eligibility:
- Continuous eligibility 6 mo prior to tamoxifen initiation
- Tamoxifen naïve (6 mo negative history)
- Tamoxifen duration ≥ 24 months
- Medication possession ratio of ≥ 0.7

(n = 1659)



- Retrospective cohort analysis of medical and pharmacy claims from the Medco Health Solutions integrated database
- Primary endpoint: hospitalization for breast cancer (event-free survival)
- Median duration of overlap between CYP2D6 inhibitors and tamoxifen: 287 days

Aubert et al. *J Clin Oncol* 2009; 27 (suppl): 18s (abstract CRA508).

Risk of breast cancer recurrence in women initiating tamoxifen with CYP2D6 inhibitors

	N	Breast cancer recurrence	HR*	*P* value
No CYP2D6 inhibitors	945	7.5%	reference	reference
Moderate/severe CYP2D6 inhibitors	407	14%	1.92 (1.36-2.73)	.0002
SSRIs				
Weak	137	9%	1.07 (0.79-1.45)	.677
Moderate/potent	213	16%	2.20 (1.46-3.31)	.0002

* HR relative to no CYP2D6 inhibitor group

- Concomitant use of tamoxifen with moderate-severe CYP2D6 inhibitors significantly increases the risk of breast cancer recurrence
- Moderate-potent SSRIs double the risk of recurrence, while weak SSRIs were not associated with increased risk

Aubert et al. *J Clin Oncol* 2009; 27 (suppl): 18s (abstract CRA508).

Concomitant CYP2D6 inhibitor use and tamoxifen adherence in early-stage breast cancer: A pharmacoepidemiologic study

V. Dezentje, N. J. Van Blijderveen, H. Gelderblom, H. Putter, M. P. Van Herk - Sukel, M. K. Casparie, A. C. Egberts, J. W. Nortier, H. J. Guchelaar; Leiden University Medical Center, Leiden, Netherlands; PHARMO institute for Drug Outcomes Research, Utrecht, Netherlands; Palga Foundation, Utrecht, Netherlands; Utrecht University, Pharmaceutical Sciences, Utrecht, Netherlands

Abstract CRA 509

Concomitant CYP2D6 inhibitor use and tamoxifen adherence in early stage breast cancer

Inclusion criteria:
- breast cancer resection
- Tamoxifen use ≥ 120 days
- CYP2D6 inhibitor use ≥ 60 days

(n = 3147)

→ Tamoxifen only (n = 1749)

→ Tamoxifen + CYP2D6 inhibitor (n = 150)

- **Retrospective pharmaco-epidemiologic study**
- **Databases: PHARMO, PALGA, Dutch Medical Register**
- **Univariate Cox regression of event-free time:**

- **No difference when only strong CYP2D6 inhibitors included**

CYP2D6 inhibitor use	HR	95% CI	*P* value
No use	1.00	reference	reference
Use ≥ 60 days	0.95	0.60-1.50	0.73

Dezentje et al. *J Clin Oncol* 2009; 27 (suppl): 18s (abstract CRA509).

Practice-changing?

- Definitely
  - PARP inhibitor in TN breast cancer (soon)
  - Capecitabine just as good as taxanes with bevazicumab (but this kind of was SOC?)
- Probably
  - Single agent cisplatin in TN breast cancer, especially if BRCA1-related
  - T-DM1 in HER2-positive breast cancer
- Possibly
  - Full axillary dissection for micromets (especially high grade, ER-negative, ? triple negative)
- Jurys out
  - CYP2D6 inhibitors in patients receiving tamoxifen
  - Post-mastectomy XRT for 1 to 3 positive axillary LNs