Associazione Italiana Radioterapia Oncologica
Gruppo di Studio per la Patologia Mammaria

III Zoom Journal Club 2013

Non un Congresso "classico" né un Corso, ma un'occasione per concreti aggiornamenti, confronto e dibattito su alcuni "Hot Topics 2013" dalla letteratura relativa alla radioterapia mammaria.

Bologna
21 Febbraio 2014
NH Hotel De La Gare

NOVITA' DAL 2013 ANNUAL MEETING SAN ANTONIO BREAST CANCER SYMPOSIUM

CATIA ANGIOLINI
Oncologia Medica
Ospedale San Jacopo

ITT Istituto Toscano Tumori

SST Azienda USL 3 Pistoia
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SAN ANTONIO BREAST CANCER SYMPOSIUM®

2013

BREAST CANCER RISK REDUCTION (PREVENTION)

Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial

*Jack Cuzick, Ivana Sestak, John F Forbes, Mitch Dowsett, Jill Knox, Simon Cawthorn, Christobel Saunders, Nicola Roche, Robert E Mansel, Gunter von Minckwitz, Bernardo Bonanni, Tiina Palva, Anthony Howell, on behalf of the IBIS-II investigators**

Trial schema

Postmenopausal women:
- Ages 40-70
- Increased risk of breast cancer:
  - Family history
  - Atypia / LCIS
  - Breast density
- No HRT

N=3864

Anastrozole 1 mg/day (N=1920)

Matching placebo (N=1944)

5 years

FU Ongoing

	Baseline	6 M	12 M	24 M	36 M	48 M	60M
Clinic visit	X	X	X	X	X	X	X
Mammogram	X			X		X	
Blood	X		X				X
DXA	X						

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Endpoints

- Primary endpoint:
  - Breast cancer incidence
    (both invasive and DCIS)

- Secondary endpoints:
  - ER-positive invasive breast cancer
  - Breast cancer mortality
  - Non-breast cancer deaths
  - Other cancers
  - Cardiovascular/thromboembolic disease
  - Fractures
  - Adverse events

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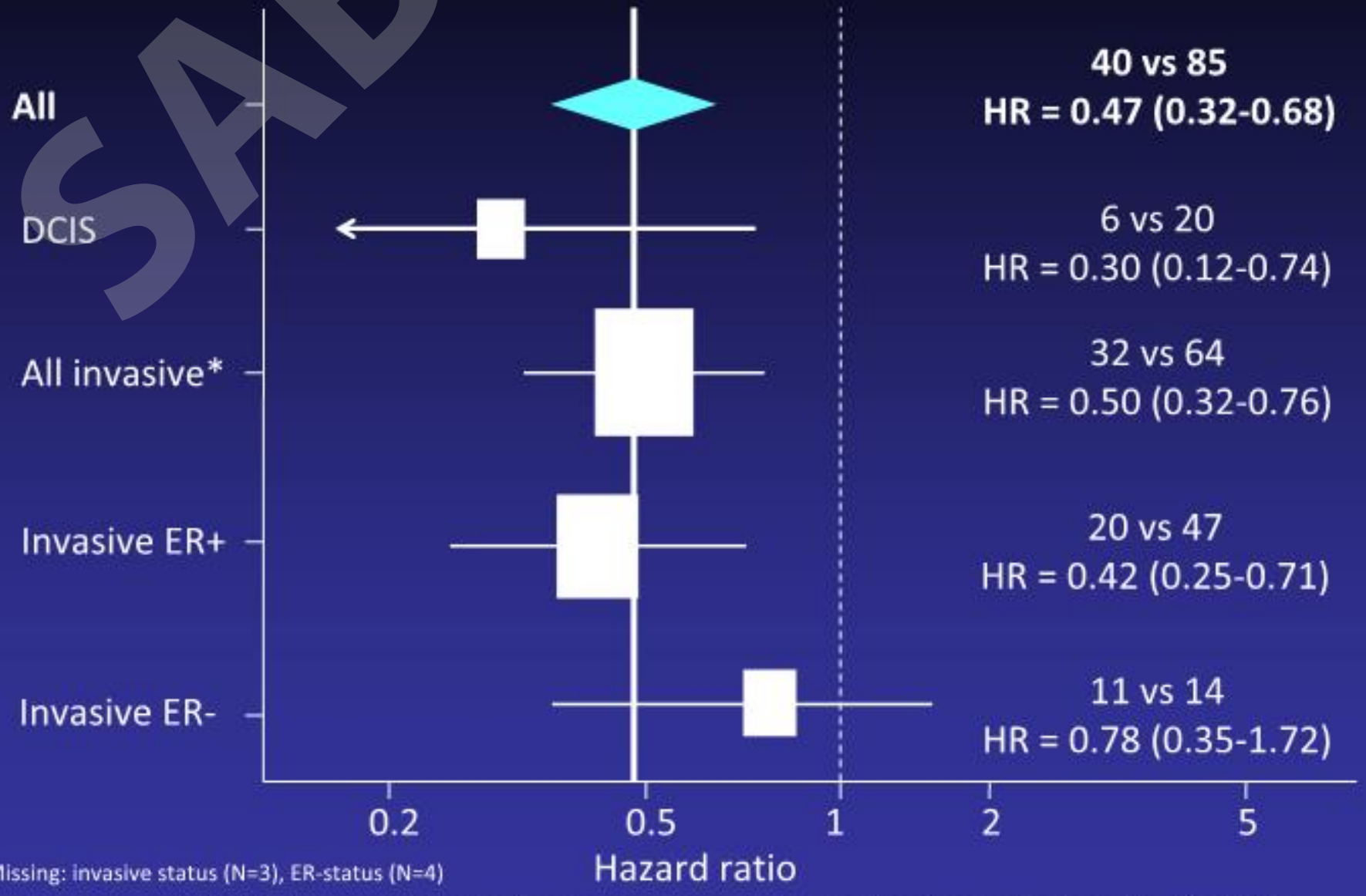
Subgroup analysis



*Missing: invasive status (N=3), ER-status (N=4)

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Preventive Anastrozole Reduced Incidence of Breast Cancers

- Significant reduction in incidence of all breast cancers with anastrozole vs placebo (*P* < .0001)

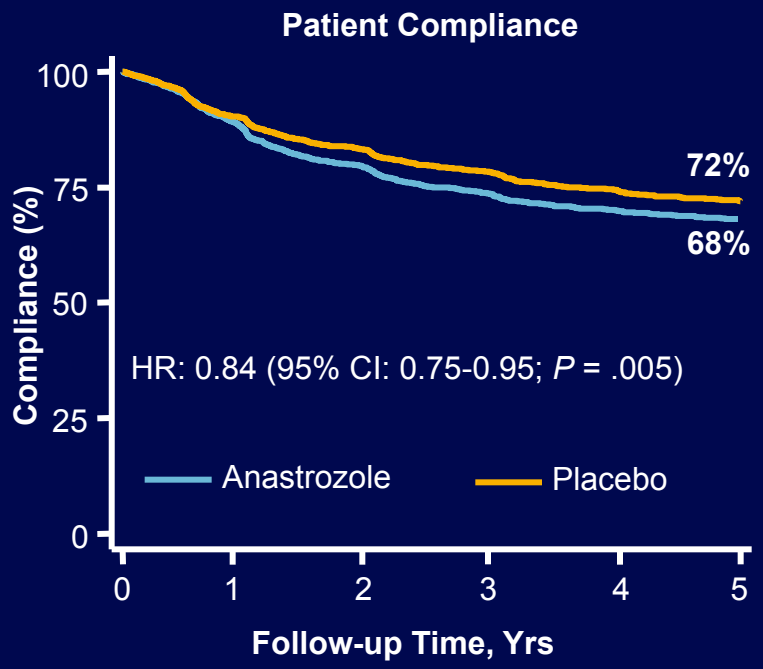
Cancer Type, n	Anastrozole (n = 1920)	Placebo (n = 1944)	HR (95% CI; *P* Value)
All breast cancer	40	85	0.47 (0.32-0.68; < .0001)
Nonbreast cancers	40	70	
▪ Skin	14	27	
▪ Gastrointestinal	4	12	
▪ Gynecologic	8	12	
▪ Other	14	19	

- Unexpected reduction in other cancers with anastrozole vs placebo (2.1% vs 3.6%; RR: 0.58; 95% CI: 0.39-0.85)

Cuzick J, et al. SABCS 2013. Abstract S3-01. Cuzick J, et al. Lancet. 2013;[Epub ahead of print].

Preventive Anastrozole: Toxicity and Patient Compliance

Select Adverse Events, %	Anastrozole (n = 1920)	Placebo (n = 1944)	RR (95% CI)
Fractures	8.5	7.7	1.11 (0.90-1.38)
Musculoskeletal	63.9	57.8	1.10 (1.05-1.16)
▪ Arthralgia (any)	50.6	46.0	1.10 (1.03-1.18)
▪ Arthralgia (severe)	8	6	1.24 (0.99-1.56)
▪ Joint stiffness	7.4	4.9	1.51 (1.17-1.94)
▪ Carpal tunnel/ nerve compression	3.5	2.2	1.58 (1.08-2.30)
Vasomotor (any)	56.8	49.4	1.15 (1.08-1.22)
Vasomotor (severe)	8	7	1.20 (0.95-1.50)
Gynecologic	23.9	21.8	1.10 (0.98-1.24)
▪ Vaginal dryness	19	16	1.19 (1.03-1.37)



- Total mortality 0.9% for both arms (RR: 1.07; 95% CI: 0.55-2.07)

Cuzick J, et al. SABCS 2013. Abstract S3-01. Cuzick J, et al. Lancet. 2013;[Epub ahead of print].
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IBIS-II: Trial Conclusions

- 53% reduction in breast cancer incidence compared with placebo in high-risk postmenopausal women
  - Unexpected reduction in incidence of other cancer types
- Anastrozole well tolerated compared with placebo by most high-risk postmenopausal women
  - Small, nonsignificant increase in fractures
  - 10% increase in musculoskeletal adverse events
- Anastrozole effective risk-reduction option for high-risk postmenopausal women

Cuzick J, et al. SABCS 2013. Abstract S3-01. Cuzick J, et al. Lancet. 2013;[Epub ahead of print].

SAN ANTONIO BREAST CANCER SYMPOSIUM®

2013

NEOADJUVANT THERAPY

SAN ANTONIO BREAST CANCER SYMPOSIUM

San Antonio Breast Cancer Symposium - Cancer Therapy and Research Center at UT Health Science Center – December 10-14, 2013

NEO-ALTTO

Neo-Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation Trial

The association between event-free survival and pathological complete response to neoadjuvant lapatinib, trastuzumab or their combination in HER2-positive breast cancer. Survival follow-up analysis of the NeoALTTO study (BIG 1-06)

Martine Piccart-Gebhart, Andrew P Holmes, Evandro de Azambuja, Serena Di Cosimo, Ramona Swaby, Michael Untch, Christian Jackisch, Istvan Lang, Ian Smith, Fran Boyle, Binghe XU, Carlos Barrios, Richard Gelber, Holger Eidtmann, José Baselga

On behalf of the NeoALTTO Study Team

BIG Breast International Group

SOLTI

gsk

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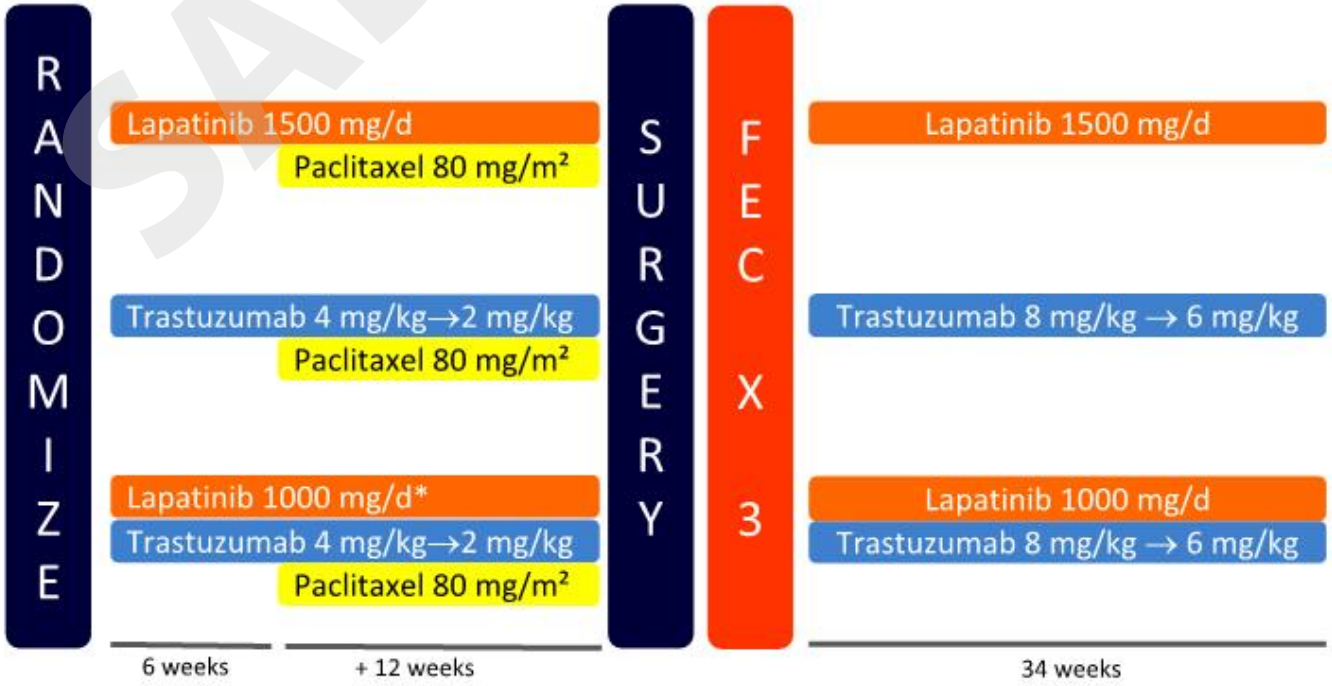
NeoALTTO TRIAL in 455 WOMEN WITH HER2+ (ASCO/CAP 2007) BREAST CANCER ≥ 2 CM



**Amendment-2 October 2008, reduced dose of lapatinib to 750 mg/d with paclitaxel 54/152 had protocol-driven reduction*

Baselga J et al; SABCS 2010; Lancet 2012

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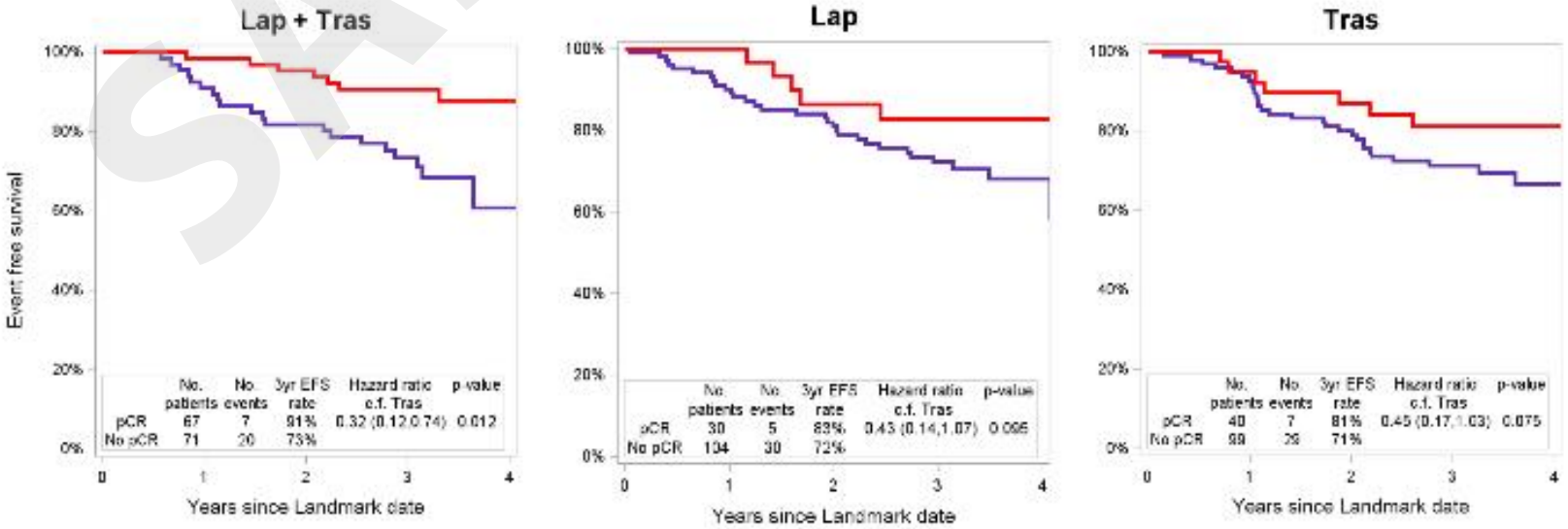
LANDMARK POPULATION BY ARM: EFS BY PCR



Tests for interaction:

Lap + Tras vs. Tras x pCR, p=0.42

Lap vs. Tras x pCR, p=0.94

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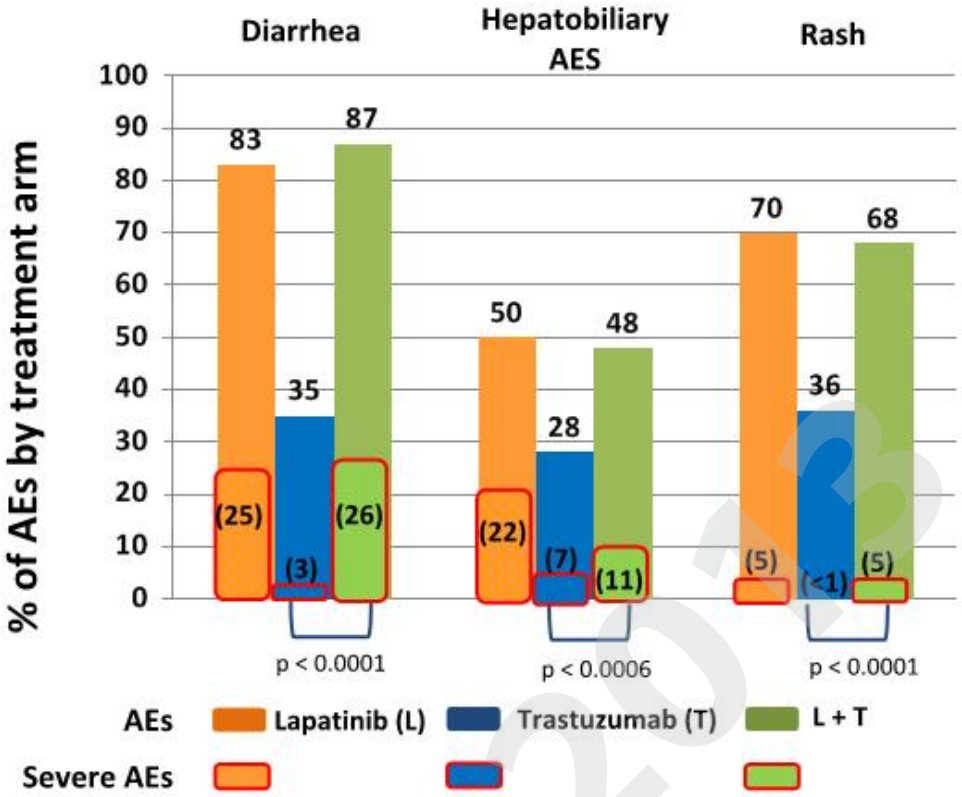
MAIN DIFFERENCES IN AEs BY TREATMENT ARM



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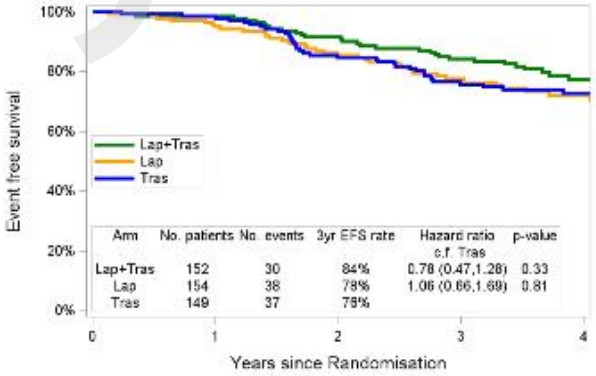
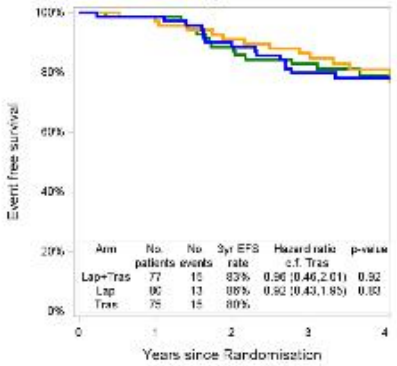
EVENT-FREE SURVIVAL (EFS) ANALYSIS

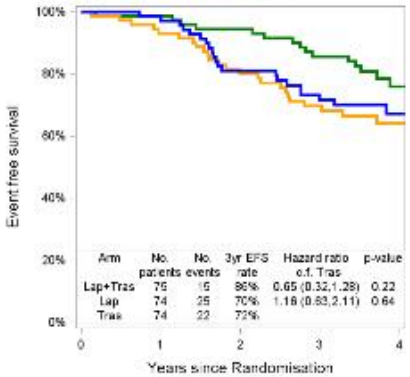
All patients



HR positive



HR negative



Tests for interaction according to HR status

Lap + Tras vs. Tras p=0.48

Lap vs. Tras p=0.56

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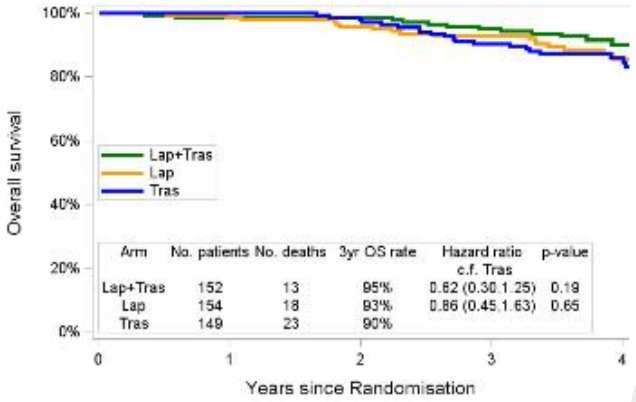
OVERALL SURVIVAL (OS) ANALYSIS

All patients



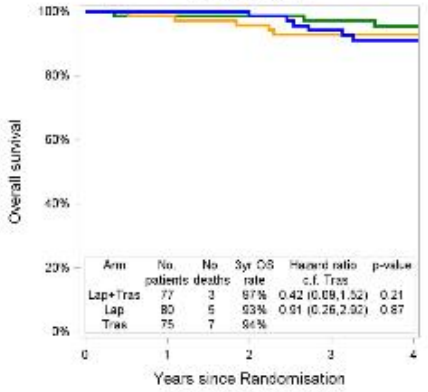
Arm	No. patients	No. deaths	3yr OS rate	Hazard ratio c.f. Tras	p-value
Lap+Tras	152	13	95%	0.62 (0.30,1.25)	0.19
Lap	154	18	93%	0.86 (0.45,1.63)	0.65
Tras	149	23	90%		

Tests for interaction according to HR status

Lap + Tras vs. Tras p=0.54

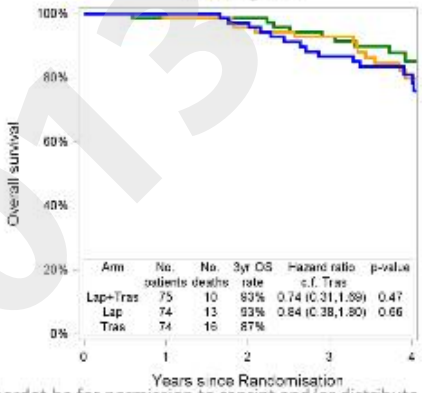
Lap vs. Tras p=0.90

HR positive



Arm	No. patients	No. deaths	3yr OS rate	Hazard ratio c.f. Tras	p-value
Lap+Tras	77	3	97%	0.42 (0.09,1.52)	0.21
Lap	80	5	93%	0.91 (0.26,2.92)	0.87
Tras	75	7	94%		

HR negative



Arm	No. patients	No. deaths	3yr OS rate	Hazard ratio c.f. Tras	p-value
Lap+Tras	75	10	93%	0.74 (0.31,1.89)	0.47
Lap	74	13	93%	0.84 (0.38,1.80)	0.66
Tras	74	16	87%		

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NEO-ALTTO/BIG 1-06: Conclusions

- Patients achieving pathologic CR had significantly better outcome compared with patients not achieving pathologic CR
- Adverse events consistent with established safety profile for lapatinib and/or trastuzumab
- Ongoing ALTTO trial will provide additional data on the long-term outcome in the adjuvant setting with dual HER2+ blockade

Piccart-Gebhart M, et al. SABCS 2013. Abstract S1-01.

San Antonio Breast Cancer Symposium Cancer Therapy and Research Center at UT Health Science Center December 10–14, 2013

Final Analysis of a Phase II, 3-Arm, Randomized Trial of Neoadjuvant Trastuzumab or Lapatinib or the Combination of Trastuzumab and Lapatinib, Followed by 6 cycles of Docetaxel and Carboplatin with Trastuzumab and/or Lapatinib in Patients with HER2+ Breast Cancer (TRIO-US B07)

Sara Hurvitz, Jeffrey Miller, Robert Dichmann, Alejandra Perez, Ravindranath Patel, Lee Zehngebot, Heather Allen, Linda Bosserman, Brian DiCarlo, April Kennedy, Armando Giuliano, Carmen Calfa, David Molthrop, Aruna Mani, Judy Dering, He-Jing Wang, Brad Adams, Diego Martinez, Hsiao-Wang Chen, Jason Zoeller, Joan Brugge, Dennis Slamon

TRIO Translational Research In Oncology

UCLA

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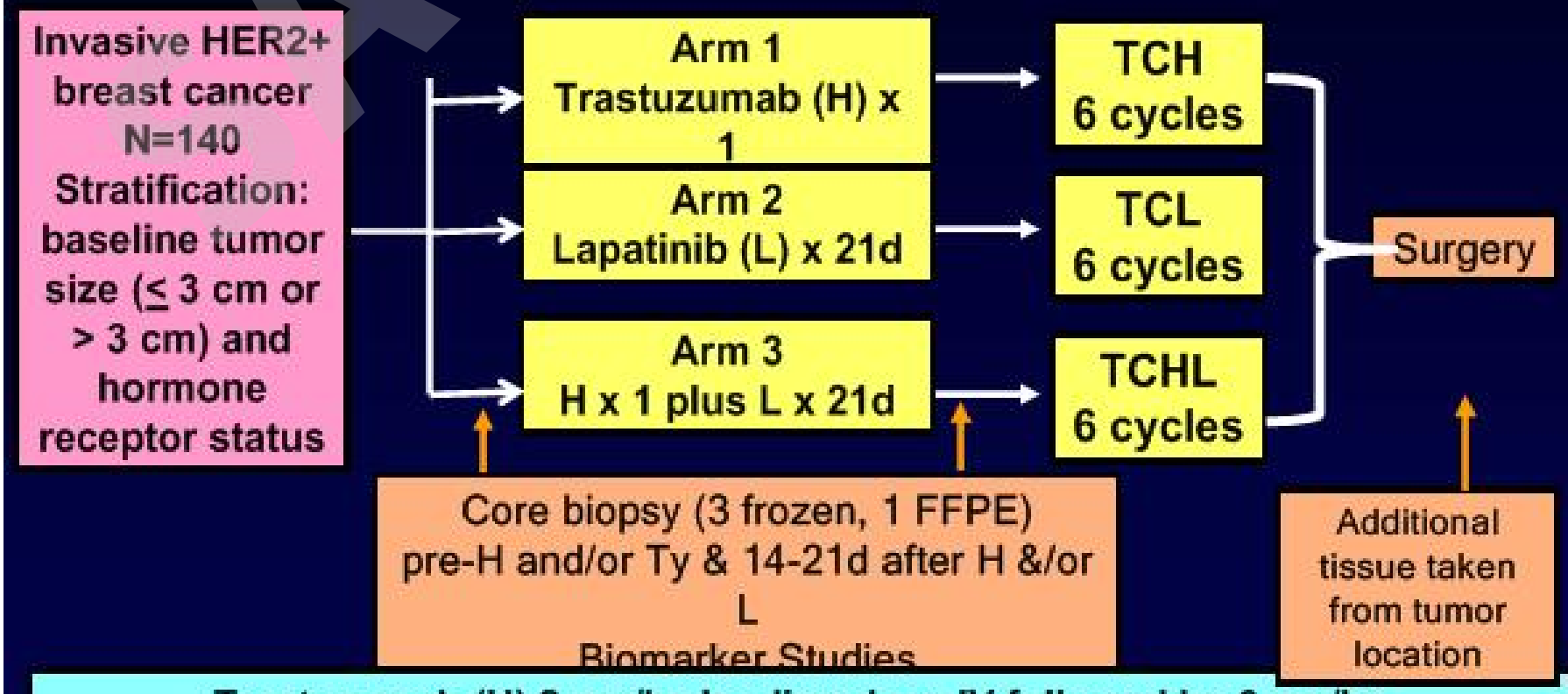
TRIO-US B07: Study Design



Trastuzumab (H) 8 mg/kg loading dose IV followed by 6 mg/kg
Lapatinib (L) 1000 mg po daily
Docetaxel (T) 75 mg/m2 Carboplatin (C) AUC 6 IV q3 week
First 20 patients on TCHL; then randomize 1:1:1

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Major Eligibility Criteria

- Women aged 18 to 70 years, inclusive
- Her2+ by FISH or SISH (local)
- Stage I, II or III breast ca
  - If stage I, tumor size must be at least 1 cm and must be either
    - (1) grade > 1,
    - (2) ER & PR negative, or
    - (3) patient 35 years of age or younger
  - Inflammatory breast cancer allowed
- No bilateral breast cancer or metastatic disease

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Endpoints

- Primary
  - Pathologic Complete Response (pCR) rate (absence of invasive cancer in the breast and axilla)

- Secondary
  - Safety and tolerability
  - Rate of CHF or drop in LVEF (>10% points from baseline and below lower limits of normal) in each of the three treatment arms
  - Molecular analyses
    - gene expression and/or biomarker changes that may be correlated with or predict pCR

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Intent to Treat (ITT) Population

- From October 2008-December 2012, 130 patients enrolled
- Study closed at 130 patients due to end in funding
- ITT Population: Any eligible patient who received at least one dose of study treatment (N=128)
  - Two patients of 130 excluded from ITT analyses (1 ineligible, 1 withdrew consent prior to receiving any treatment)
- 25 off study prior to end of tx, 103 completed all tx

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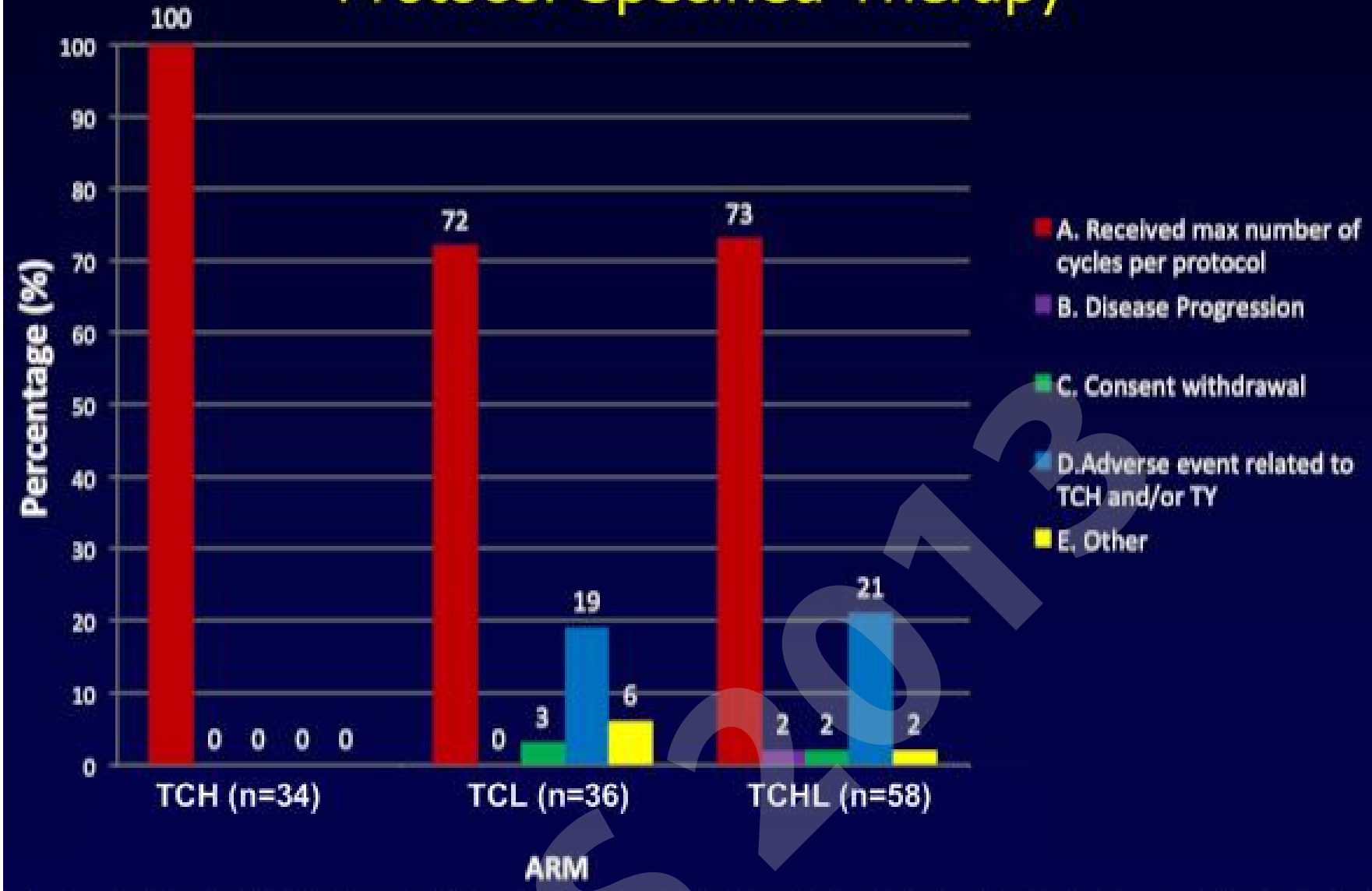
100% of Patients in TCH Arm Completed All Protocol-Specified Therapy



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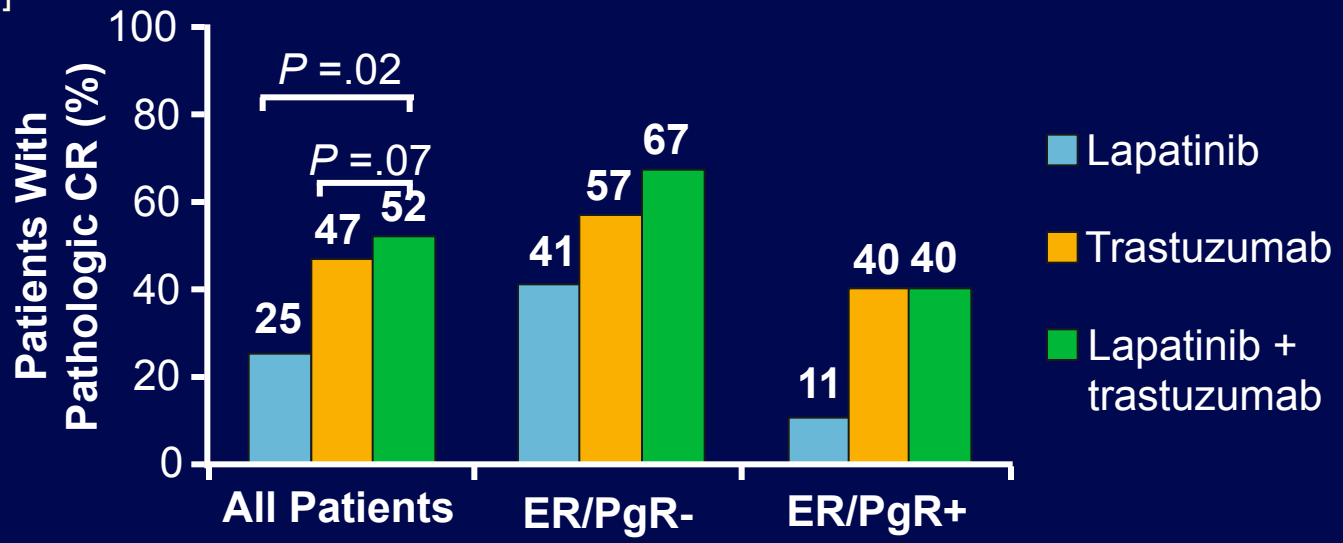
TRIO-US B07: Pathologic Complete Response of Lapatinib and/or Trastuzumab

- Other trials suggest trastuzumab plus lapatinib may potentially improve pCR vs lapatinib or trastuzumab alone[1-4]
- Current study suggests pCR similar for trastuzumab and trastuzumab plus lapatinib; lapatinib alone less favorable than other treatment arms[5]



1. Baselga J, et al. Lancet. 2012;18:633-640. 2. Robidoux A, et al. Lancet Oncol. 2013;14:1183-1192. 3. Carey LA, et al. ASCO 2013. Abstract 500. 4. Guarneri, et al. J Clin Oncol. 2012;30:1989-1995. 5. Hurvitz S, et al. SABCS 2013. Abstract S1-02. *Reproduced with permission.*

TRIO-US B07: Safety of Lapatinib and/or Trastuzumab

Grade 3/4 Toxicity ≥ 5%, %	TCH (n = 34)	TCL (n = 36)	TCHL (n = 58)
Diarrhea	**3**	14	**28**
Pain	9	19	19
Neutropenia	12	14	13
Infection	6	14	9
Anemia	9	8	7
Hypokalemia	6	6	7
Fatigue	6	8	5
Dehydration	3	0	9
Thrombocytopenia	3	9	3

Cardiac Safety, n	TCH (n = 34)	TCL (n = 36)	TCHL (n = 58)
> 10% LVEF decline and below LLN	1	2	1
Left ventricular dysfunction			
▪ All grade	2	2	2
▪ Grade 3/4	0	0	0
Total	3	4	3

Hurvitz S, et al. SABCS 2013. Abstract S1-02. *Reproduced with permission.*

TRIO-US B07: Conclusions

- Neoadjuvant chemotherapy with lapatinib and/or trastuzumab achieved similar rate of pCR
  - Differs from findings of other studies of lapatinib and/or trastuzumab
- Addition of lapatinib increased treatment-related toxicity
  - May limit planned chemotherapy and HER2-targeted therapy dose and schedule
- Molecular analyses ongoing to evaluate specific genes and signaling pathways that may affect treatment response

Hurvitz S, et al. SABCS 2013. Abstract S1-02.

Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant weekly paclitaxel followed by dose-dense AC on pathologic complete response rates in triple-negative breast cancer: CALGB/Alliance 40603

William M Sikov, Donald A Berry, Charles M Perou, Baljit Singh, Constance Cirrincione, Sara Tolaney, Charles S Kuzma, Timothy J Pluard, George Somlo, Elisa Porte, Mehra Golshan, Jennifer R Bellon, Deborah Collyar, Olwen M Hahn, Lisa A Carey, Clifford Hudis, and Eric P Winer for the CALGB/Alliance

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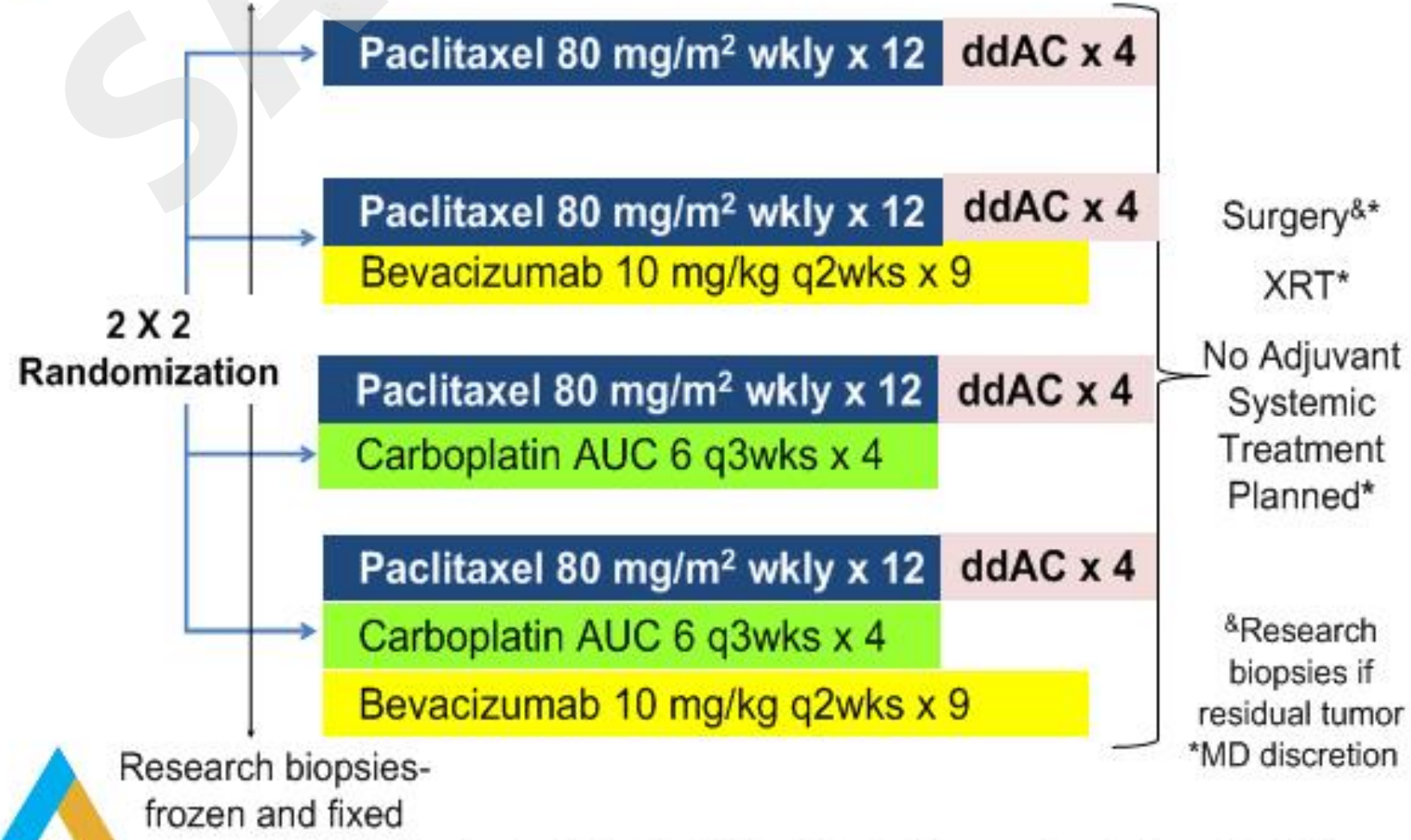
CALGB 40603: Schema – Randomized Phase II



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Statistical Design – Primary Endpoints

Primary endpoint – pCR Breast (ypT0/is N any)

- Assuming a pCR rate of 35% with standard regimen
  - >95% power to detect an increase of pCR with carboplatin or bevacizumab (1-sided alpha of <0.05)
  - Goal of 362 raised to 445 for correlative studies
  - Including pCR rates in basal-like subset
- Stratified by clinical stage II vs. III
- **Not powered to compare individual treatment arms or to detect differences in RFS or OS**

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CALGB 40603: Eligibility

- Clinical Stage II-III (except T4d – inflammatory BC)
- ER + PR ≤10%, HER(-) (IHC 0-1+ or FISH <2.0)
- No contraindication to treatment with bevacizumab
- Baseline evaluation including breast MRI (or US)
- FNA or biopsy of suspicious axillary LN recommended
- Pre-treatment SLN sampling permitted in clinical N0

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Select Grade ≥3 Toxicities

	Chemo	Chemo + Bev	Chemo + Carbo	Chemo + Carbo + Bev
Neutropenia	22%	27%	56%	67%
Thrombocytopenia	4%	3%	20%	26%
Febrile neutropenia	7%	9%	12%	24%
Hypertension	2%	12%	0%	10%*
Nausea / Vomiting	4% / 2%	4% / 2%	3% / 2%	8% / 4%
Fatigue	10%	12%	10%	20%
Stopped treatment due to toxicity	0%	10%	6%	12%

* One cardiac death attributed to uncontrolled HTN

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

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Serious Adverse Events

	Chemo	Chemo + Bev	Chemo + Carbo	Chemo + Carbo + Bev
Total (# pts)	15	39	39	46
FN during AC	5	15	8	16
N/V/dehydration	1	5	5	6
Bleeding	0	2	0	5
DVT or PE	1	6	1	4
Infections (nl ANC)	4	10	2	9
GI perforation	0	1	0	1

Early post-op complications (hematoma/seroma) +/- Bev: 9% vs. 5%
Delayed surgical complications (wound healing) +/- Bev: 4% vs. 1%

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CALGB 40603: Pathologic CR

pCR Breast (ypT0/is N any), %	No Carbo (n = 212)	Carbo (n = 221)	Bev Effect	
No bev (n = 218)	42	53	48	Odds ratio: 1.58;
Bev (n = 215)	50	67	59	*P* = .0089
Carbo effect	46 Odds ratio: 1.76;	60 *P* = .0018	Carbo/bev interaction *P* = .52	

pCR Breast /Axilla (ypT0/is N0), %	No Carbo (n = 212)	Carbo (n = 221)	Bev Effect	
No bev (n = 218)	39	49	44	Odds ratio: 1.36;
Bev (n = 215)	43	60	52	*P* = .0570
Carbo effect	41 Odds ratio: 1.71;	54 *P* = .0029	Carbo/bev interaction *P* = .43	

Sikov WM, et al. SABCS 2013. Abstract S5-01. *Reproduced with permission.*

CALGB 40603: Conclusions

- No interaction between bevacizumab and carboplatin for efficacy
- Addition of bevacizumab increased pCR in breast but not in breast/axilla
  - Increases in grade 3 hypertension, febrile neutropenia, serious infections, bleeding, thromboembolic and surgical complications
- pCR benefit may be outweighed by increased toxicity
- Addition of carboplatin increased pCR in breast and breast/axilla
  - Increases in grade 3/4 neutropenia, thrombocytopenia
  - Also increased frequency of paclitaxel dose modifications
- pCR benefit independent of bevacizumab
- Optimal dose with paclitaxel not yet known

Sikov WM, et al. SABCS 2013. Abstract S5-01.

SAN ANTONIO BREAST CANCER SYMPOSIUM®

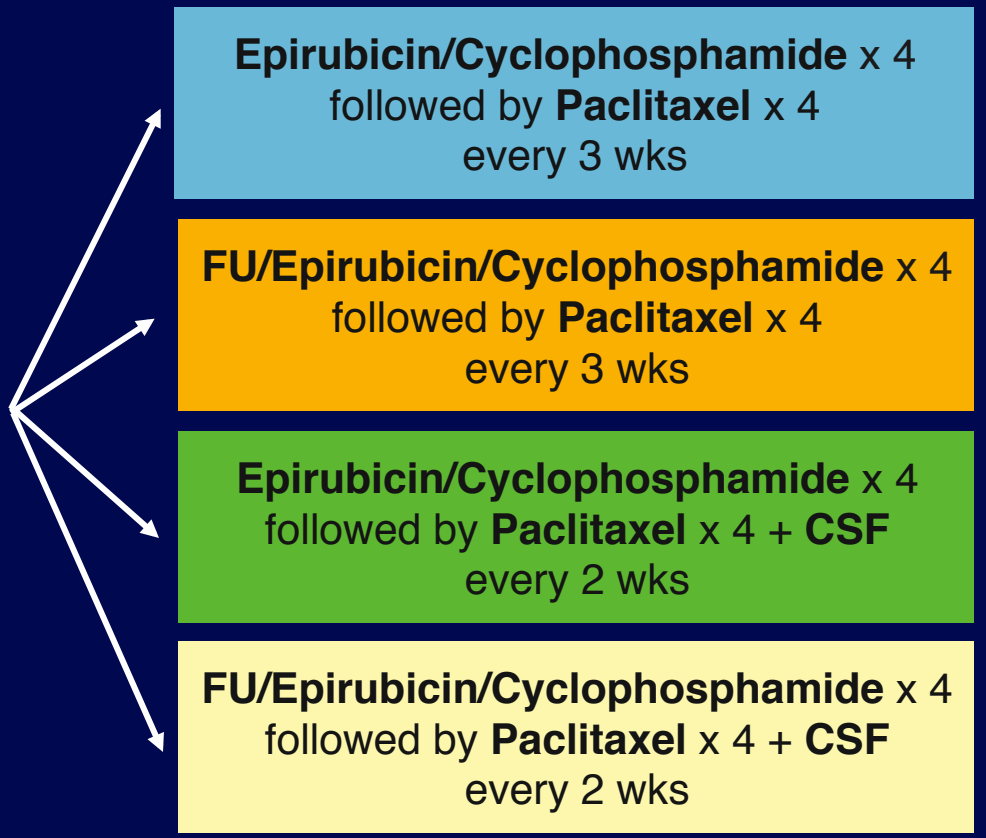
2013

ADJUVANT THERAPY

GIM-2 Trial: EC or FEC Followed by Trastuzumab in Early Breast Cancer

- Final results of the randomized phase III trial

Patients 18-70 yrs of age with completely resected invasive breast cancer; ≥ 1 positive regional node; any menopausal status, any ER status (N = 2091)
Accrual 4/2003-7/2006



Median follow-up: 7 yrs

Cognetti F, et al. SABCS 2013. Abstract S5-06.

GIM-2 Efficacy: Outcome by Treatment or Schedule

Outcome, %	Epirubicin/ Cyclophosphamide	FU/ Epirubicin/ Cyclophosphamide	*P* Value
Invasive DFS	79	78	.526
OS	92	91	.227

Outcome, %	Every 2 Wks	Every 3 Wks	*P* Value
Invasive DFS	81	76	.002
OS	94	89	< .0001

Cognetti F, et al. SABCS 2013. Abstract S5-06.

GIM-2: Grade 3/4 Adverse Events by Treatment Schedule

Grade 3/4 Adverse Events in ≥ 1% of Patients in Either Arm, %	Every 2 Wks (n = 988)	Every 3 Wks (n = 1069)
Neutropenia*	14.9	42.8
Nausea	4.0	3.3
Neuropathy	3.5	2.6
Bone pain	3.1	2.0
Myalgia	3.1	1.6
Vomiting	2.7	1.9
Asthenia	2.8	1.6
ALT	1.9	0.5
Anemia*	1.4	0.2

*Statistically significant difference.

Cognetti F, et al. SABCS 2013. Abstract S5-06.

GIM-2: Conclusions

- Dose-dense adjuvant chemotherapy in patients with node-positive early breast cancer improves invasive DFS and OS
  - However, addition of fluorouracil to epirubicin and cyclophosphamide did not improve clinical outcomes
  - Use of colony-stimulating factor allowed safe administration of every-2-wk dosing
- Dose-dense chemotherapy regimen used (epirubicin + cyclophosphamide) is an option for adjuvant treatment of patients with node-positive early breast cancer

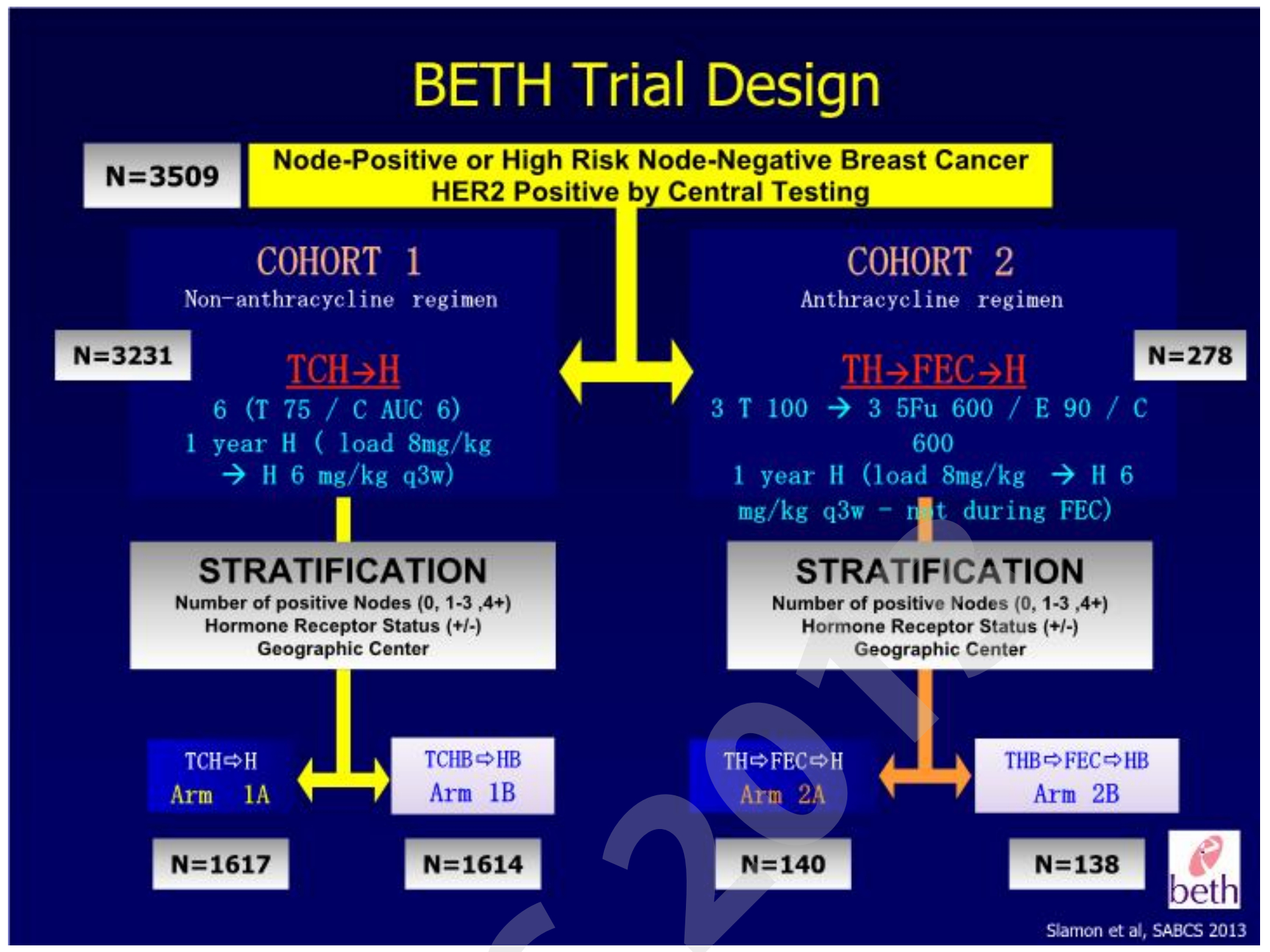
Cognetti F, et al. SABCS 2013. Abstract S5-06.

BETH: A Randomized Phase III Study Evaluating Adjuvant Bevacizumab Added to Trastuzumab/Chemotherapy for Treatment of HER2+ Early Breast Cancer

TRIO -011 / NSABP B-44-1 / BO20906

D.Slamon, S.Swain, M.Buyse, M.Martin, C.Geyer, Y-H.Im, T.Pienkowski, S-B.Kim, N.Robert, G.Steger, J.Crown, S.Verma, W.Eiermann, J.Costantino, SA.Im, E.Mamounas, L.Schwartzberg, A.Paterson, J.Mackey, L.Provencher, M.Press, M.Thirlwell, V.Bee-Munteanu, V.Henschel, A.Crepelle-Flechais, N.Wolmark

BETH Trial Design



Slamon et al, SABCS 2013

High Risk HER2+ eBC Defined as:

- **HER2+, Node-positive disease**
- **HER2+, Node-negative disease and at least one of the following criteria:**
  - Pathologic tumor size >2.0 cm
  - ER negative and PgR negative
  - Histologic and/or nuclear grade 2 or 3
  - Age <35 years

SABCS

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Slamon et al, SABCS 2013

Study Objectives

Primary Objective

Compare invasive disease-free survival (IDFS) in pts treated with chemo+trastuzumab vs chemo+trastuzumab+bevacizumab

- 296 events required for 85% power to detect a HR of 0.70

Secondary Objectives

- IDFS within chemotherapy cohorts
- Disease-free survival (DFS)
- Overall survival (OS)
- Recurrence-free interval (RFI)
- Distant recurrence-free interval (DRFI)
- Cardiac toxicity
- Non-cardiac toxicity
- Molecular predictors of efficacy and cardiac dysfunction

2013

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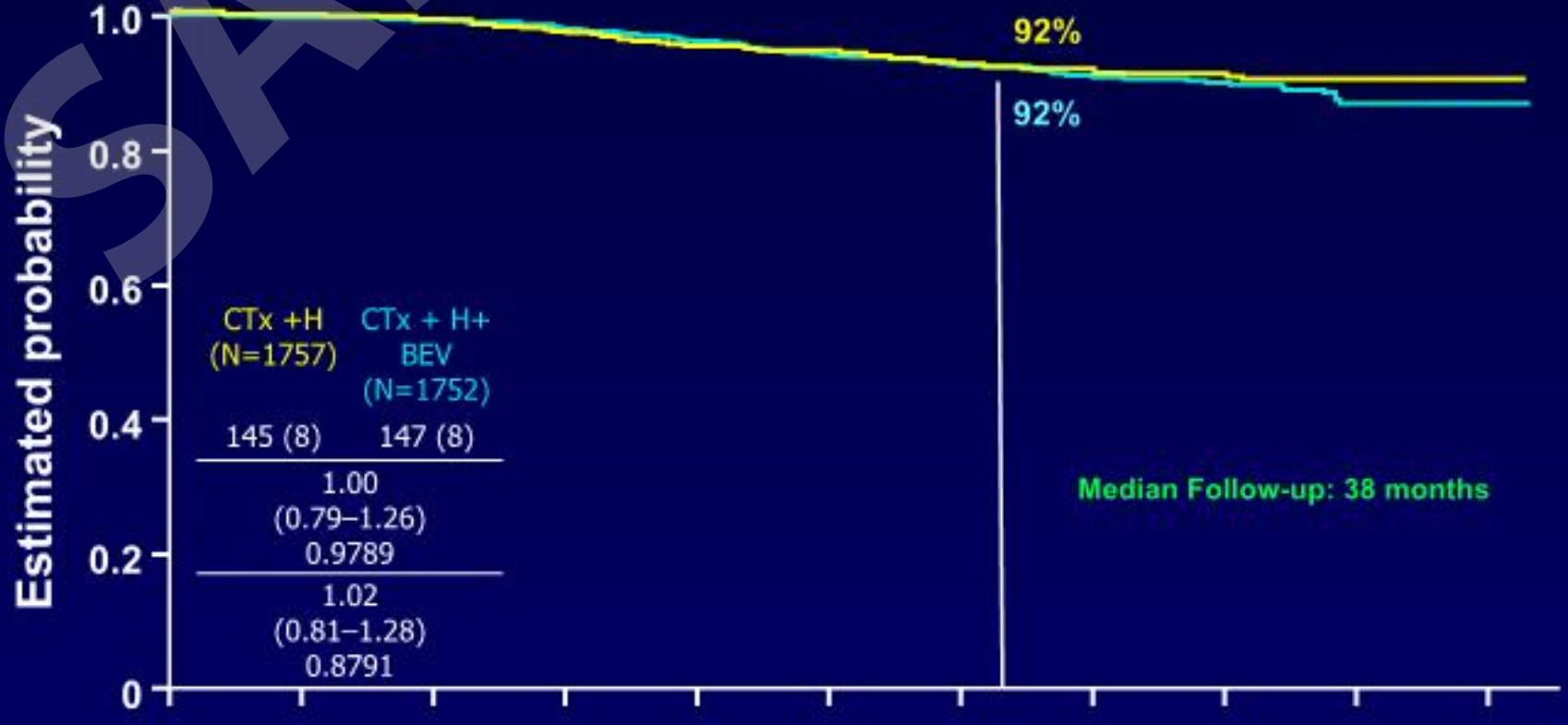
Primary Endpoint:
IDFS for overall study population



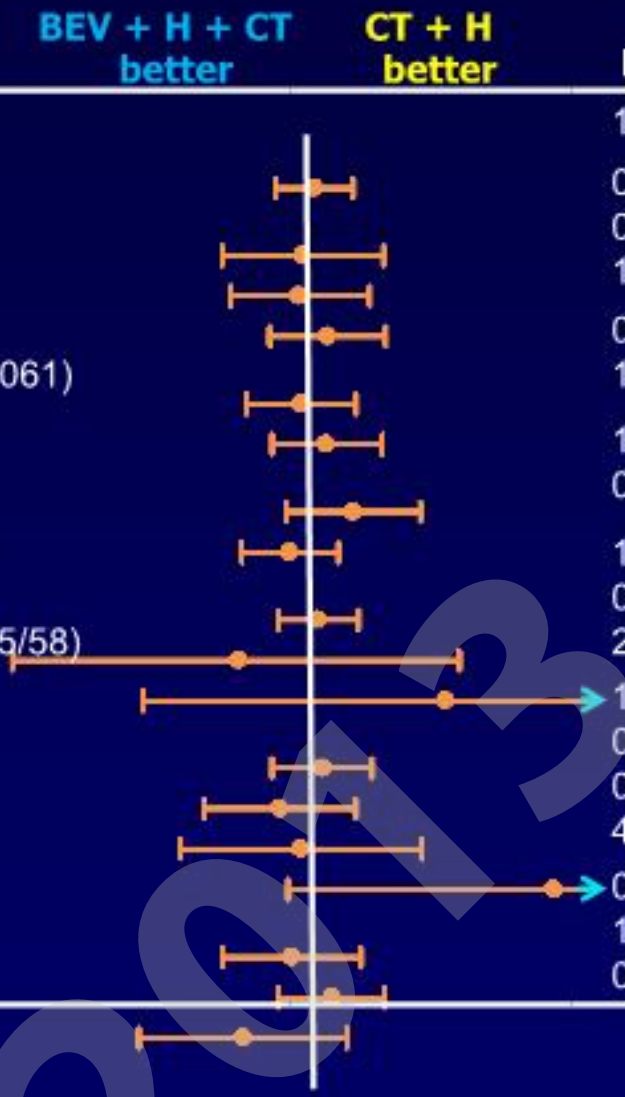
No. at risk:

CTxHB-HB	1752	1692	1672	1648	1601	1510	1108	641	287	62	3
CTxH-H	1757	1717	1690	1657	1607	1518	1106	642	282	57	1

Slamon et al, SABCS 2013

IDFS subgroup analyses (unstratified 2)

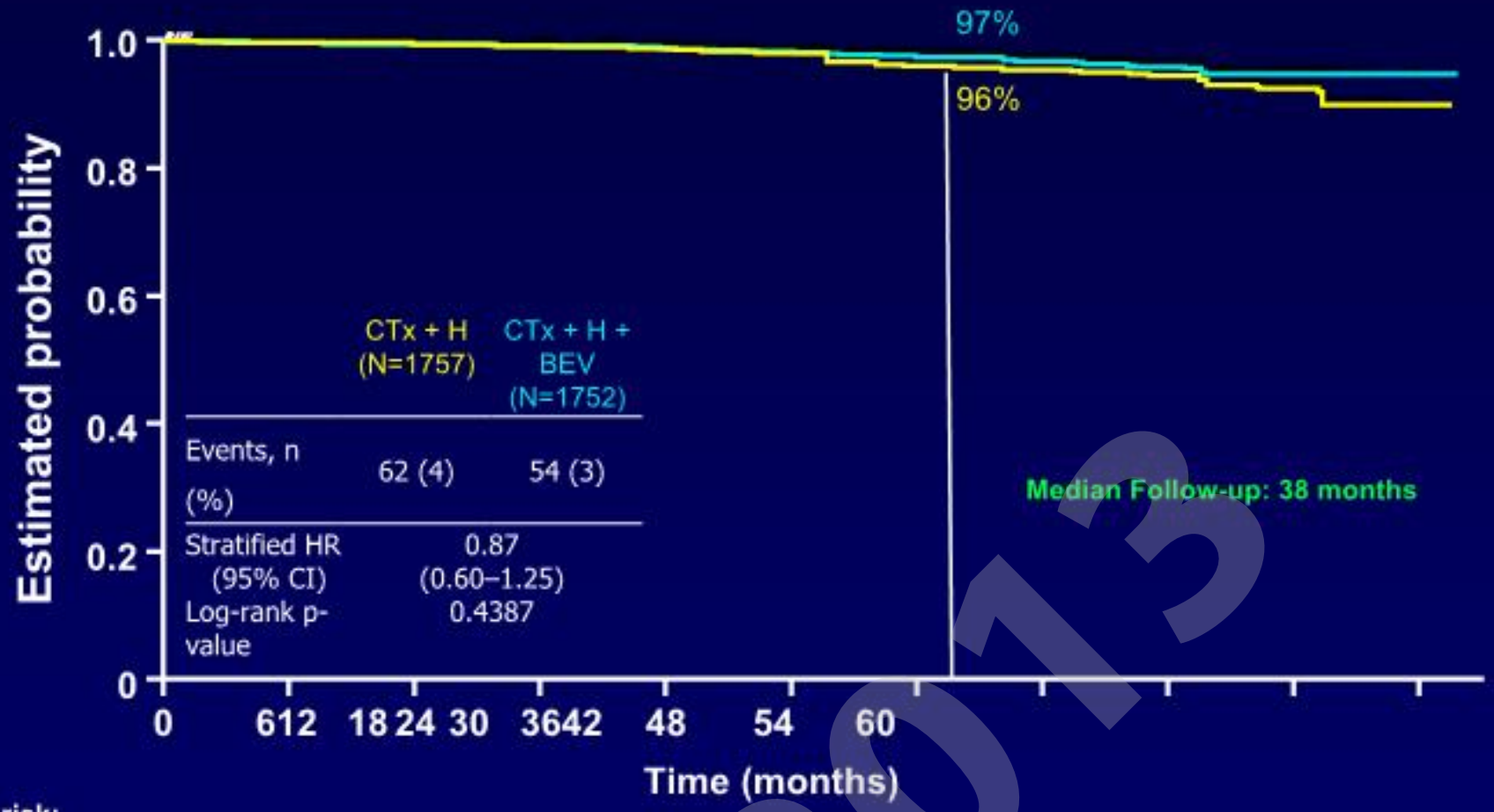
Category	Subgroup	HR	95% CI
All	All (292/3509)	1.02	(0.81–1.28)
Positive axillary lymph nodes (IVRS)	0 (68/1688)	0.95	(0.59–1.53)
	1–3 (91/1092)	0.93	(0.62–1.41)
	≥4 (133/729)	1.10	(0.78–1.55)
Hormonal receptor status (IVRS)	Negative (149/1447)	0.94	(0.68–1.30)
	ER &/or PgR positive (143/2061)	1.09	(0.79–1.52)
Type of surgery	Lumpectomy (99/1722)	1.28	(0.86–1.90)
	Mastectomy (193/1787)	0.88	(0.66–1.17)
Histopathology	Invasive ductal (275/3310)	1.04	(0.82–1.32)
	Invasive lobular (9/81)	0.65	(0.17–2.40)
	Invasive ductal and lobular (5/58)	2.21	(0.37–13.25)
Histological grade	High (176/1970)	1.07	(0.79–1.43)
	Intermediate (77/1218)	0.83	(0.53–1.30)
	Low (30/243)	0.94	(0.46–1.92)
	Unknown (9/78)	4.19	(0.87–20.16)
Tumour size	≤2 cm (90/1704)	0.89	(0.59–1.34)
	>2, ≤5 cm (159/1625)	1.13	(0.82–1.54)
	>5 cm (41/176)	0.67	(0.36–1.23)



2013

Slamon et al, SABCS 2013

Overall Survival for overall study population



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Slamon et al, SABCS 2013

AEs of Special Interest Grade 3/4

AEs, # of patients (%)	Chemo-Trastuzumab (n=1750)	Chemo-Trastuzumab Bevacizumab (n=1722)	p value
All grade 3/4 AEs of special interest	143 (8%)	463 (27%)	<0.0001
Hypertension	78 (4%)	329 (19%)	<0.0001
Thromboembolic event	42 (2%)	50 (3%)	
Bleeding	9 (<1%)	42 (2%)	<0.0001
CHF	12 (<1%)	23 (2.1%)	0.0621
Wound healing complication	10 (<1%)	15 (<1%)	
Proteinuria	1 (<1%)	21 (1%)	<0.0001
Gastrointestinal perforations	1 (<1%)	11 (<1%)	0.0031
Fistula/Abscess	3 (<1%)	3 (<1%)	

Slamon et al, SABCS 2013

2013

Overview of Cardiac Adverse Events*

AEs, # of patients (%)	Chemo-Trastuzumab (n = 1750)	Chemo-Trastuzumab Bevacizumab (n = 1722)	p value
Any AE	428 (24%)	875 (51%)	<0.0001
Grade 3/4 AE	96 (5%)	365 (21%)	<0.0001
Fatal AE	0 (0%)	3 (<1%)	0.1219
SAE	19 (1%)	35 (2%)	0.0278
AE leading to study treatment (any agent) discontinuation	25 (1%)	142 (8%)	<0.0001
AE leading to bevacizumab discontinuation	N/A	115 (7%)	

* Including hypertension, cardiac ischemia/infarction, left ventricular systolic dysfunction, left ventricular diastolic dysfunction, sudden death.

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BETH: Conclusions

- Addition of bevacizumab to adjuvant chemotherapy + trastuzumab did not prolong IDFS in patients with HER2+ early breast cancer (P = .9610)
  - IDFS rate similar to that reported in previous studies of trastuzumab-containing regimens
  - Docetaxel/carboplatin/trastuzumab effective for adjuvant therapy: 92% IDFS rate (median follow-up: 38 mos)
- Safety profile of bevacizumab similar to previously reported events
- Continued follow-up needed to further evaluate long-term safety and efficacy of bevacizumab combination

Slamon DJ, et al. SABCS 2013. Abstract S1-03.

San Antonio Breast Cancer Symposium – December 10-14, 2013
Cancer Therapy and Research Center at UT Health Science Center

Effects Of Bisphosphonate Treatment On Recurrence And Cause-specific Mortality In Women With Early Breast Cancer: A Meta-analysis Of Individual Patient Data From Randomised Trials

R Coleman, M Gnant, A Paterson, T Powles, G von Minckwitz, K Pritchard, J Bergh, J Bliss, J Gralow, S Anderson, D Cameron, V Evans, H Pan, R Bradley, C Davies, R Gray.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)'s Bisphosphonate Working Group.

Meta-analysis: Adjuvant Bisphosphonate Treatment in Women With EBC

- Bisphosphonates may reduce distant metastases, particularly bone recurrence[1-4]
  - Improved disease outcome in postmenopausal women
- Current study: meta-analysis of individual patient outcomes for adjuvant bisphosphonate vs no bisphosphonate or placebo[5]
  - Analysis includes time to recurrence, time to first distant recurrence, mortality

Trials	Trials Included, n	Patients, N	Patient Data Included, %
All	36	22,982	77
Oral clodronate	7	5174	98
Aminobisphosphonates	29	17,808	72

1. Gnant M, et al. Lancet Oncol. 2011;12:631-641. 2. Paterson AH, et al. Lancet Oncol. 2012;13:734-42. 3. Coleman RE. Curr Opin Support Palliat Care. 2012;6:322-329. 4. Coleman R, Ann Oncol. 2013;24:398-405. 5. Coleman R, et al. SABCS 2013. Abstract S4-07. *Reproduced with permission.*

Planned Subgroup Analyses

- **Site of recurrence: distant metastasis, local recurrence or contralateral breast cancer**
- **Site of first distant metastasis: bone ± other, not bone**
- **Menopausal status: pre, peri, postmenopausal (natural/induced)**
- **Type of bisphosphonate: aminobisphosphonate, clodronate**
- **Schedule of bisphosphonate: advanced cancer, bone protection**
- Age: <45, 45-54, 55-69, ≥70
- ER status
- Nodal status: negative, N = 1-3+, N = ≥4+
- Histological grade
- Duration of bisphosphonate: <1 year, 1-2 years, ≥ 2years
- Presence/ absence of chemotherapy
- Recurrence rates in years 0-1, 2-4, 5-9, & 10+ after randomisation

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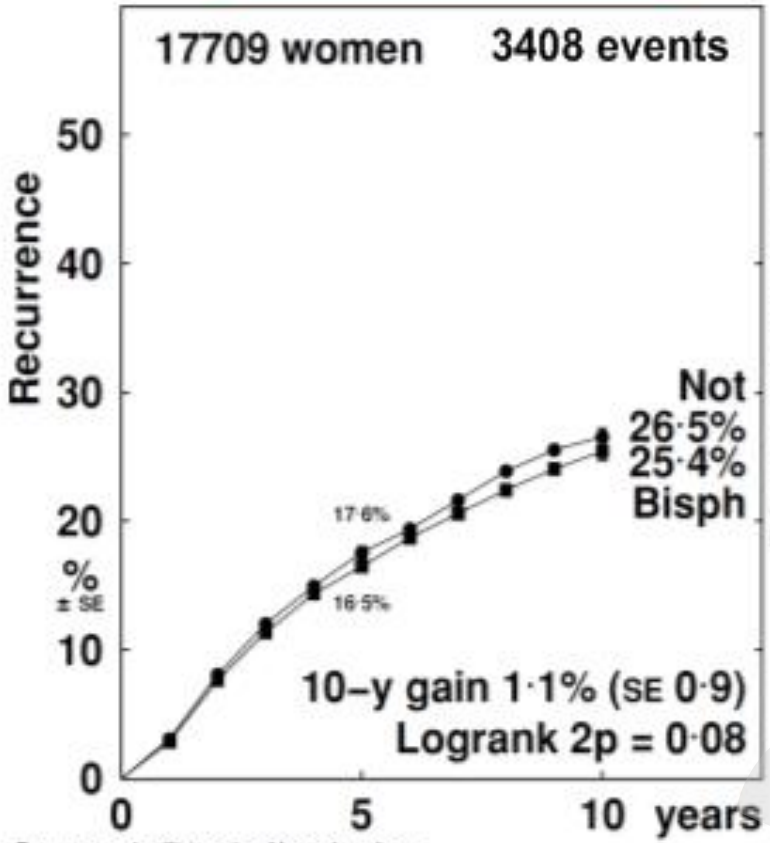
Breast Cancer Recurrence: All Women

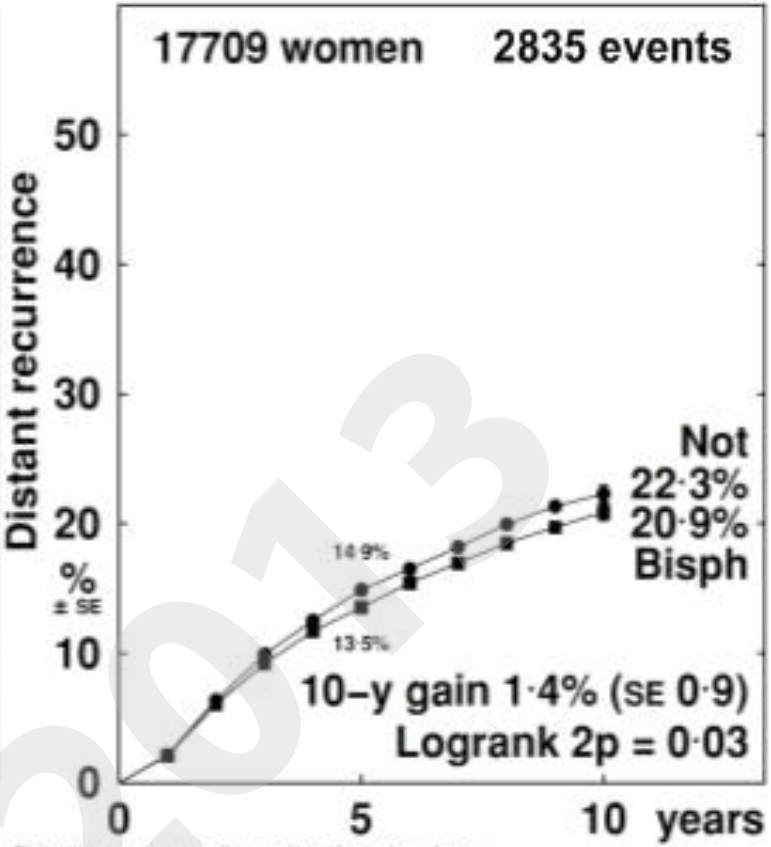
All Recurrences



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Bisph	3·68 (1382 / 37591)	2·43 (319 / 13112)	1·04 (18 / 1730)
Not	3·89 (1344 / 34519)	2·43 (322 / 13268)	1·28 (23 / 1793)
Rate ratio, from (O–E) / V	0·93 se 0·04 −40·1 / 579·7	0·97 se 0·08 −3·9 / 143·6	0·66 se 0·33 −2·7 / 6·3

Distant recurrences



Distant recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Bisph	2·97 (1135 / 38174)	1·93 (264 / 13699)	0·88 (17 / 1940)
Not	3·21 (1127 / 35109)	1·90 (264 / 13880)	1·44 (28 / 1944)
Rate ratio, from (O–E) / V	0·91 se 0·04 −47·8 / 483·8	0·98 se 0·09 −1·8 / 118·3	0·47 se 0·25 −5·5 / 7·2

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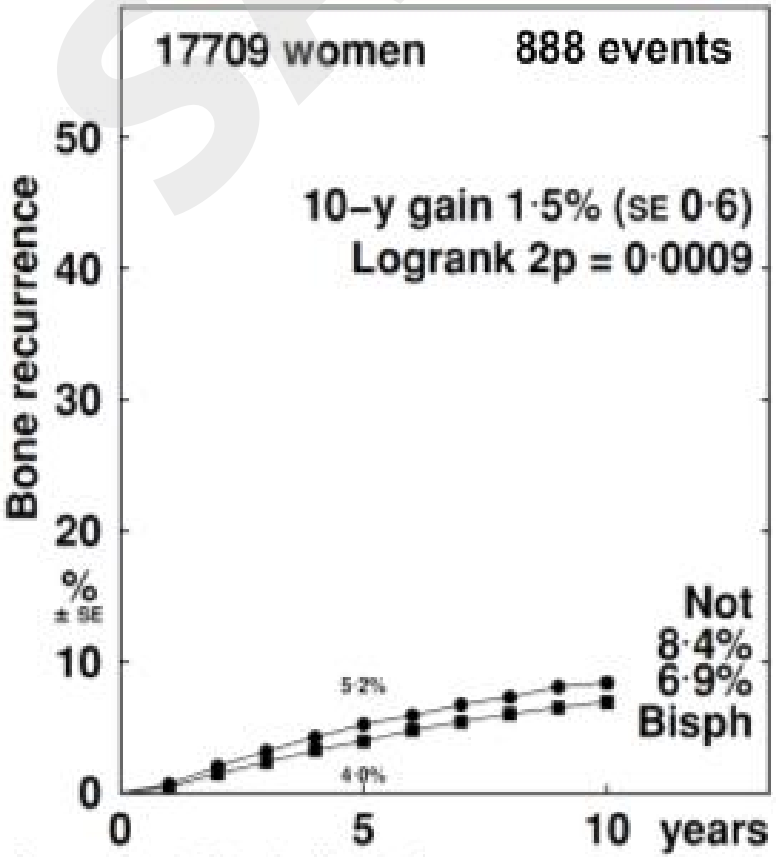
Distant Recurrence: All Patients

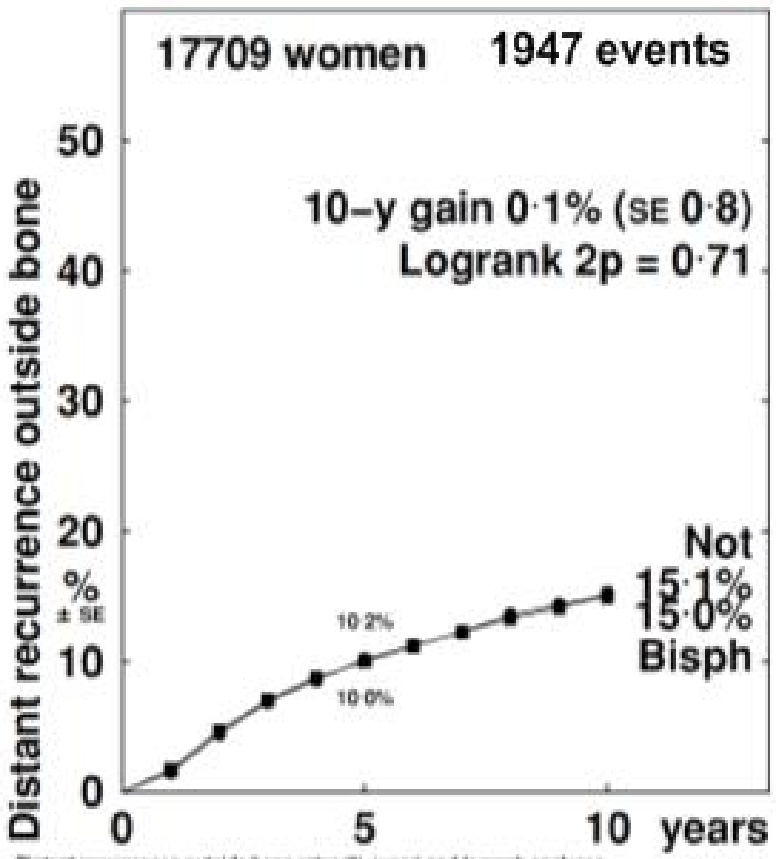
Bone Recurrence



Bone recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Bisph	0·84 (319 / 38174)	0·72 (98 / 13699)	0·15 (3 / 1940)
Not	1·04 (394 / 35109)	0·71 (99 / 13880)	0·26 (5 / 1944)
Rate ratio, from	0·75 se 0·07	0·96 se 0·15	0·59 se 0·88
(O–E) / V	–45·2 / 157·2	–1·9 / 45·6	–0·3 / 0·9

Non-bone Recurrence



Distant recurrences outside bone rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Bisph	2·14 (816 / 38174)	1·21 (166 / 13699)	0·72 (14 / 1940)
Not	2·17 (763 / 35109)	1·19 (165 / 13880)	1·18 (23 / 1944)
Rate ratio, from	0·99 se 0·05	1·00 se 0·12	0·46 se 0·27
(O–E) / V	–2·6 / 337·0	0·0 / 74·1	–5·1 / 6·6

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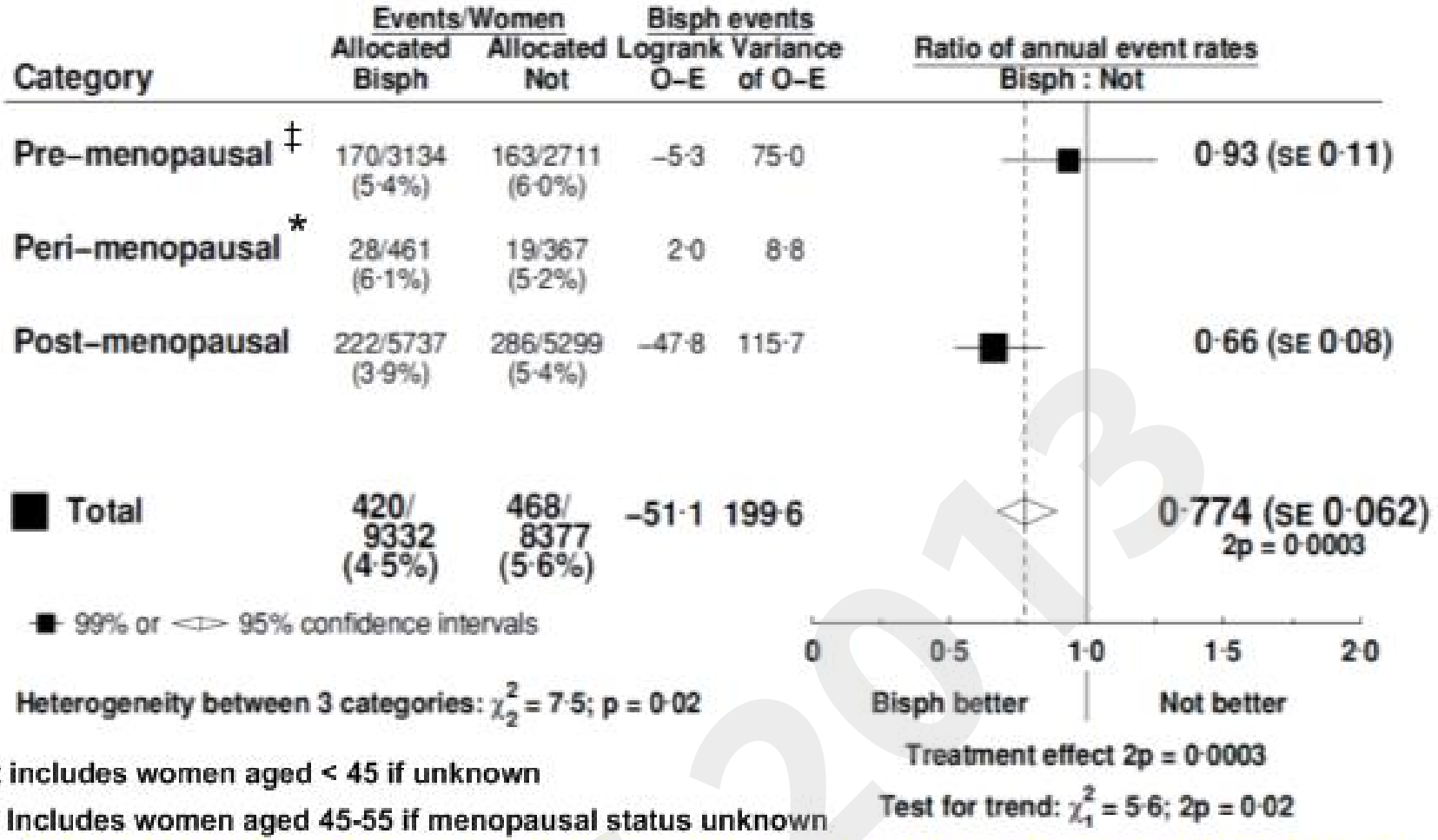
Bone Recurrence By Menopausal Status



‡ includes women aged < 45 if unknown

* Includes women aged 45-55 if menopausal status unknown

Significantly Reduced Bone Recurrence in Postmenopausal Women

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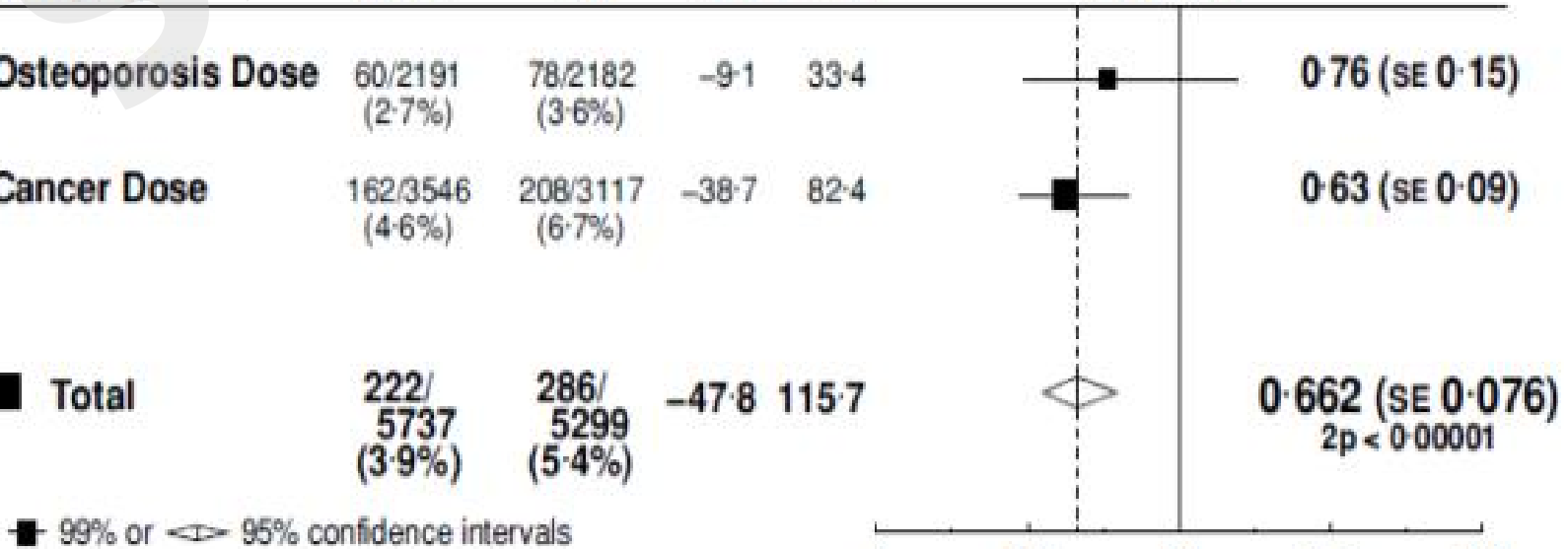
Bone Recurrence By Bisphosphonate Schedule: Postmenopausal Women

Category	Events/Women Allocated Bisph	Events/Women Allocated Not	Bisph events Logrank O–E	Bisph events Variance of O–E	Ratio of annual event rates Bisph : Not
Osteoporosis Dose	60/2191 (2·7%)	78/2182 (3·6%)	–9·1	33·4	0·76 (SE 0·15)
Cancer Dose	162/3546 (4·6%)	208/3117 (6·7%)	–38·7	82·4	0·63 (SE 0·09)
■ Total	222/5737 (3·9%)	286/5299 (5·4%)	–47·8	115·7	0·662 (SE 0·076) 2p < 0·00001



Difference between treatment effects in 2 categories: $\chi^2_1 = 0{\cdot}9$; $2p > 0{\cdot}1$; NS

Treatment effect $2p < 0{\cdot}00001$

Test for trend: $\chi^2_1 = 0{\cdot}9$; $2p > 0{\cdot}1$; NS

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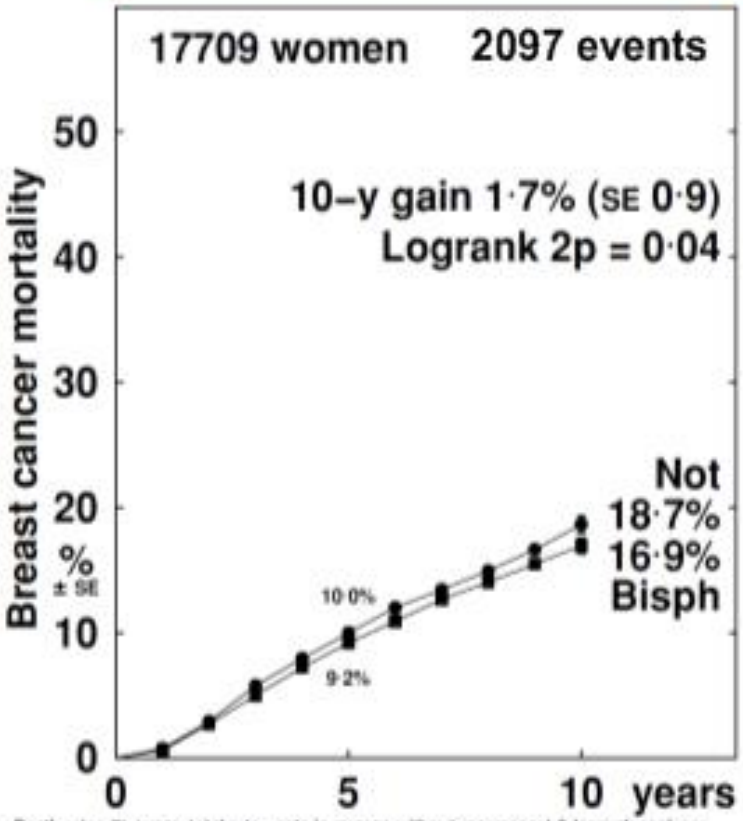
Mortality – All Women

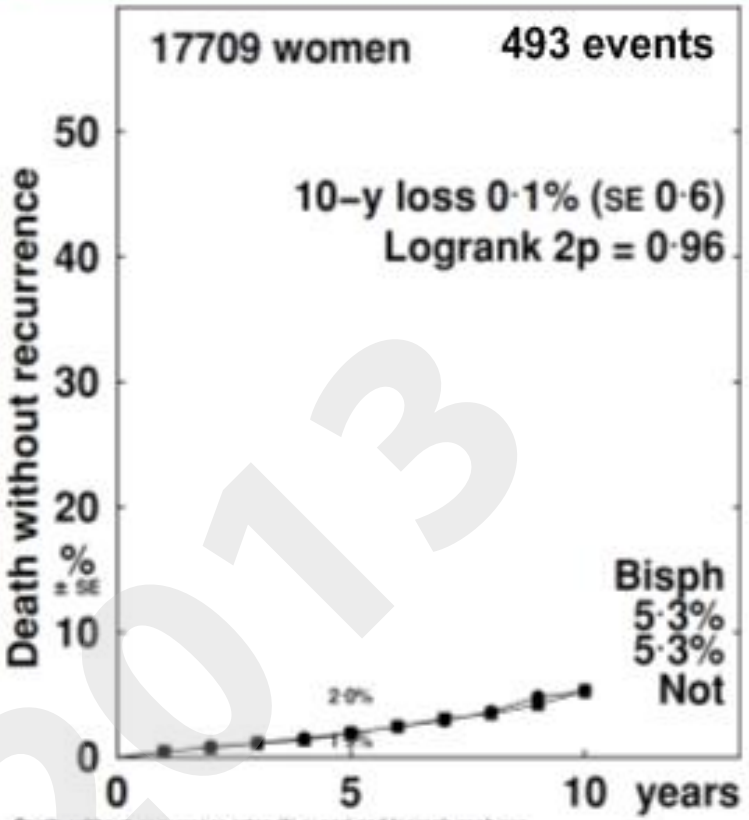
Breast cancer mortality



Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Bisph	1·89 (SE 0·07)	1·83 (SE 0·11)	1·21 (SE 0·25)
Not	2·05 (SE 0·08)	1·98 (SE 0·12)	1·69 (SE 0·29)
Rate ratio, from (O–E) / V	0·91 (SE 0·05) −30·0 / 319·2	0·93 (SE 0·09) −8·5 / 121·3	0·66 (SE 0·25) −4·5 / 10·9

Non-breast cancer mortality



Death–without–recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Year 10+
Bisph	0·38 (142 / 37991)	0·61 (80 / 13112)	1·39 (24 / 1730)
Not	0·41 (141 / 34519)	0·63 (83 / 13268)	1·28 (23 / 1793)
Rate ratio, from (O–E) / V	0·98 (SE 0·12) −1·5 / 65·6	0·97 (SE 0·16) −1·0 / 36·8	1·25 (SE 0·37) 2·0 / 9·1

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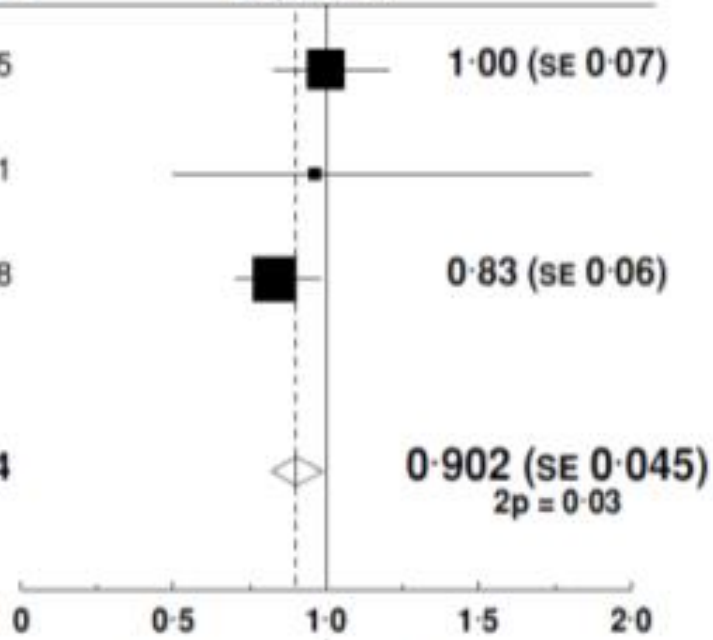
Breast Cancer Mortality By Menopausal Status

Category	Events/Women Allocated Bisph	Events/Women Allocated Not	Bisph events Logrank O–E	Bisph events Variance of O–E
Pre–menopausal	445/3134 (14·2%)	426/2711 (15·7%)	–0·2	186·5
Peri–menopausal	42/461 (9·1%)	38/367 (10·4%)	–0·6	15·1
Post–menopausal	544/5737 (9·5%)	602/5299 (11·4%)	–45·2	241·8
Total	1031/9332 (11·0%)	1066/8377 (12·7%)	–45·9	443·4



■ 99% or ◁▷ 95% confidence intervals

Heterogeneity between 3 categories: $\chi^2_2 = 3{\cdot}7$; $p > 0{\cdot}1$; NS

Treatment effect 2p = 0·03

Test for trend: $\chi^2_1 = 3{\cdot}7$; 2p = 0·06

Significantly Improved Survival in Postmenopausal Women

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Adjuvant Bisphosphonates: Conclusions

- Adjuvant bisphosphonate therapy reduced bone recurrences by 34% and breast cancer mortality by 17% in postmenopausal women with early breast cancer
  - Benefits independent of ER status, node status, use/nonuse of chemotherapy, and type of bisphosphonate used
  - Disease outcomes not significantly improved in premenopausal women
  - No significant effects on nonbreast cancer deaths, contralateral breast cancer, or locoregional recurrence
- Bisphosphonate treatment should be considered for postmenopausal women with breast cancer

Coleman R, et al. SABCS 2013. Abstract S4-07.

Randomized Trial of Exercise vs. Usual Care on Aromatase Inhibitor-Associated Arthralgias in Women with Breast Cancer

Melinda Irwin, Brenda Cartmel, Cary Gross, Elizabeth Ercolano, Martha Fiellin, Scott Capozza, Marianna Rothbard, Yang Zhou, Maura Harrigan, Tara Sanft, Kathryn Schmitz, Tuhina Neogi, Dawn Hershman, Jennifer Ligibel

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HOPE

Hormones & Physical Exercise

Primary Aims: To examine, in 121 women who have been taking an AI for at least 6 months and are experiencing at least mild arthralgia, the yearlong effect of exercise vs. usual care on side effects of AI use:

- Severity of arthralgia
- Endocrine-related quality of life (QOL)
- Mechanisms influencing the effect of exercise on arthralgia severity
  - Pro-inflammatory biomarkers
  - Bone mass, Lean body mass, Body weight and Body fat
  - Cardiorespiratory fitness
  - Muscular strength
  - Psychological outcomes

R01CA132931

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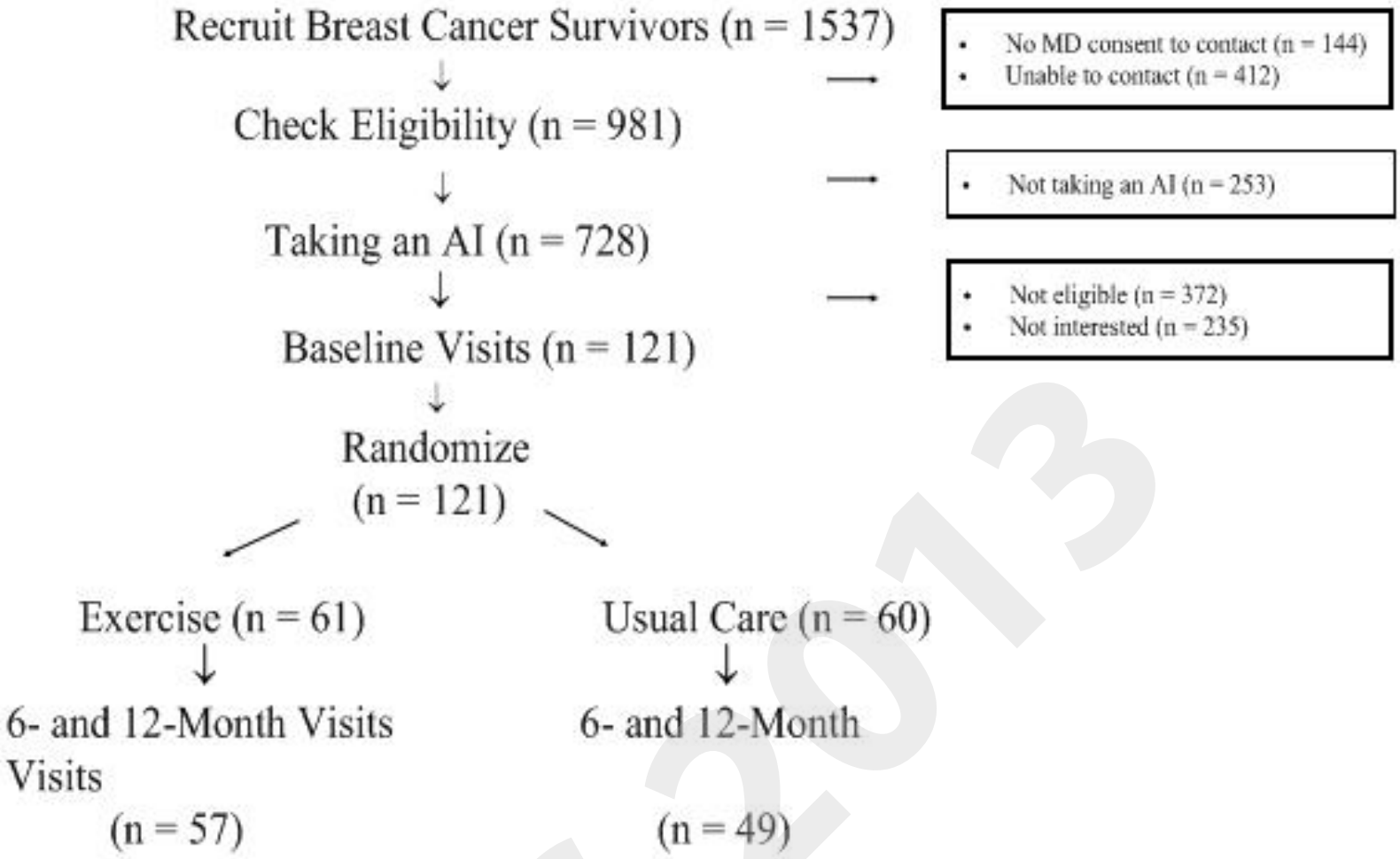
HOPE
Hormones & Physical Exercise

Eligibility Criteria

- AJCC Stages I-IIIC breast cancer
- Hormone Receptor Positive and **taking AI for at least 6 months**
- Currently experiencing **at least mild arthralgia** (measured via BPI)
- Able to exercise, yet physically inactive (< 90 min/wk)
- Agrees to random assignment

HOPE
Hormones & Physical Exercise

Study Design



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HOPE
Hormones & Physical Exercise

Study Groups

- **Yearlong Exercise Program**
  - Twice weekly supervised strength training sessions
    - Six common strength-training exercises, 8-12 reps, 3 sets
  - 2.5 hrs/wk of moderate-intensity aerobic exercise (e.g., treadmill)
  - Heart rate monitors to determine intensity

- **Usual Care**
  - Provided written information (e.g., DHHS physical activity recommendations)
  - Monthly phone calls to assess AI adherence
  - End of study visit with exercise trainer

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Change in Exercise and Body Weight

Baseline to 12 Month Changes in Physical Activity (N=121)	Exercisers	Usual Care	*P*
Change in Physical Activity min/wk Mean (SD)	158.9 (136.3)	48.9 (86.1)	.0001
Attendance to twice-weekly strength training sessions Mean (SD)	70% (28%)	not applicable	
% Change in VO_2max Mean (SD)	+6.5% (8.7%)	-1.8% (11.3%)	.0013
% Change in body weight Mean (SD)	-3.0% (6.9%)	0.0% (4.8%)	.026

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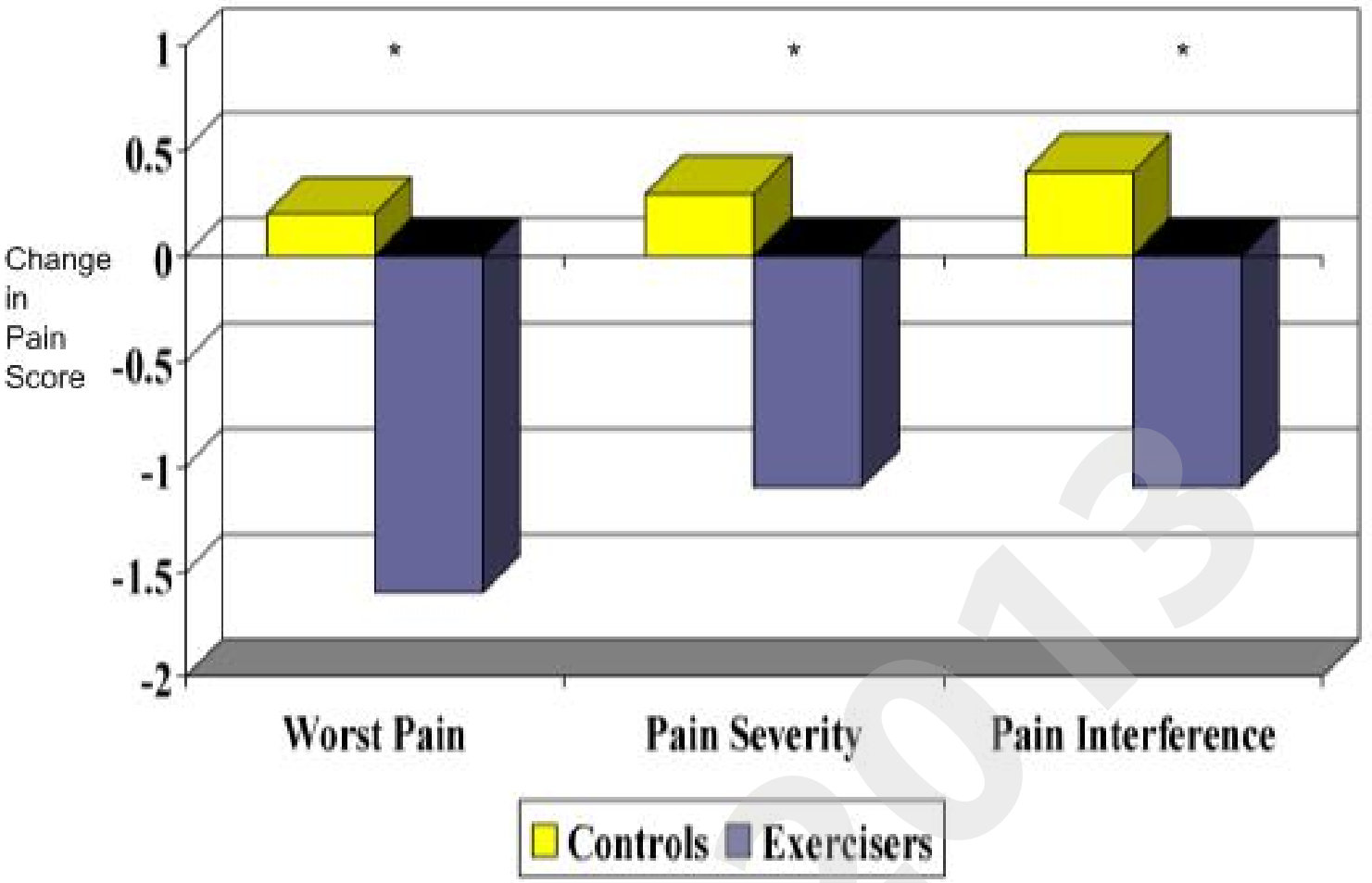
12 Month Change in BPI Scores



*p < .05

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HOPE
Hormones & Physical Exercise

Conclusions

Our findings of exercise improving a common AI side effect may, in turn, improve AI adherence, quality of life and breast cancer recurrence and mortality risk.

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SAN ANTONIO BREAST CANCER SYMPOSIUM®

2013

SPECIAL TOPICS

Surgical Removal Of Primary Tumor And Axillary Lymph Nodes In Women With Metastatic Breast Cancer At First Presentation : A Randomized Controlled Trial

PI: R A Badwe

Professor Surgical Oncology(Breast)

Tata Memorial Centre
Mumbai , India

Co-Investigators
V Parmar, R Hawaldar , N Nair, R Kaushik, S Siddique, A Nawle, A Budrukkar, I Mittra, S Gupta

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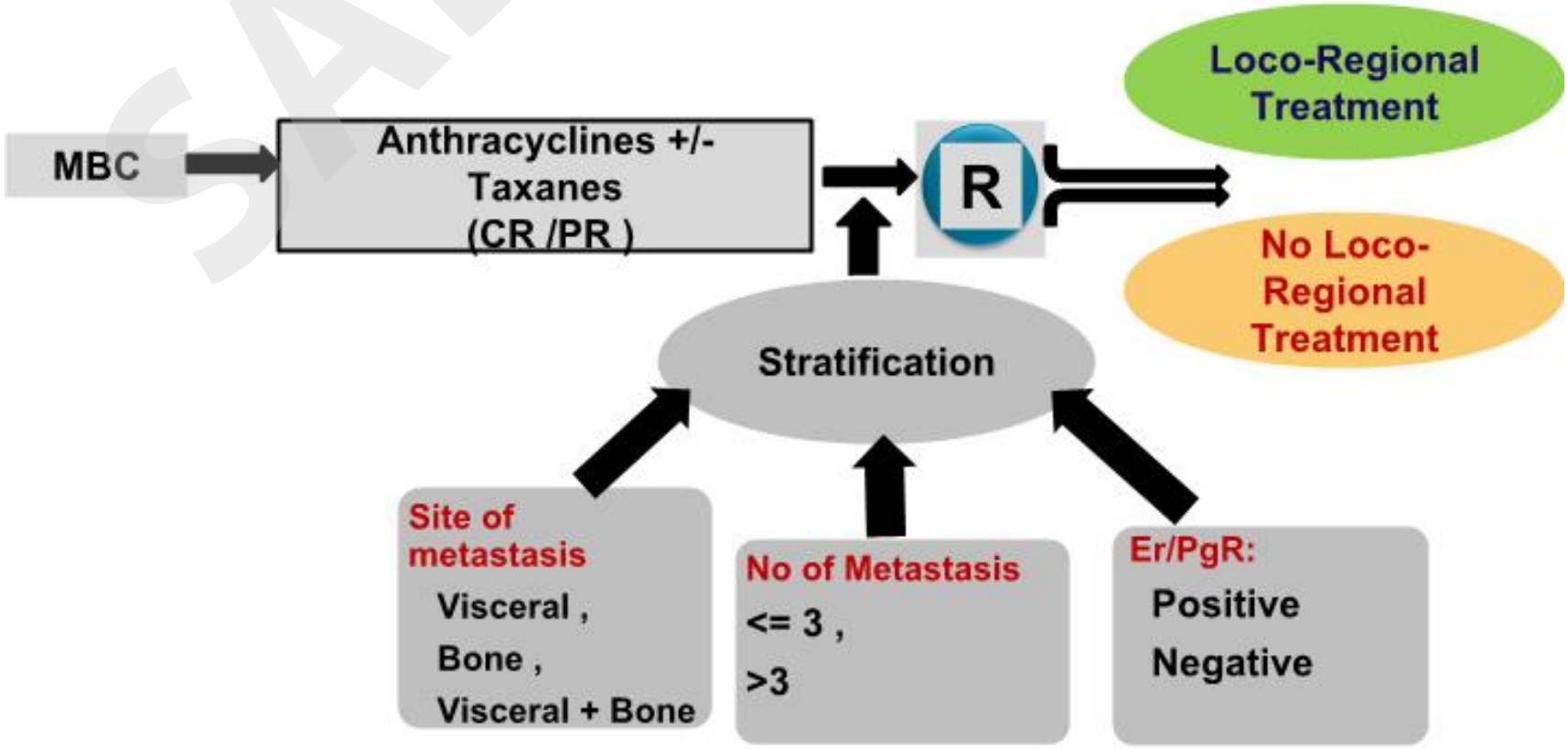

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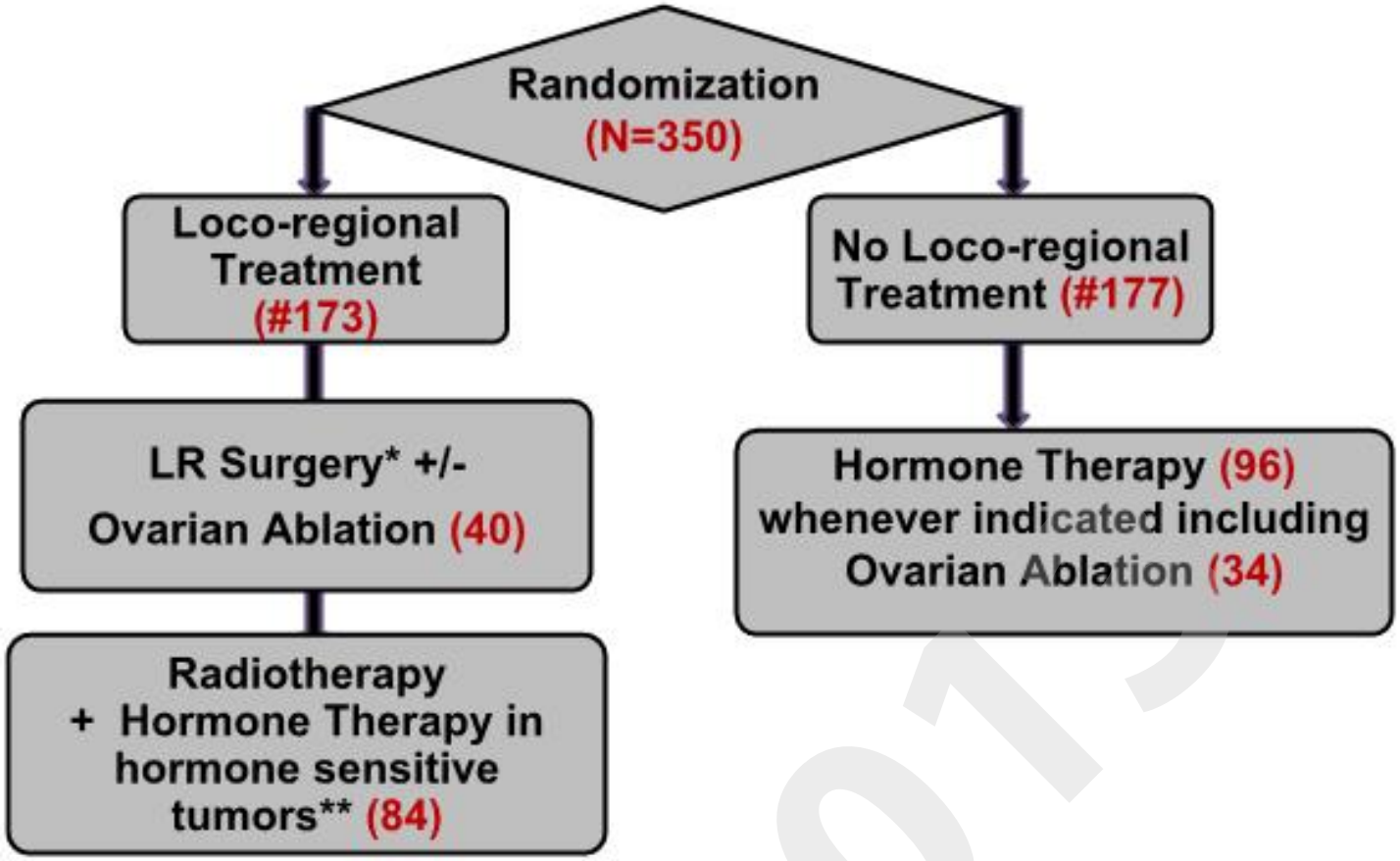
TRIAL SCHEMA



*Loco-regional Therapy : BCT / MRM with supraclavicular lymph node clearness whenever indicated

** Tamoxifen in pre menopausal women and AI in Post menopausal women/ post Oophorectomy in pre menopausal women

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STRATIFICATIONS

	NO LRT (#177) N (%)	LRT (#173) N (%)	TOTAL
Site of Metastasis			
Bone	50 (50.0)	50 (50.0)	100
Visceral	77 (50.7)	75 (49.3)	98
Bone + Visceral	50 (51.0)	48 (49.0)	152
No. of Metastasis			
<= 3	45 (50.6)	44 (49.4)	89
>3	132 (50.6)	129 (49.4)	261
ER/PgR			
Positive	106 (51.0)	102 (49.0)	208
Negative	71 (50.0)	71 (50.0)	142
Age (Median)	47	48	47
Menopausal status			
Pre	88 (54.3)	74 (45.7)	162
Post	89 (47.3)	99 (52.7)	186

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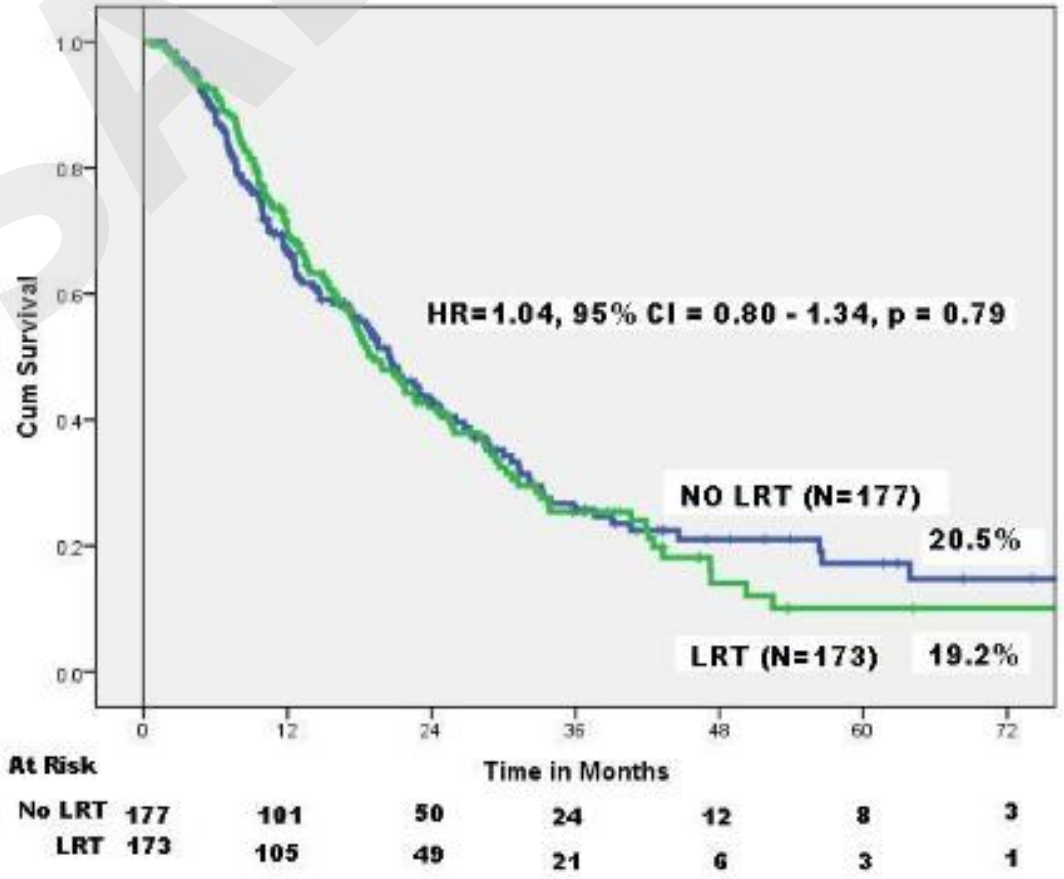
OVERALL SURVIVAL



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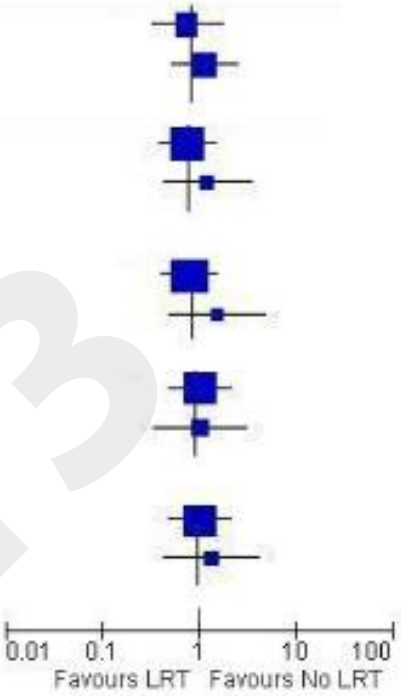
SUBGROUP ANALYSIS

Subgroup	LRT Events	LRT Total	NO LRT Events	NO LRT Total	Odds Ratio M-H, Fixed, 95% CI
Menopausal status-Pre	50	74	61	88	0.92 [0.47, 1.79]
Menopausal Status-Post	68	99	56	89	1.29 [0.71, 2.37]
Met site - Bone+Visceral	83	123	86	127	0.99 [0.58, 1.68]
Met site-Bone Only	35	50	31	50	1.43 [0.62, 3.29]
Met no >3	87	129	90	132	0.97 [0.58, 1.62]
Met no 1-3	31	44	27	45	1.59 [0.66, 3.83]
ErPgR+	60	102	60	106	1.10 [0.63, 1.90]
ErPgR-	58	71	57	71	1.10 [0.47, 2.54]
Her2neu -ve	83	121	70	104	1.06 [0.61, 1.86]
Her2neu +ve	28	40	38	59	1.29 [0.55, 3.05]



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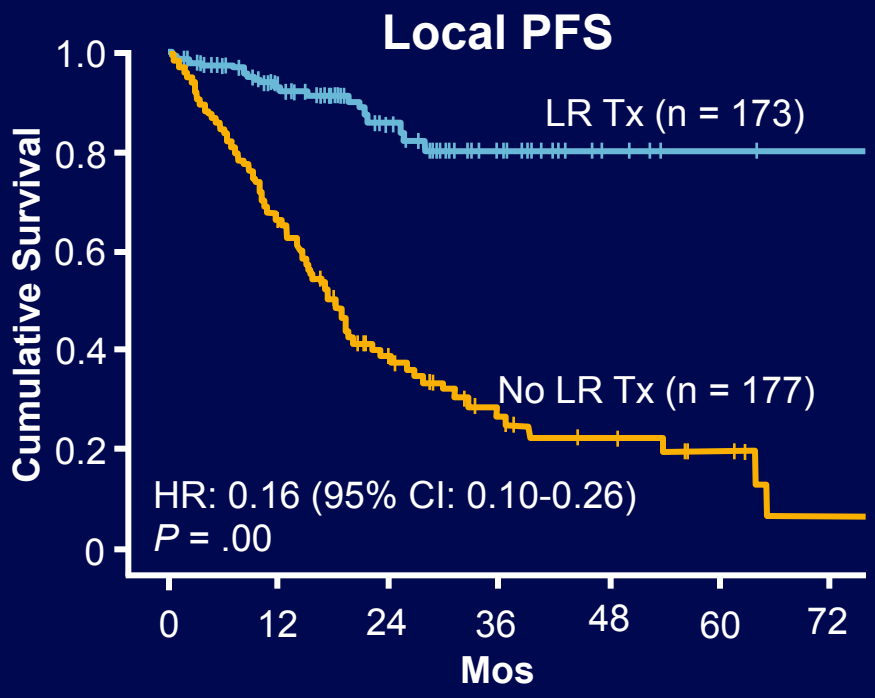
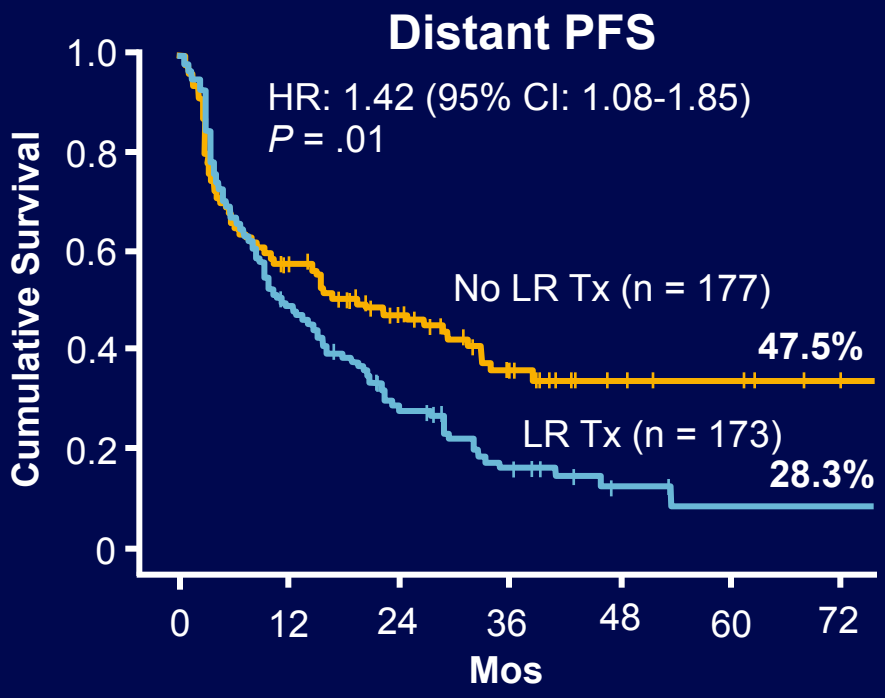
Locoregional Control in MBC at First Presentation

- Local surgical control increase local PFS but decreased distant PFS rates compared with no locoregional control





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Locoregional Control of MBC: Conclusions

- Surgical removal of primary tumor in women presenting with MBC did not result in OS benefit
  - Surgical removal of primary tumor decreased distant PFS vs no locoregional control (47.5% vs 28.3%; *P* = .01)
- Based on current data, surgical removal of primary tumor in women with MBC at first presentation should not be offered as a routine practice

Badwe R, et al. SABCS 2013. Abstract S2-02.

San Antonio Breast Cancer Symposium Cancer Therapy and Research Center at UT Health Science Center - December 10-14, 2013

Breast cancer incidence after hormonal infertility treatments: systematic review and meta-analysis of population based studies

Alessandra Gennari[1], Mauro Costa[2], Laura Paleari[3], Matteo Puntoni[1], Maria Pia Sormani[4], Andrea De Censi[1], Paolo Bruzzi[3]

[1]Medical Oncology, Galliera Hospital, Genoa; [2]Reproductive Medicine, Evangelico International Hospital, Genoa; [3]Epidemiology and Biostatistics, IRCCS A.O.U. San Martino-National Cancer Institute, Genoa, [4]DISSAL University of Genoa, Genoa, Italy

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Included

19 Studies included in quantitative synthesis (meta-analysis)

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Characteristics of the Identified Studies

Study, year	Country	Enrollment yrs	Control	Intervention	Cases/Exposed	FU years	Overall Effect
Rossing MA, 96	USA	1974-85	population	IVF/HITs	27/3837	≥ 10	ns
Venn A, 99	AU	< 1994	population	IVF only	87/20656	< 10	ns
Potashnik G, 99	IL	1960-84	population	IVF/HITs	16/780	≥ 10	ns
Dor J, 02	IL	1981-92	population	IVF only	11/5026	< 10	ns
Doyle P, 02	UK	1975-89	both	IVF/HITs	43/4188	< 10	ns
Lerner-Geva L, 03	IL				2	< 10	ns
Gauthier E, 04	FR				34	< 10	ns
Brinton LA, 04	USA				47	≥ 10	↑ risk
Terry KL, 06	USA				98	≥ 10	↓ risk
Jensen A, 07	DK				9	< 10	ns
Pappo I, 08	IL				75	< 10	ns
Van den Belt S, 08	NL	1980-95	population	IVF/HITs	24/8716	≥ 10	↑ risk
Orgéas C, 09	SE	1961-76	population	HITs only	54/1135	≥ 10	ns
Calderon-M R, 09	IL	1974-76	population	HITs only	32/567	≥ 10	↑ risk
Kallen B, 11	SE	1982-06	population	IVF only	91/24058	< 10	↑ risk
Lerner-Geva L, 12	IL	1964-74	population	HITs only	153/2431	≥ 10	ns
Yli-Kuha AN, 12	FI	1996-98	population	IVF only	55/9175	< 10	ns
Stewart LM, 12	AU	1983-02	infertile	IVF only	148/7381	≥ 10	ns
Brinton LA, 13	IL	1994-11	infertile	IVF/HITs	389/NR	< 10	ns

>100,000 exposed
1960 - 2011
1,498 BC cases

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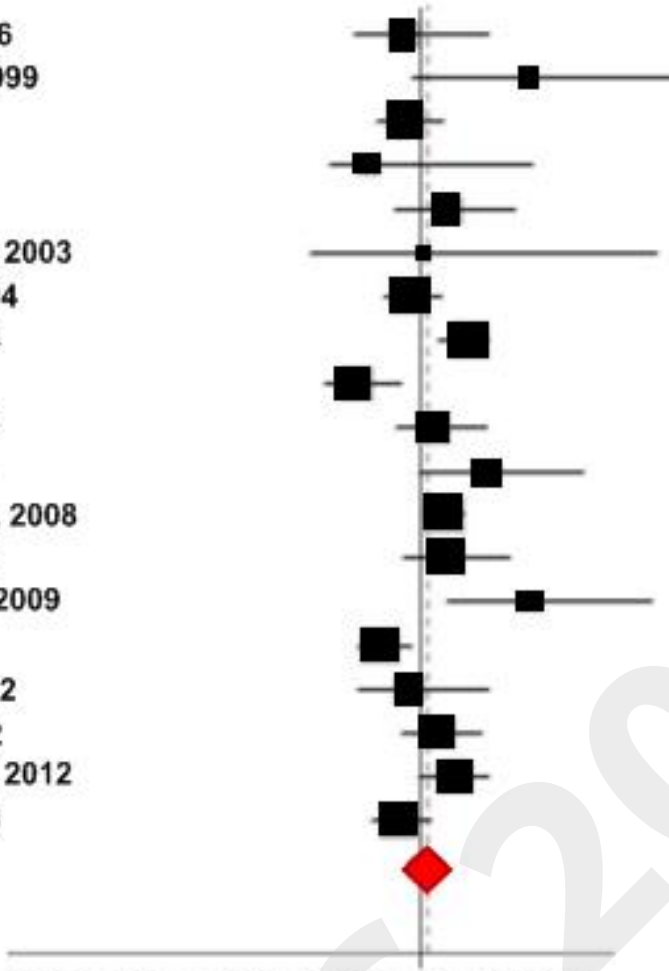
HITs and BC Risk: Overall Effect



Author, publication yr	SIR/RR/HR	Weight (%)
Rossing, 1996	0.90 [0.60-1.40]	4.06
Potashnik, 1999	1.65 [0.94-2.68]	1.31
Venn, 1999	0.91 [0.74-1.13]	7.13
Dor, 2002	0.69 [0.46-1.66]	2.38
Doyle, 2002	1.16 [0.84-1.56]	4.55
Lerner-Geva, 2003	1.02 [0.33-2.39]	0.97
Gauthier, 2004	0.94 [0.78-1.12]	7.56
Brinton, 2004	1.29 [1.10-1.40]	7.89
Terry, 2006	0.62 [0.43-0.88]	6.62
Jensen, 2007	1.08 [0.85-1.39]	5.87
Pappo, 2008	1.40 [0.98-1.96]	3.17
Van den Belt, 2008	1.14 [1.02-1.26]	8.35
Orgèas, 2009	1.16 [0.89-1.52]	5.17
Calderon-M, 2009	1.65 [1.15-2.36]	2.35
Kallen, 2011	0.76 [0.62-0.94]	7.73
Yli-Kuha, 2012	0.93 [0.62-1.40]	4.18
Stewart, 2012	1.10 [0.88-1.36]	6.36
Lerner-Geva, 2012	1.20 [0.98-1.40]	6.87
Brinton, 2013	0.87 [0.71-1.06]	7.47
Overall	1.03 [0.93-1.14]	100 p 0.72

Test for heterogeneity: I-squared = 69.2%, p= 0.0002

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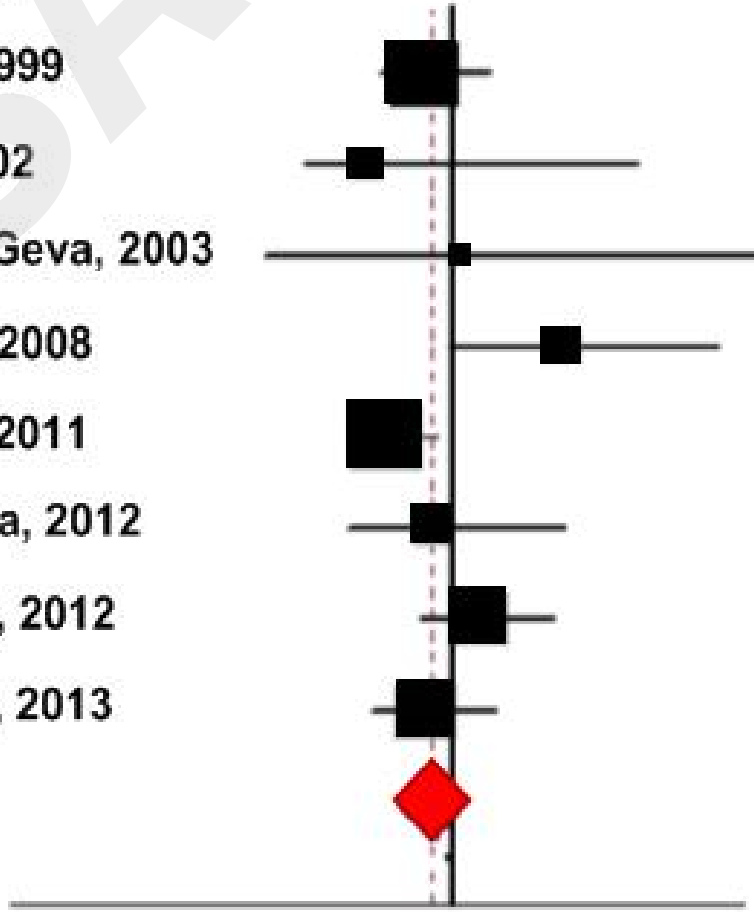
In Vitro Fertilization (IVF) and BC Risk



Study, year	SIR/RR/HR	Weight (%)
Venn, 1999	0.91 [0.74-1.13]	20.96
Dor, 2002	0.69 [0.46-1.66]	3.85
Lerner-Geva, 2003	1.02 [0.33-2.39]	1.38
Pappo, 2008	1.40 [0.98-1.96]	5.53
Kallen, 2011	0.76 [0.62-0.94]	25.3
Yli-Kuha, 2012	0.93 [0.62-1.40]	8.13
Stewart, 2012	1.10 [0.88-1.36]	16.5
Brinton, 2013	0.90 [0.80-1.05]	18.3
Overall	0.92 [0.80-1.05]	100 p 0.34

Test for heterogeneity: I-squared = 31.1%, p= 0.179

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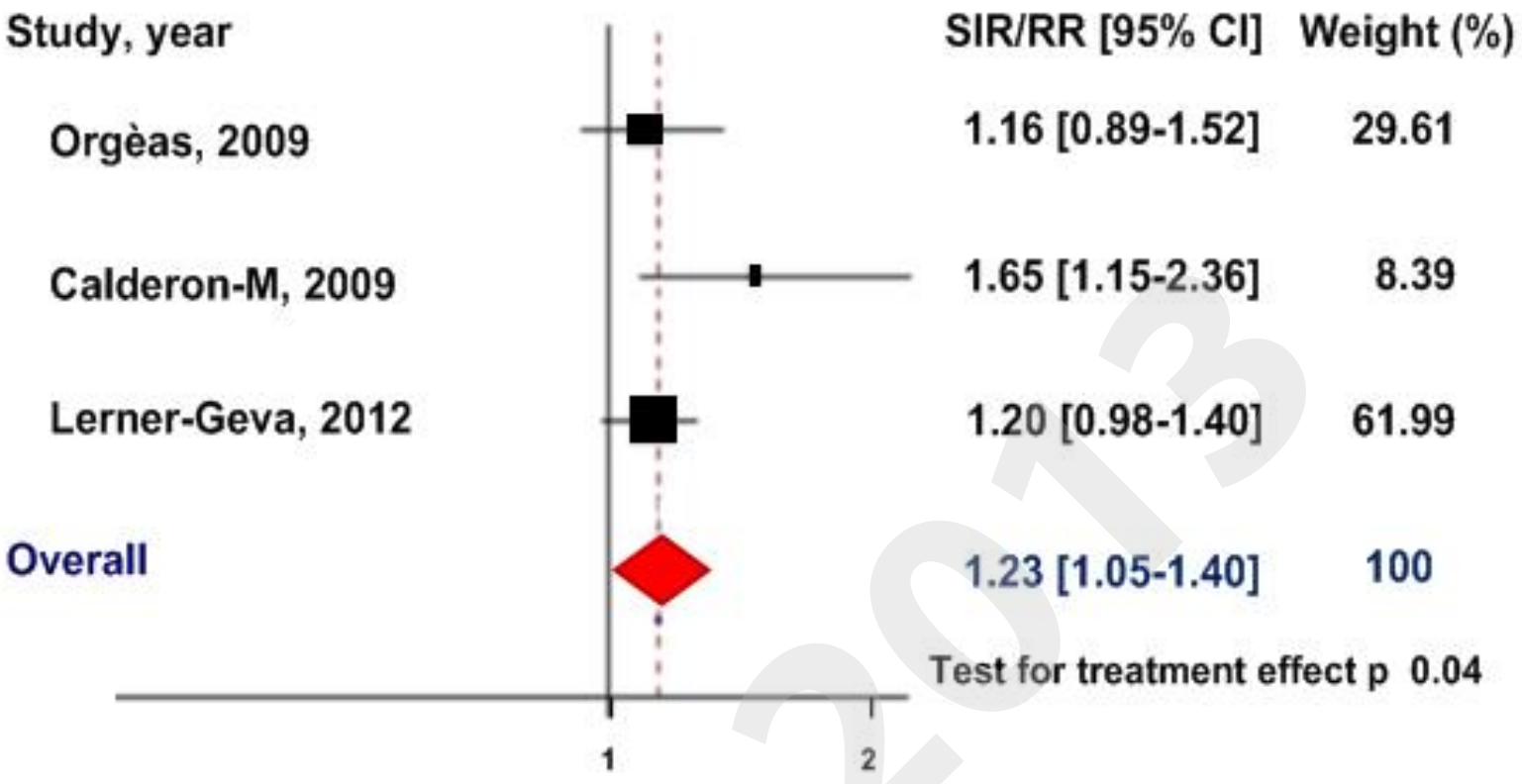
NO-IVF and BC Risk
(enrollment ≤ 1979)



Test for heterogeneity: I-squared = 5.4%, p= 0.348

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HITs and BC Risk - Subgroup Analyses

Subgroups	N° of studies	RR/SIR	95% CI	p interaction
Type of intervention				
IVF	8	0.92	0.80-1.05	0.03
NO-IVF	3	1.23	1.05-1.40	
Not Specified	*8*	*1.00*	*0.82-1.19*	
Length of FU				
< 10 yrs	10	0.88	0.83-1.02	
≥ 10 yrs	9	1.12	0.96-1.28	0.1
Type of control				
Infertile women	3	0.90	0.73-1.07	0.4
Population based	16	1.04	0.91-1.17	

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HITs and BC Incidence: Conclusions

- Overall, HITs were **NOT** associated with increased BC risk: **- RR = 1.03 [0.93-1.14]**
- Moderate increase in women treated prior to IVF:
  - NO IVF: RR = 1.23 [1.05-1.40]
  - different drug use, longer drug exposure
- Longer FU associated with an increased BC risk, possibly confounded by the effect of type of intervention
  - longer FU in earlier studies with NO-IVF

Take Home Message

Women wishing to undergo HITs should not be alarmed about the associated BC risk

Safety of long-term administration of hormones in repeated empirical ovarian stimulations needs to be further explored


grazie per l'attenzione