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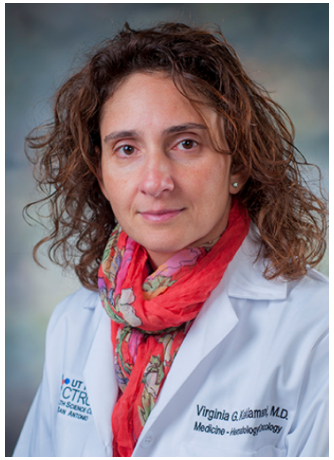
January 27, 2018

SABCS 2017 Breast Cancer Updates: Survivorship



VIRGINIA KAKLAMANI, MD, DSc
Professor of Medicine
Ruth McLean Bowman Bowers Chair in Breast Cancer Research and Treatment
A.B. Alexander Distinguished Chair in Oncology
Associate Director for Clinical Research
Leader, Breast Oncology Program
CTRC, University of Texas Health Science Center San Antonio
San Antonio, TX (USA)

Disclosure(s)

VIRGINIA KAKLAMANI, MD, DSc

Research Support:	**EISAI**
Speaker's Bureau:	**EISAI, Genentech, Genomic Health, Pfizer, Novartis**
Advisory Panel/Consultant:	**Celgene, Pfizer, Novartis, Astrazeneka**
Stock/Shareholder:	
Employee:	

Topics to Discuss

- Compliance
- Fertility preservation
- Obesity and weight loss
- Adjuvant bisphosphonates
- Symptom management and incidence

Mammography screening non-participants are more likely to have late surgery, discontinuing adjuvant hormone therapy, and have a worse prognosis of breast cancer

Wei He, Louise Eriksson, Sven Törnberg, Fredrik Strand, Per Hall, Kamila Czene

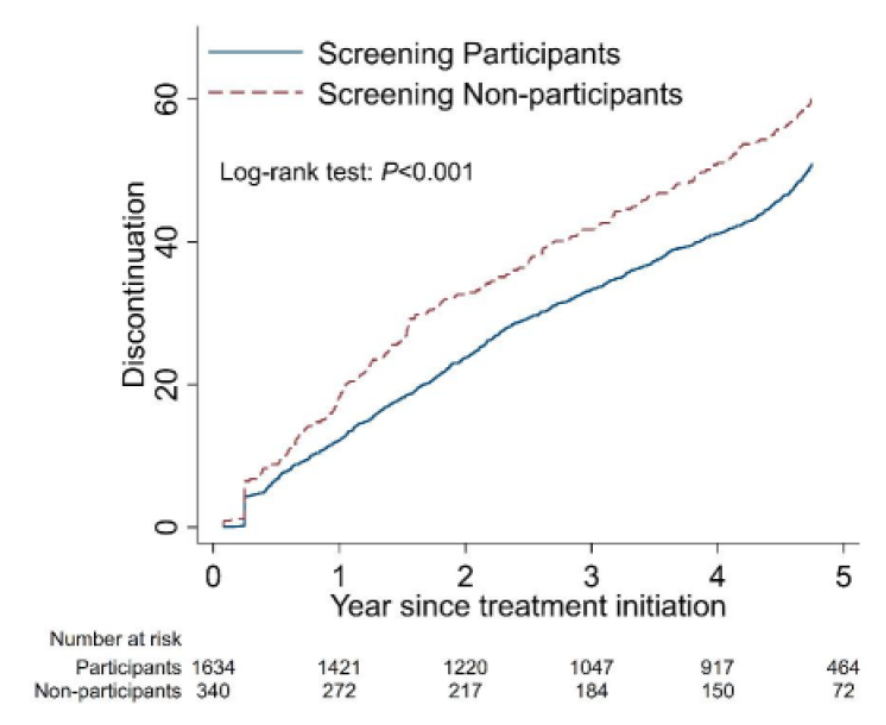


Figure 2. Kaplan-Meier curve for discontinuation of adjuvant hormone therapy among women diagnosed with estrogen receptor-positive breast cancer in Stockholm, Sweden, 2005-2008, screening non-participants versus participants.

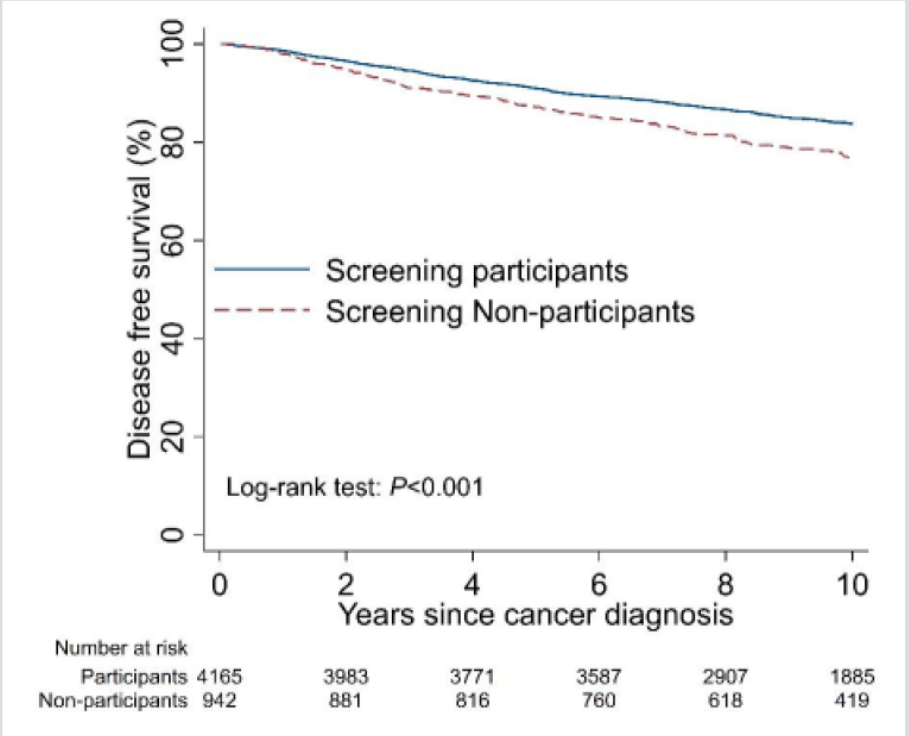


Figure 3, Kaplan-Meier curve for disease-free survival among women diagnosed with breast cancer in Stockholm, Sweden, 2001-2008, screening non-participants versus participants.

Pooled analysis of five randomized trials investigating temporary ovarian suppression with gonadotropin-releasing hormone analogs during chemotherapy as a strategy to preserve ovarian function and fertility in premenopausal early breast cancer patients

Matteo Lambertini[1], Halle C.F. Moore[2], Robert C.F. Leonard[3], Sibylle Loibl[4], Pamela Munster[5], Marco Bruzzone[6], Luca Boni[7], Joseph M. Unger[8], Richard A. Anderson[9], Keyur Mehta[4], Susan Minton[10], Francesca Poggio[6], Kathy S. Albain[11], Douglas J.A. Adamson[12], Bernd Gerber[13], Amy Cripps[14], Gianfilippo Bertelli[15], Sabine Seiler[4], Marcello Ceppi[6], Ann H. Partridge[16], and Lucia Del Mastro[6]

[1]Institut Jules Bordet and Université Libre de Bruxelles (U.L.B.), Brussels, Belgium. [2]Cleveland Clinic Foundation, Taussig Cancer Institute, Cleveland, OH. [3]Imperial College, London, UK. [4]GBG - German Breast Group, Neu-Isenburg, Germany. [5]UCSF - University of California, San Francisco, CA. [6]Ospedale Policlinico San Martino-IST, Genova, Italy. [7]AOU Careggi and Istituto Toscano Tumori, Firenze, Italy. [8]SWOG Statistical Center, Fred Hutchinson Cancer Research Center, Seattle, WA. [9]MRC Centre for Reproductive Health, University of Edinburgh, Edinburgh, UK. [10]Moffitt Cancer Center, Tampa, FL. [11]Loyola University Medical Center, Cardinal Bernardin Cancer Center, Maywood, IL. [12]Tayside Cancer Centre, Ninewells Hospital, Dundee, UK. [13]University Hospital Rostock, Rostock, Germany. [14]Nexgen Oncology, Dallas, TX. [15]Singleton Hospital, Swansea, UK. [16]Dana-Farber Cancer Institute, Boston, MA.

Background

- Fertility preservation and pregnancy-related issues are high priority areas of concern for young women with breast cancer
- Oocyte/embryo cryopreservation are standard strategies for fertility preservation but they do not prevent the risk of chemotherapy-induced premature ovarian insufficiency (POI)
- Temporary ovarian suppression with GnRHa during chemotherapy has been studied in several RCTs as a strategy to preserve ovarian function and potential fertility
- However, data are mixed and its role remains controversial

Paluch-Shimon S et al, *Breast* 2017;35:203-17. Loren AW et al, *J Clin Oncol* 2013;31:2500-10. Peccatori F et al, *Ann Oncol* 2013;24 Suppl 6;vi160-70. Lambertini M et al, *Ann Oncol* 2015;26:2408-19. Lambertini M et al, *Eur J Cancer* 2017;71:25-33.

The NEW ENGLAND JOURNAL of MEDICINE

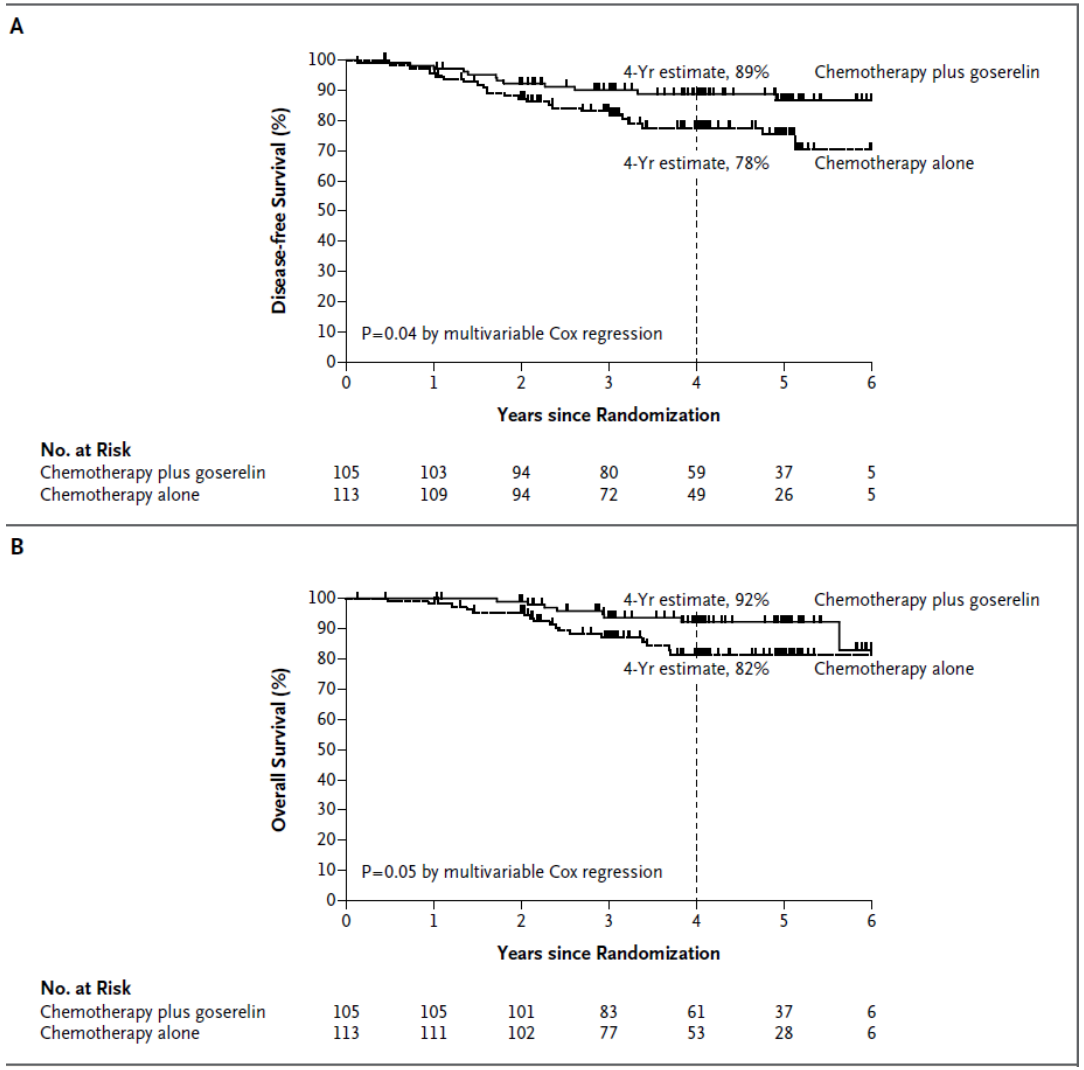
ORIGINAL ARTICLE

Goserelin for Ovarian Protection during Breast-Cancer Adjuvant Chemotherapy

Halle C.F. Moore, M.D., Joseph M. Unger, Ph.D., Kelly-Anne Phillips, M.D., Frances Boyle, M.B., B.S., Ph.D., Erika Hitre, M.D., David Porter, M.D., Prudence A. Francis, M.D., Lori J. Goldstein, M.D., Henry L. Gomez, M.D., Carlos S. Vallejos, M.D., Ann H. Partridge, M.D., M.P.H., Shaker R. Dakhil, M.D., Agustin A. Garcia, M.D., Julie Gralow, M.D., Janine M. Lombard, M.D., John F. Forbes, M.B., B.S., Silvana Martino, D.O., William E. Barlow, Ph.D., Carol J. Fabian, M.D., Lori Minasian, M.D., Frank L. Meyskens, Jr., M.D., Richard D. Gelber, Ph.D., Gabriel N. Hortobagyi, M.D., and Kathy S. Albain, M.D., for the POEMS/S0230 Investigators

Table 3. Pregnancy Outcomes.

Outcome	Chemotherapy Alone (N=113)	Chemotherapy plus Goserelin (N=105)	Odds Ratio with Goserelin	P Value*
Attempted pregnancy — no. of patients (%)	18 (16)	25 (24)	1.78	0.12
Achieved pregnancy — no. of patients (%)	12 (11)	22 (21)	2.45	0.03
≥1 delivery — no. of patients (%)	8 (7)	16 (15)	2.51	0.05
Delivery or ongoing pregnancy — no. of patients (%)	10 (9)	19 (18)	2.45	0.04
Babies born — no.†	12	18		
Ongoing pregnancies at last report — no.	3	5		
Adverse pregnancy event — no. of events				
Miscarriage	5	4		
Elective termination	3	2		
Delivery complication	2	2		



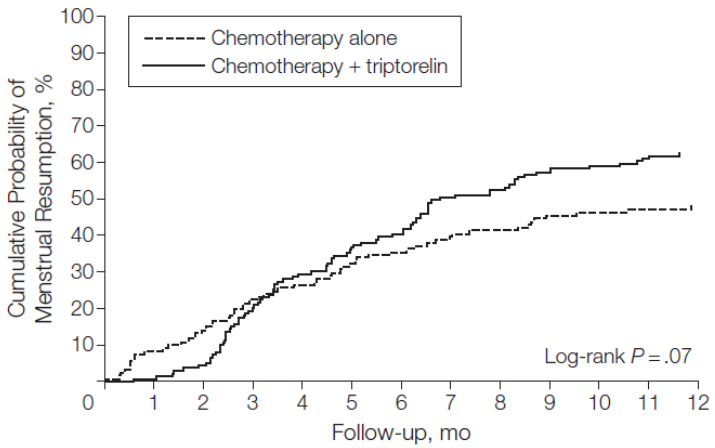
Effect of the Gonadotropin-Releasing Hormone Analogue Triptorelin on the Occurrence of Chemotherapy-Induced Early Menopause in Premenopausal Women With Breast Cancer

A Randomized Trial

JAMA, July 20, 2011—Vol 306, No. 3

281 patients randomized

Figure 2. Time to Resumption of Menstrual Activity



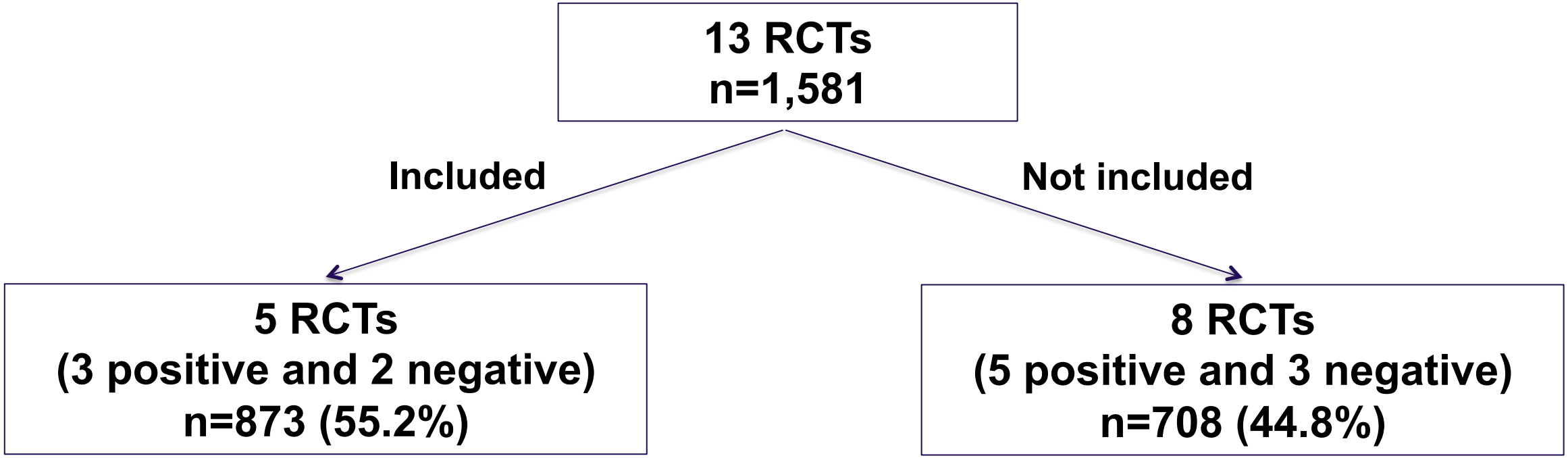
No. at risk

Chemotherapy alone	121	111	104	94	89	82	78	73	71	66	65	64	62
Chemotherapy + triptorelin	139	138	133	111	98	88	83	69	66	59	57	54	50

After 12 mo rate of early menopause was 25.9% in chemotherapy alone vs 8.9% in triptoreline group (p<0.001)

Study Methods

- Systematic review and meta-analysis of individual patient data from RCTs that investigated the role of temporary ovarian suppression with GnRHa during chemotherapy for early breast cancer patients



PROSPERO registration number: CRD42014015638

Study Characteristics

	PROMISE-GIM6[1,2]	POEMS/SWOG S0230[3]	Moffitt-led trial[4]	GBG-37 ZORO[5]	Anglo Celtic Group OPTION[6]
Definition of POI	No resumption of menstrual activity and postmenopausal levels of FSH and E2	Amenorrhea for the prior 6 months and postmenopausal levels of FSH	No maintenance of menses and no resumption of menses	No re-appearance of two consecutive menstrual periods within 21 to 35 days	Amenorrhea with elevated FSH
Timing of POI after chemotherapy	12 months	24 months	24 months	6 months	Between 12 and 24 months
Sample size	281	257	48	60	227
ER status for eligibility	ER-positive and ER-negative	ER-negative only	ER-positive and ER-negative	ER-negative only	ER-positive and ER-negative
Upper age limit for eligibility	≤ 45 years	≤ 49 years	≤ 44 years	≤ 45 years	None
Type of GnRHa	Triptorelin	Goserelin	Triptorelin	Goserelin	Goserelin

1. Del Mastro L et al, *JAMA* 2011;306:269-76. 2. Lambertini M et al, *JAMA* 2015;314:2632-40. 3. Moore HCF et al, *N Engl J Med* 2015;372:923-32.
4. Munster P et al, *J Clin Oncol* 2012;30:533-38. 5. Gerber B et al, *J Clin Oncol* 2011;29:2334-41. 6. Leonard RCF et al, *Ann Oncol* 2017;28:1811-16.

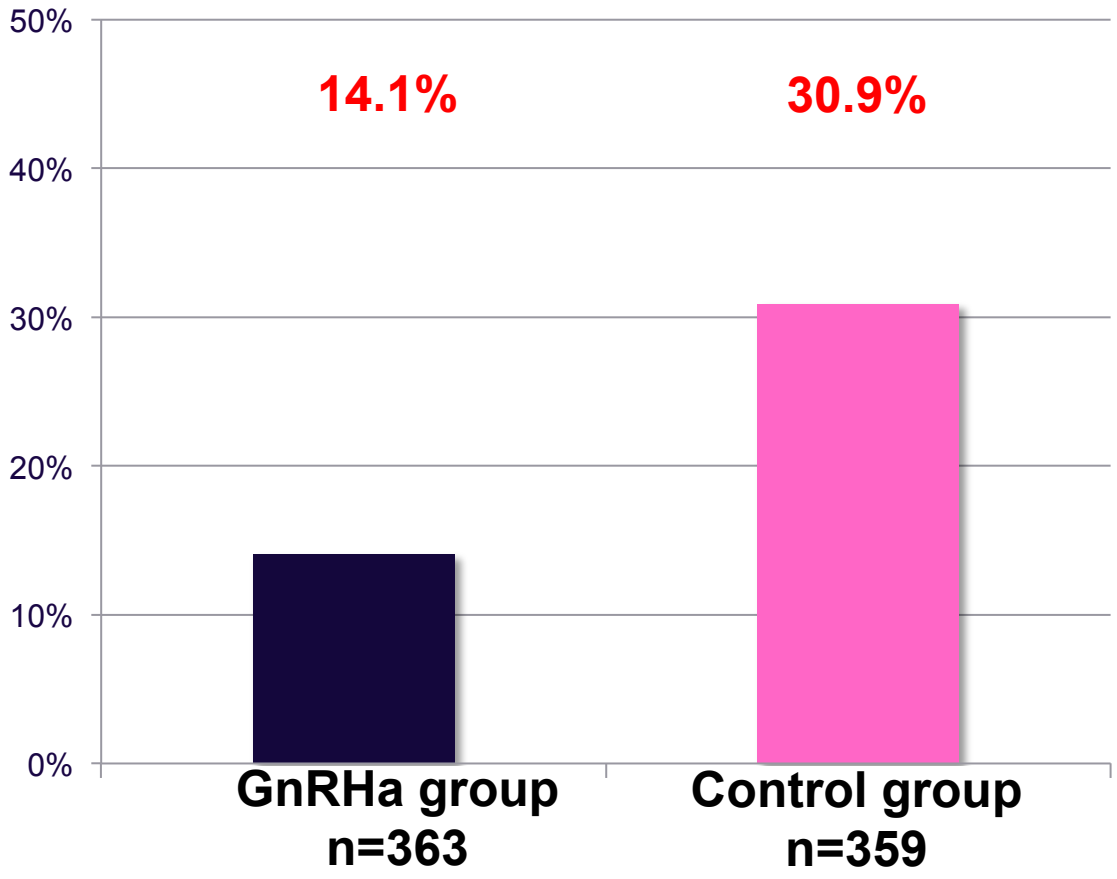
Baseline Characteristics

	GnRHa group (n=436) No. (%)	Control group (n=437) No. (%)	p value*
Age, median (interquartile range), years	38 (34-42)	39 (35-42)	0.258
Age distribution, years ≤ 40 ≥ 41	 297 (68.1) 139 (31.9)	 283 (64.8) 154 (35.2)	0.316
Estrogen receptor status Positive Negative Missing	 177 (40.6) 257 (58.9) 2 (0.5)	 173 (39.6) 262 (59.9) 2 (0.5)	0.782
Type of chemotherapy Anthracycline only-based Anthracycline- and taxane-based Non anthracycline-based Missing	 194 (44.5) 227 (52.1) 6 (1.4) 9 (2.1)	 198 (45.3) 210 (48.0) 13 (3.0) 16 (3.7)	0.196
Cumulative cyclophosphamide dose, median (interquartile range), mg/m^2	4000 (3420-5185)	3960 (3082-5400)	0.585

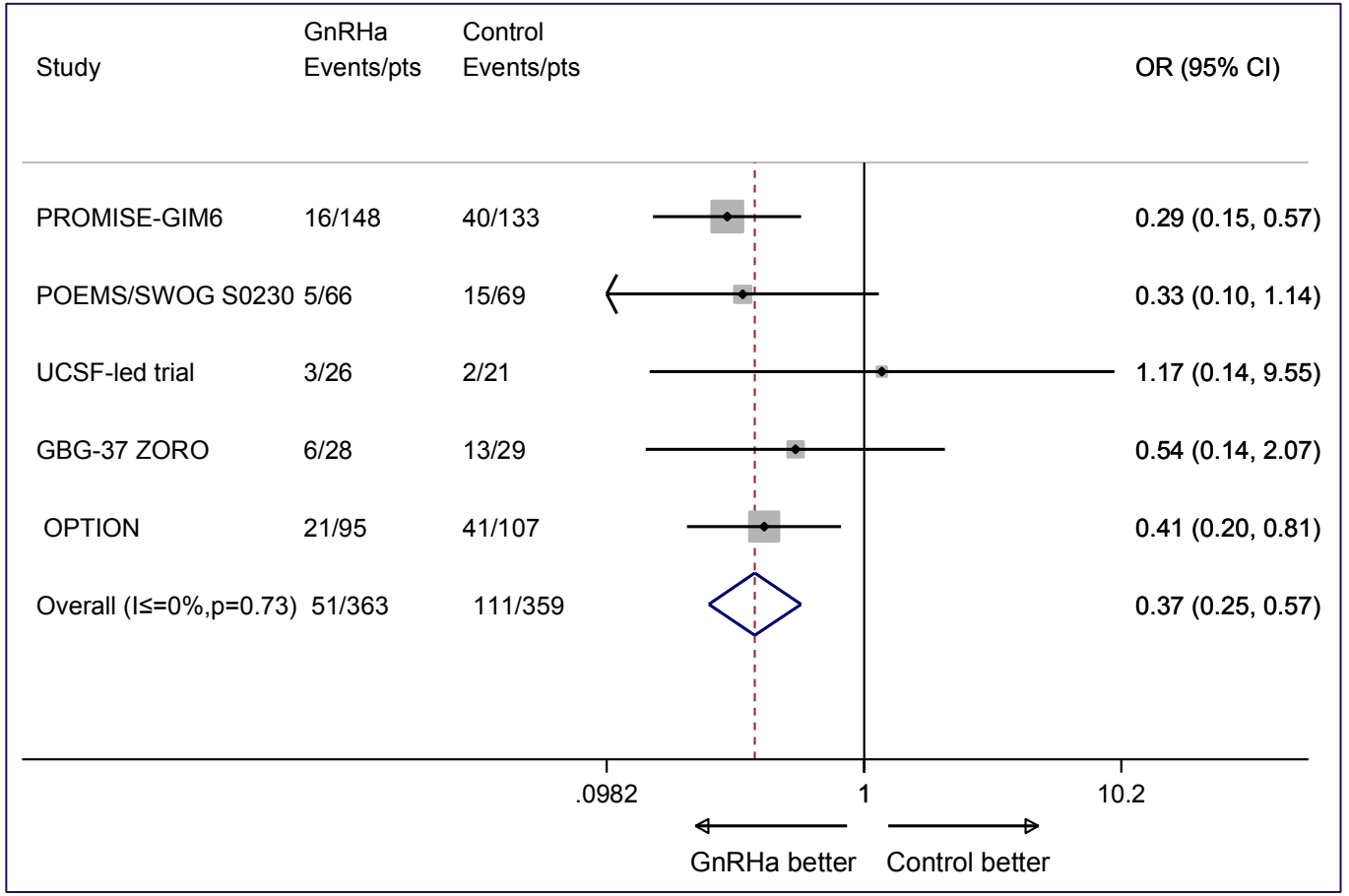
***Calculated by excluding missing data**

Premature-Ovarian Insufficiency Rate

OR* 0.38 (95% CI 0.26-0.57)
p<0.001

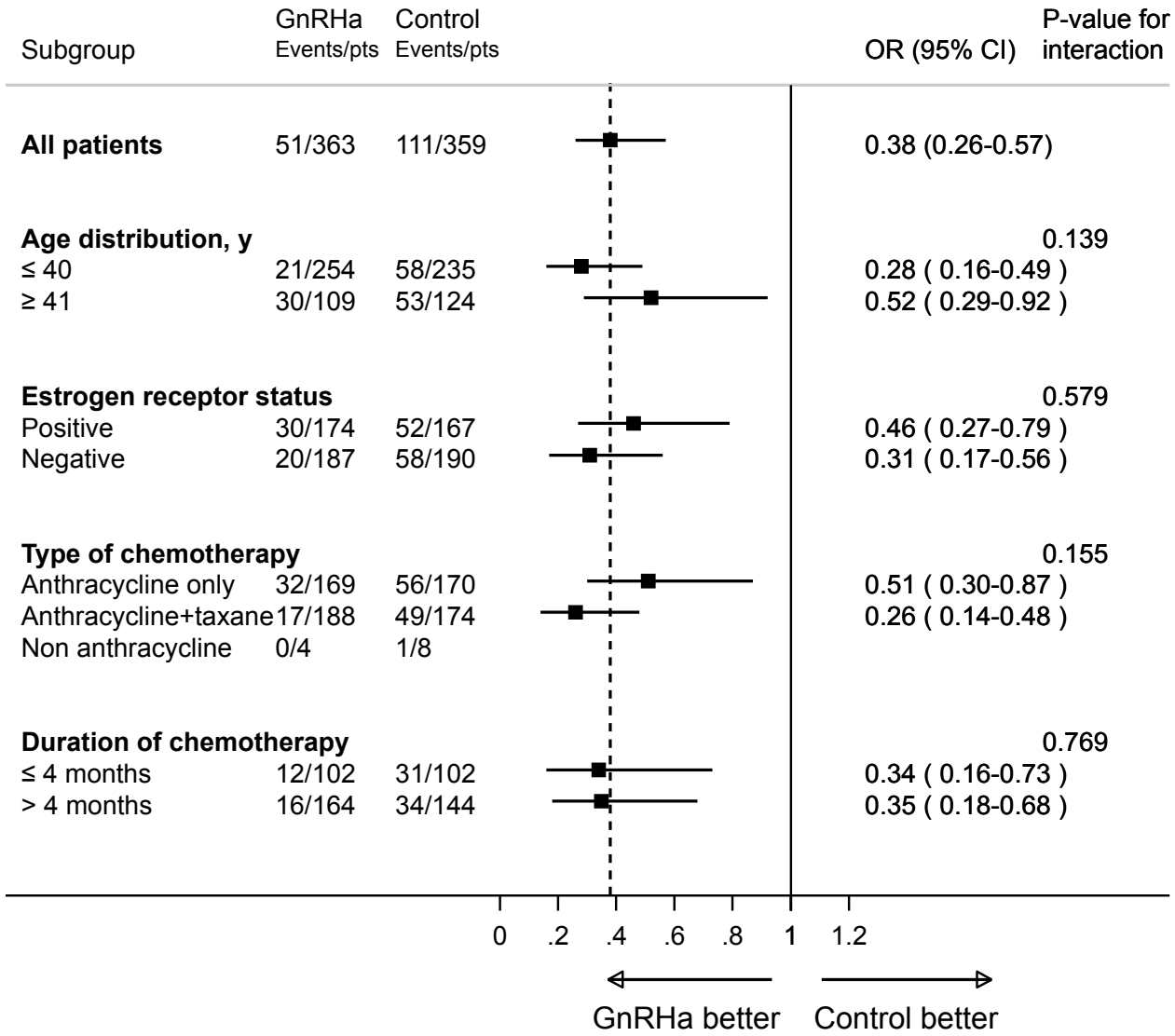


Meta-analysis approach



***Odds ratio (OR) adjusted for age, estrogen receptor status, type and duration of chemotherapy administered**

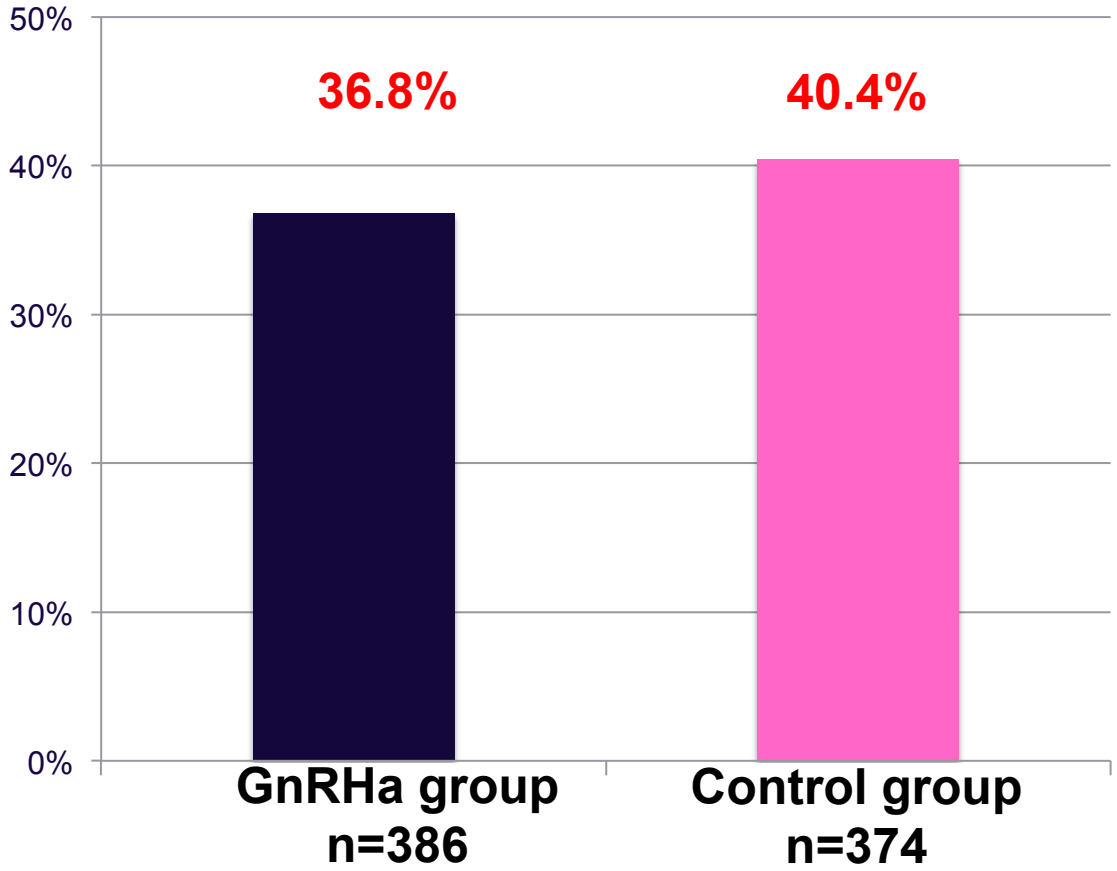
Premature-Ovarian Insufficiency Rate



Amenorrhea Rates

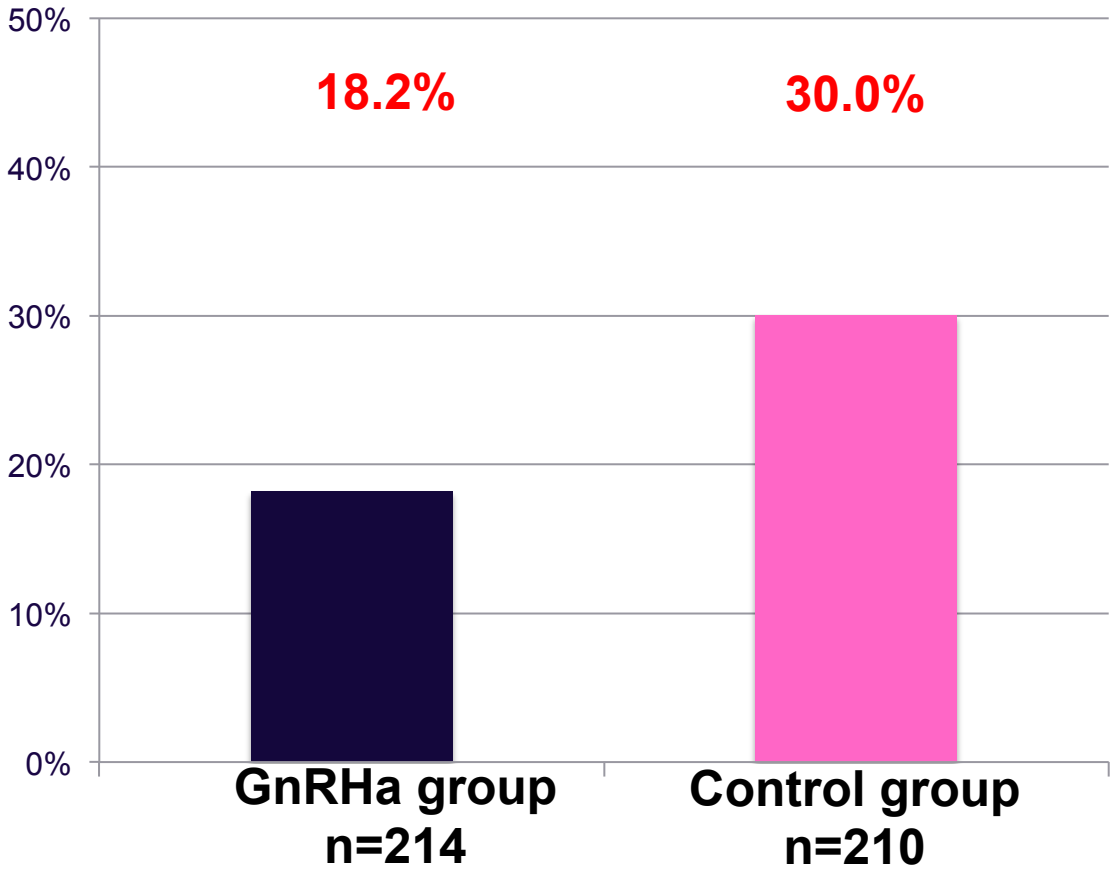
One-Year Amenorrhea

OR* 0.92 (95% CI 0.66-1.28); p=0.623



Two-Year Amenorrhea

OR* 0.51 (95% CI 0.31-0.85); p=0.009



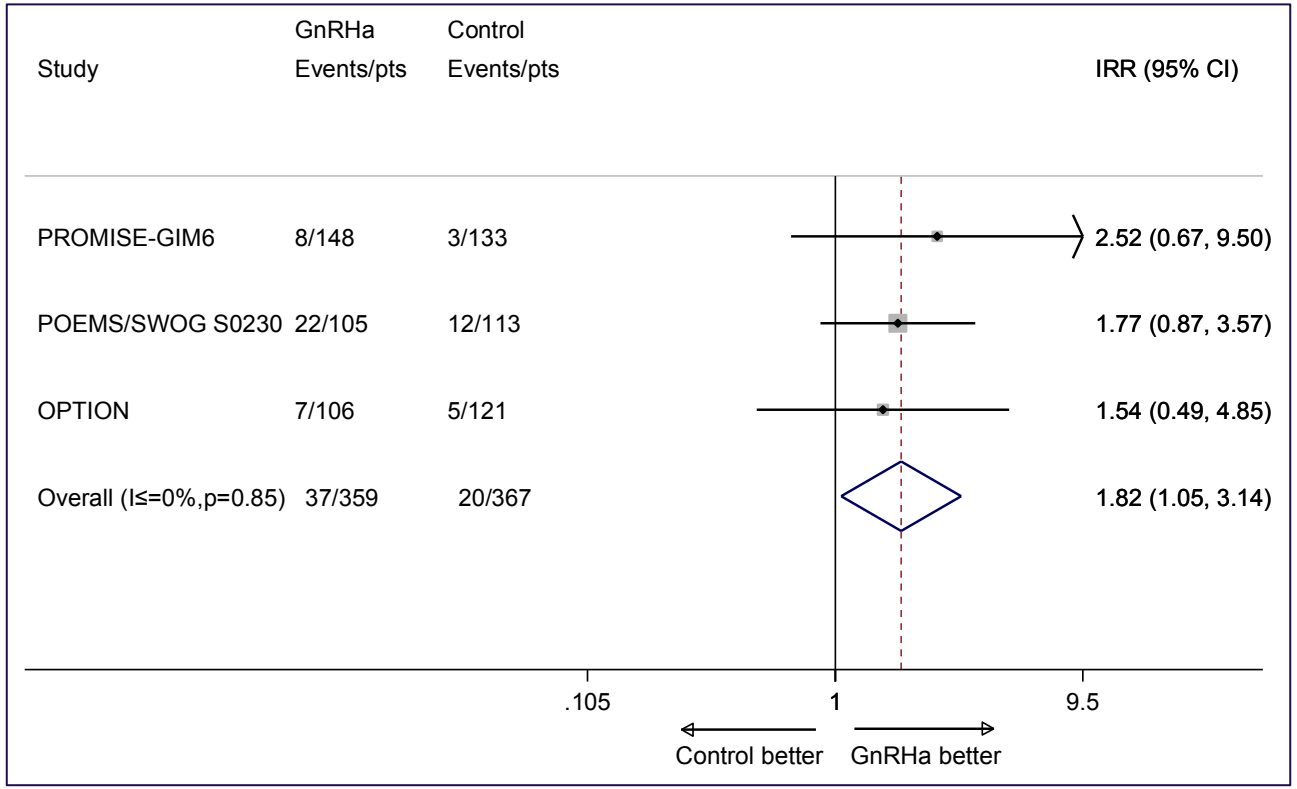
***Odds ratio (OR) adjusted for age, estrogen receptor status, type and duration of chemotherapy administered**

Post-Treatment Pregnancy Rate

GnRHa Group: 37/359 (10.3%)
vs.
Control Group: 20/367 (5.5%)

IRR* 1.83 (95% CI 1.06-3.15)
p=0.030

Meta-analysis approach

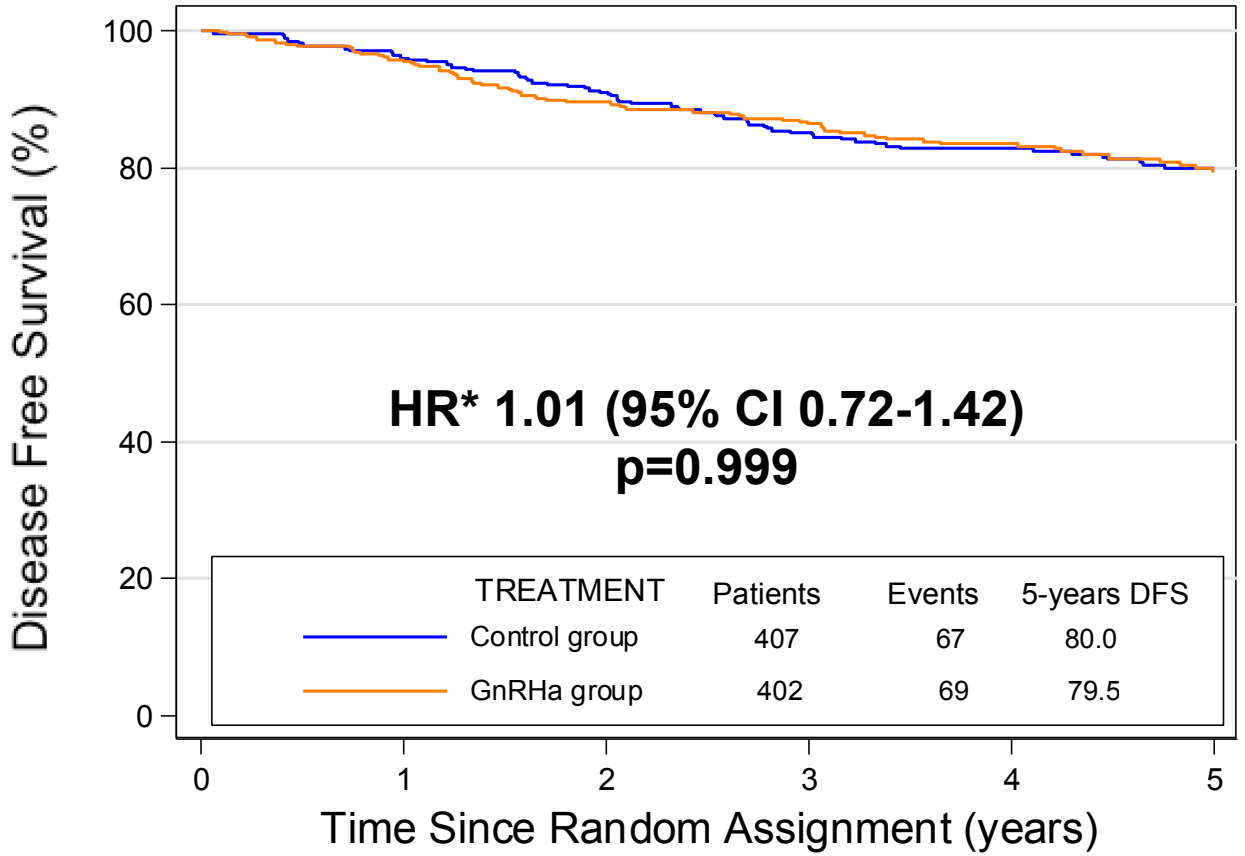


	GnRHa group (n = 37) No. (%)	Control group (n = 20) No. (%)
Age distribution, years		
≤ 40	37 (100)	20 (100)
≥ 41	0 (0.0)	0 (0.0)
Estrogen receptor status		
Positive	6 (16.2)	2 (10.0)
Negative	31 (83.8)	18 (90.0)

***Incidence rate ratio (IRR)**

Disease-Free Survival

Median follow-up = 5.0 years (IQR, 3.0 - 6.3 years)



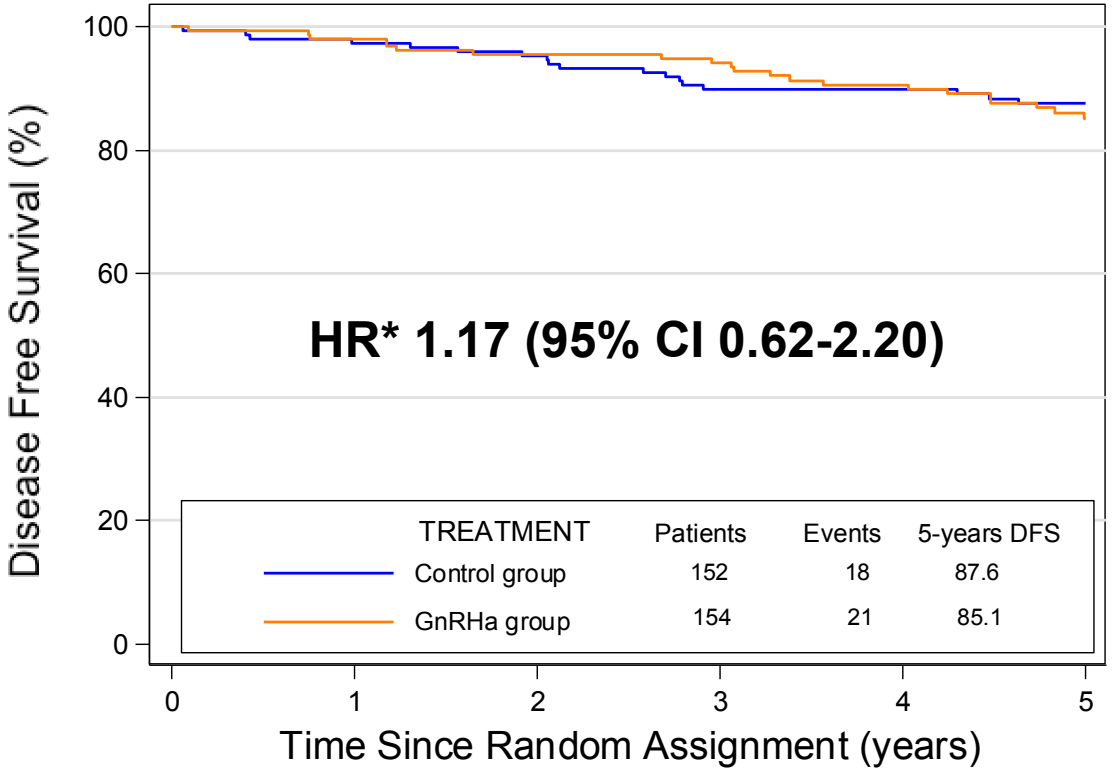
Number at risk

Control group	407	352	322	268	232	172
GnRHa group	402	356	323	286	240	174

***Hazard ratio (HR) adjusted for age, estrogen receptor status, type and duration of chemotherapy administered and tumor stage**

Disease-Free Survival

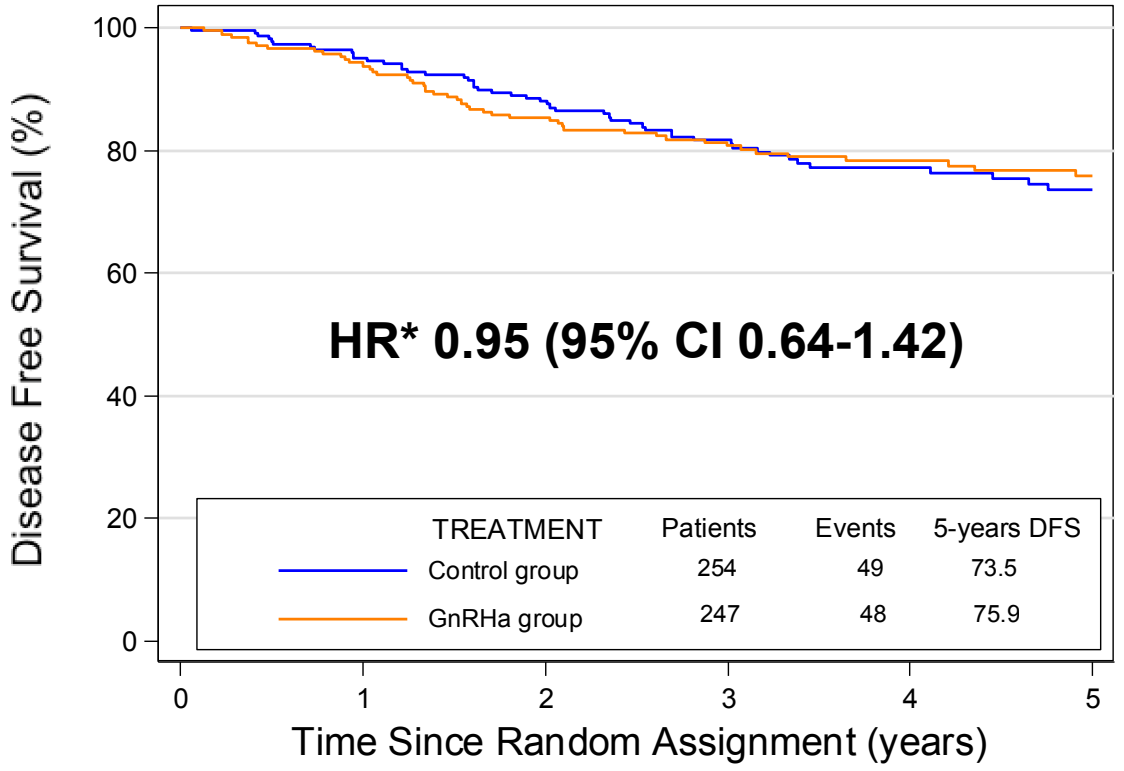
Estrogen receptor-positive disease



Number at risk

Control group	152	145	140	129	124	110
GnRHa group	154	151	144	137	123	102

Estrogen receptor-negative disease



Number at risk

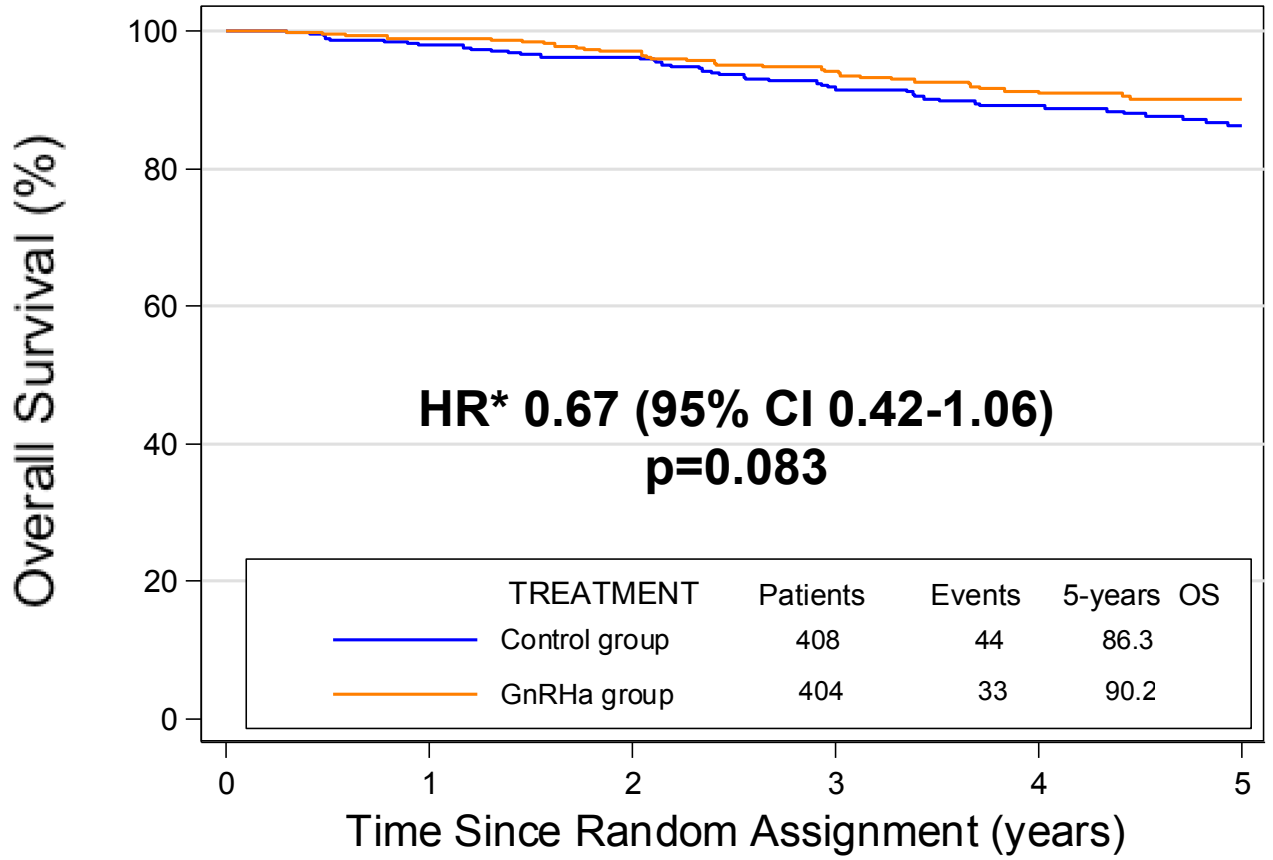
Control group	254	206	181	138	108	62
GnRHa group	247	204	178	148	116	71

***Hazard ratio (HR) adjusted for age, estrogen receptor status, type and duration of chemotherapy administered and tumor stage**

$p_{interaction}$=0.867

Overall Survival

Median follow-up = 5.0 years (IQR, 3.0 - 6.3 years)



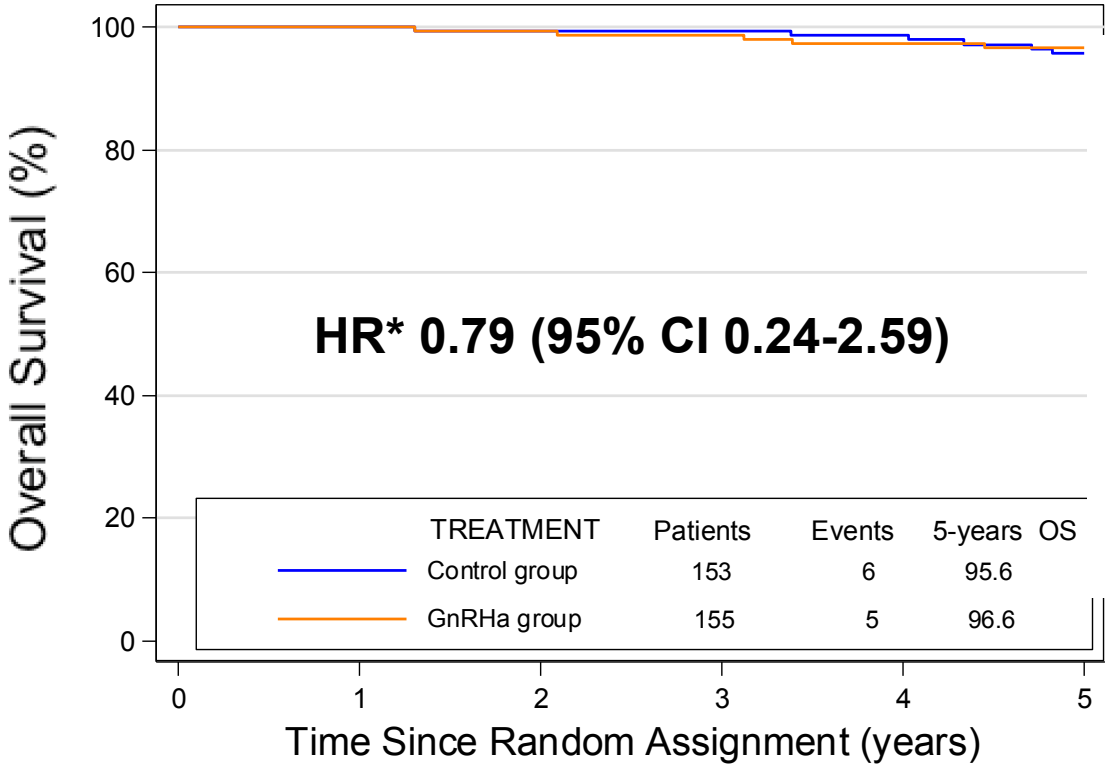
Number at risk

Control group	408	362	342	291	254	188
GnRHa group	404	370	350	313	265	199

***Hazard ratio (HR) adjusted for age, estrogen receptor status, type and duration of chemotherapy administered and tumor stage**

Overall Survival

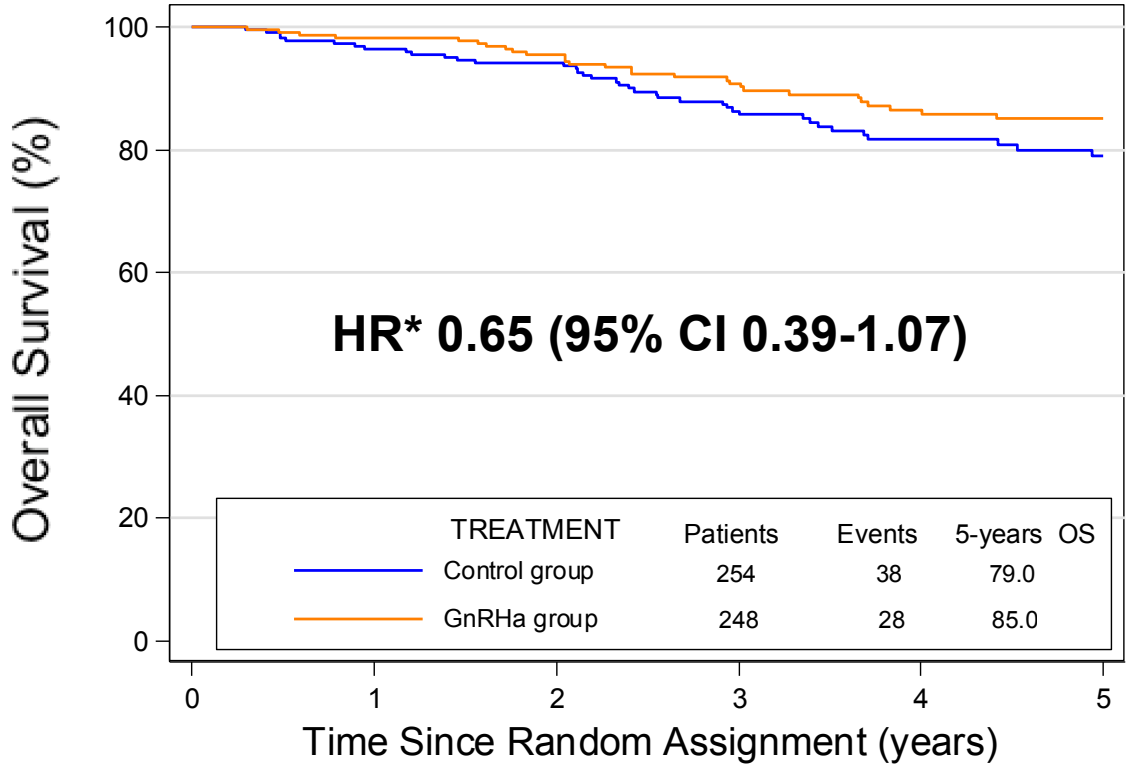
Estrogen receptor-positive disease



Number at risk

Control group	153	150	146	141	136	119
GnRHa group	155	155	151	146	135	118

Estrogen receptor-negative disease



Number at risk

Control group	254	211	195	149	118	69
GnRHa group	248	214	198	166	129	80

***Hazard ratio (HR) adjusted for age, estrogen receptor status, type and duration of chemotherapy administered and tumor stage**

$p_{interaction}=0.762$

Conclusions

- Administration of GnRHa during chemotherapy is associated with a significant reduction in the risk of chemotherapy-induced POI
- A greater number of women in the GnRHa group had a post-treatment pregnancy
- Similar DFS and OS were observed between groups irrespective of the estrogen receptor status of the disease
- This strategy should be considered as an option to reduce the likelihood of chemotherapy-induced POI and potentially improve future fertility in premenopausal early breast cancer patients undergoing (neo)adjuvant chemotherapy

Weight Loss and Breast Cancer Incidence in Postmenopausal Women

- Chlebowski RT, Luo J, Anderson GL, Barrington W, Redding K, Simon MS, Manson JE, Rohan TE, Wactawski-Wende J, Lane D, Strickler H, Mosaver-Rahmani Y, Freudenheim JL, Saquib N, Stefanick ML

- City of Hope National Medical Center
- Women's Health Initiative Investigators

Background and Study Objectives

Background

While obesity is an established risk factor for postmenopausal breast cancer,[1,2] studies of weight loss and breast cancer provide inconsistent results [3]

Consequently, the current public health message is limited to "avoid body fatness"(International Association for Research on Cancer [IARC]) [3]

Study Objectives

To evaluate associations between weight change categories and breast cancer incidence in postmenopausal women participating in the Women's Health Initiative (WHI) Observational Study

Secondary analyses explored the association of weight loss and breast cancer incidence by weight loss intentionality

Intentional Weight Loss and Endometrial Cancer Risk among 36,794 Postmenopausal Women after 11.4 Years (median) follow-up

% Weight Change	Endometrial cancers (N)	HR (95% CI)
Stable Weight (within ± 5%)	384	Reference
Weight gain (≥ 5%)	124	1.12 (0.92 to 1.38)
Weight loss (≥ 5%)	58	0.71 (0.54 to 0.95)
Intentional	33	0.60 (0.42 to 0.86)
Unintentional	25	0.94 (0.62 to 1.41)

Abbreviation: HR, hazard ratio.
*Multivariable models adjusted for age at enrollment, race/ethnicity, education, smoking pack-years, recreational physical activity, history of hormone therapy use, parity, age of menarche, age at first birth, family history of endometrial cancer, and body mass index.

Luo, J , Chlebowski, RT, Hendryx M, et al. *J Clin Oncol 2017; 35*(11), 1189-1193.

Participants and Methods

Participants in the Women's Health Initiative (WHI) Observational Study (n= 93,676)

- Postmenopausal, ages 50-79 years, with anticipated 3 year survival, recruited from 40 US Clinical Centers from 1993-1998
- 11.4 years mean follow-up through September 30, 2015

Measures

- Information on demographics, medical history and breast cancer risk factors collected at baseline by questionnaires
- Information on medication use collected at baseline during interviews including "in hand" medication container review.
- Mammograms were not protocol mandated but mammogram frequency was collected annually

Measurements

- Measured height and weight at baseline and year 3, calculated body mass index (BMI kg/m^2)
- Weight change categories calculated as measured weight at year 3 subtracted from measured weight at baseline divided by measured weight at baseline:
  - Weight stable, ≤± 5% weight change
  - Weight gain ≥ 5% increase
  - Weight loss, ≥ 5% decrease
- Self-reported weight at year 6 used in exploratory analyses
- At year 3, participants asked in a questionnaire
  - “In the past 2 years, did you gain or lose 5 or more pounds” (yes/no)
  - “Was the weight change intentional or unintentional ” (yes/no)

Baseline Characteristics by Weight Change Category

- Compared with the women with stable weight:
- Women who had ≥ 5% weight gain were more likely to be younger, Black and be heavier smokers (all P < .01)
- Women who had ≥ 5% weight loss were more likely to have higher BMI, but were less likely to be physically active or have used any menopausal hormone therapy (all P < .01)
- Other baseline characteristics including education, alcohol intake, history of estrogen alone or estrogen plus progestin, BCRAT risk score, bilateral oophorectomy, physical activity (MET-hrs/wk), BMI, and diabetes were similar among weight change category groups

Baseline Medication Use (%) by Weight loss Category

Weight change category	Metformin	NSAID
Stable Weight (within ± 5%) (n=41,139)	0.5%	8.7%
Weight gain (≥ 5%) (n=12,021)	0.7%	12.6%
Weight loss (≥ 5%) Intentional (n=4,829)	0.8%	10.3%
Weight loss (≥ 5%) Unintentional (n=3,346)	1.1%	+12.2%

Metformin use rare

Abbreviation: HR, hazard ratio.
*Multivariable models adjusted for age at enrollment, race/ethnicity, education, smoking pack-years, recreational physical activity, history of hormone therapy use, parity, age of menarche, age at first birth, family history of endometrial cancer, and body mass index.

Weight Change and Breast Cancer incidence (n= 3,061 cases) among 61,335 Postmenopausal Women after 11.4 Years (median) follow-up

- In multivariable–adjusted analyses, compared with the women with stable weight (n=41,139):
- Women who had ≥ 5% weight loss (n=8,175) had a significantly lower breast cancer incidence (HR 0.88 95% CI 0.78-0.98)
- Adjustment for mammography frequency did not alter findings (HR 0.88 95% CI 0.78-0.99)
- Women who had ≥ 5% weight gain (n=12,021) did not have a higher overall breast cancer incidence (HR 1.02 95% CI 0.93-1.11). However, women with such weight gain had a significantly higher incidence of triple negative breast cancer (HR 1.54 95% CI 1.16-2.05)

Weight Change and Breast Cancer incidence including by Weight Loss Intentionality

% Weight change between baseline And Year 3	Breast cancer cases (N)	HR (95% CI) Multivariable- adjusted
Stable Weight (within ± 5%)	2,092	Reference
Weight gain (≥ 5%)	620	1.02 (0.93-1.11)
Weight loss (≥ 5%)	349	0.88 (0.78-0.98)
Intentional	229	0.91 (0.79-1.04)
Unintentional	120	0.82 (0.68-0.99)

Statistical test between intentional and unintentional weight loss groups found no significant difference (P=0.2)

Abbreviation: HR, hazard ratio.
*Multivariable models adjusted for age at enrollment, race/ethnicity, education, smoking pack-years, recreational physical activity, history of hormone therapy use, parity, age of menarche, age at first birth, family history of endometrial cancer, and body mass index.

Summary and Conclusions

- In a large prospective study of postmenopausal women, compared to women with stable weight, women with weight loss of ≥ 5% were at a lower breast cancer risk

- There was no significant difference in breast cancer findings by weight loss intentionality

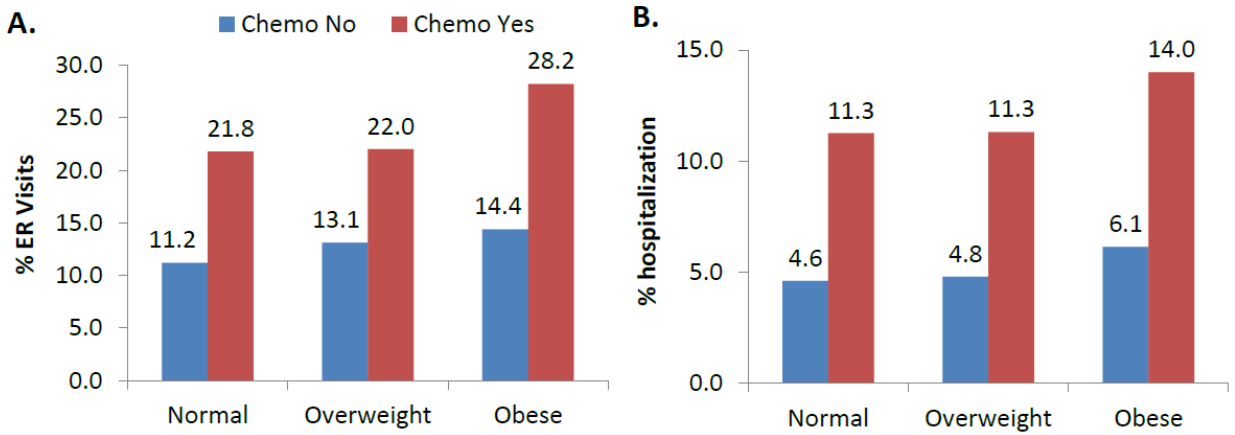
- These findings suggest that interventions in postmenopausal women designed to generate weight loss may reduce breast cancer risk.

Association of Body Mass Index (BMI) with chemotherapy administration and emergency room (ER) visits among breast cancer patients.

Sharon H. Giordano[1,2], Jiangong Niu[1], Hui Zhao[1], Daria Zorzi[1], and Mariana Chavez Mac Gregor [1,2]

[1]Department of Health Services Research, [2] Department of Breast Medical Oncology, The University of Texas M.D. Anderson Cancer Center

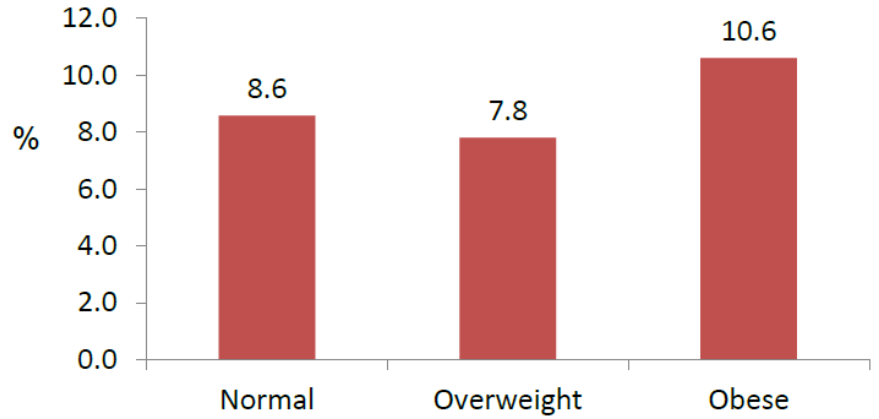
Figure-1. A) ER visits and **B)** All hospitalization rates within 6 months of diagnosis according to chemotherapy and BMI status. (ER=Emergency room).



p=0.018 - *Chemo No*
p<0.001 - *Chemo Yes*

p=0.087 - *Chemo No*
p=0.091 - *Chemo Yes*

Figure 2. Chemo-related hospitalization rates according to BMI



Obese patients with breast cancer are more likely than normal weight patients to have ER visits and hospitalizations in the 6 months after diagnosis

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Randomized Blinded Sham- and Waitlist-Controlled Trial of Acupuncture for Joint Symptoms Related to Aromatase Inhibitors in Women with Early Stage Breast Cancer (SWOG 1200)

- Dawn L. Hershman, Joseph M. Unger, Heather Greenlee, Jillian Capodice, Danika L. Lew, Amy Darke, Alice Kengla, Marianne K. Melnik, Carla W. Jorgensen, William H. Kreisle, Lori M. Minasian, Michael J. Fisch, N. Lynn Henry, Katherine D. Crew

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BACKGROUND

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- Despite the efficacy of aromatase inhibitors, many patients suffer from joint side effects > leading to non-compliance.
- Compliance to AI's is associated with improved disease-free survival.
- Acupuncture is a popular non-pharmacologic modality for the treatment of a variety of medical conditions.
- Several small studies have suggested acupuncture may be beneficial for AI-arthralgias; however others have shown no benefit.
- The overall interpretation of these trials has been uncertain due to short duration, small sample sizes and differences in methodology.

Hershman, DL. JCO,2008
Chrigwin. JH. JCO, 2016
Crew, KD. JCO, 2010

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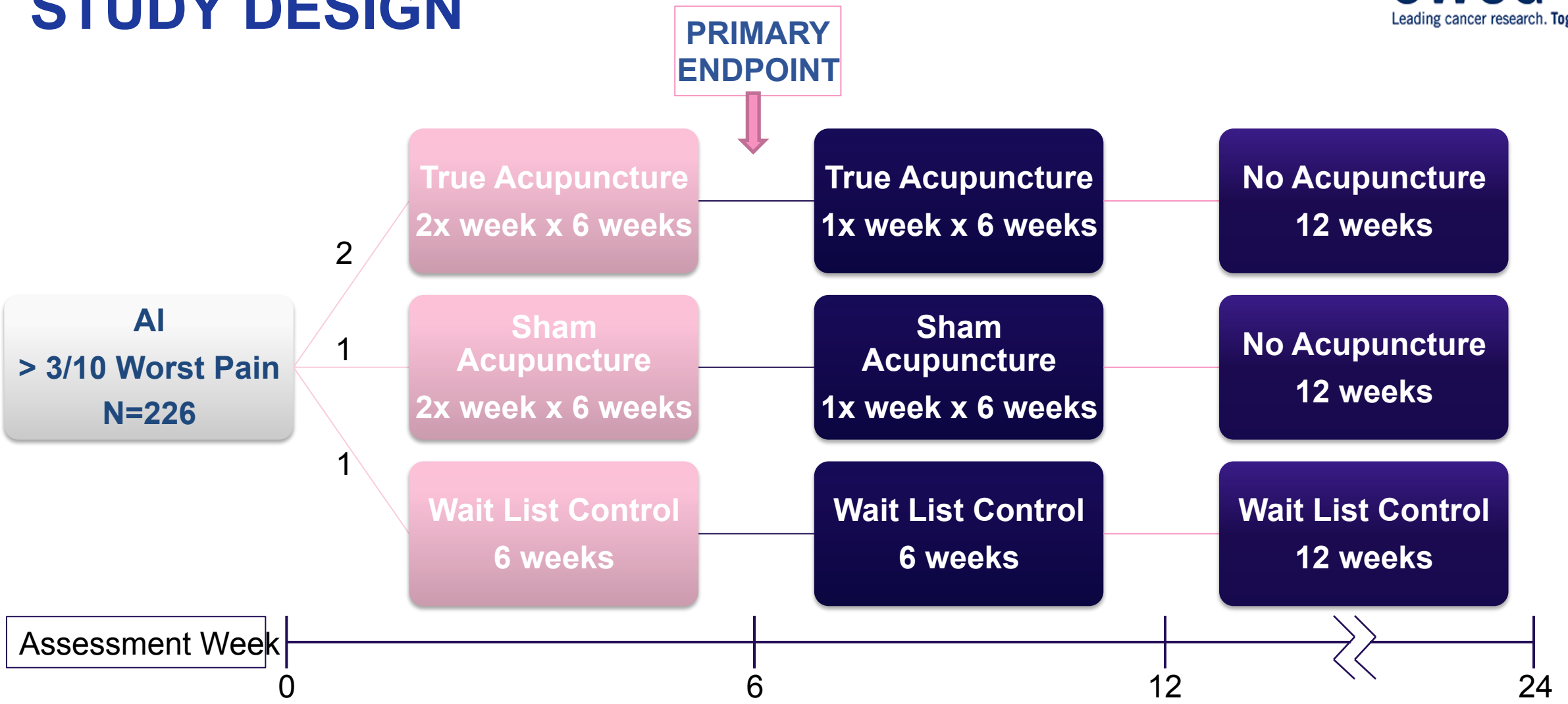
STUDY DESIGN



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ELIGIBILITY

- Stage 1-3 hormone sensitive breast cancer
- Third-generation AI for at least 30 days prior to registration
- Score of ≥3 (range, 0-10) on the worst pain item of the BPI
- Symptoms started or increased since starting AI
- No opioids or corticosteroid and no alternative/physical therapy for the treatment of joint pain within 28 days prior to registration
- No prior acupuncture treatment for joint symptoms at any time, but allowed for other reasons >12 months prior

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INTERVENTION

- **True Acupuncture**
  - Standard Traditional Chinese Medicine point prescription to reduce pain and decrease stress (30-45 min per session)
  - Full body, auricular and joint-specific acupuncture protocol tailored to the most painful joints
- **Sham Acupuncture**
  - Shallow needle insertion utilizing thin and short needles at non-acupuncture points
  - Four standardized points, auricular sham and joint-specific sham point protocols within the proximity of the specified anatomic area
- **Wait List Control**
  - True acupuncture offered after 24 weeks

Crew, KD. JCO,2010

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TRAINING

- Interventions were provided by licensed acupuncturists at 11 sites
- **Online training modules**
  - *Videos*
  - *Visuals*
- **Training manuals**
- **In-person / on-site acupuncturist training**
- **Monthly teleconference**
- **Quality assurance**
  - *Yearly quality assurance training*
  - *Web-based quiz*
  - *Practical demonstration - video based (Skype or Recorded)*

Greenlee, H.
J Acupunct Meridian Stud. 2015

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OUTCOME MEASURES

- BPI Short Form (6, 12, 16, 20, 24 weeks)
- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) – Knees and Hips
- Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH)
- The Functional Assessment of Cancer Therapy-Endocrine Symptoms (FACT-ES)
- Grip Strength / Timed Get up and Go
- AI Adherence (52 weeks)
- Serum/DNA

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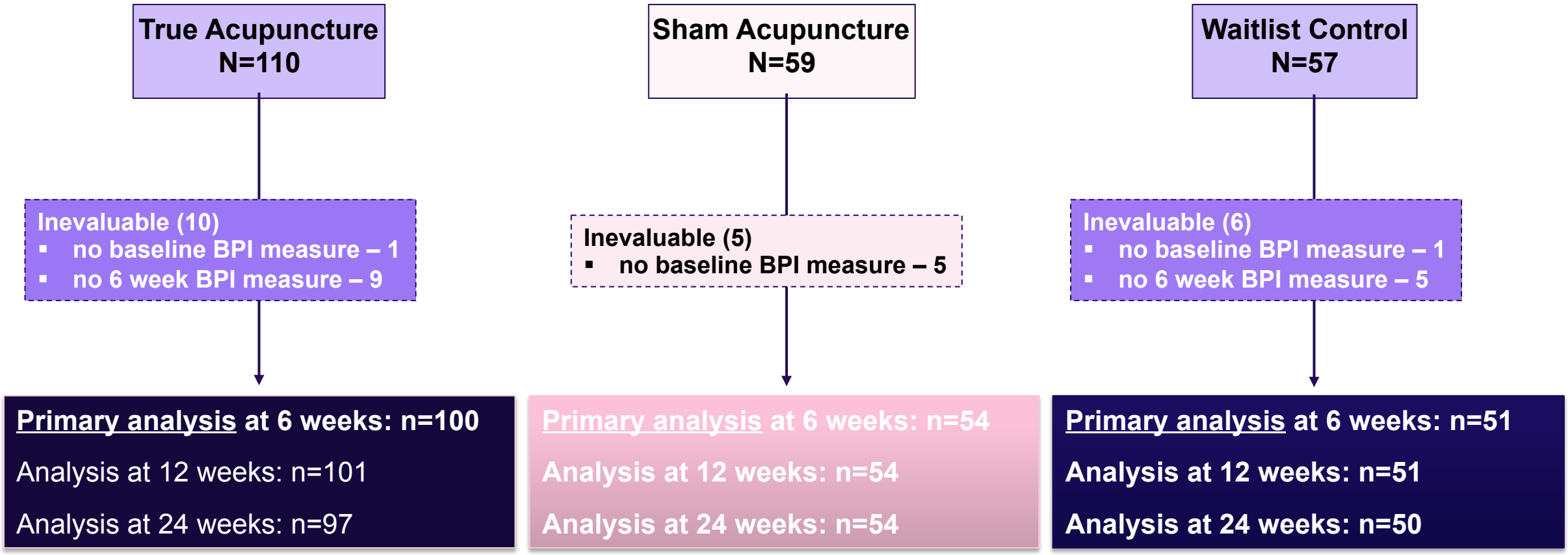
226 PATIENTS RANDOMIZED



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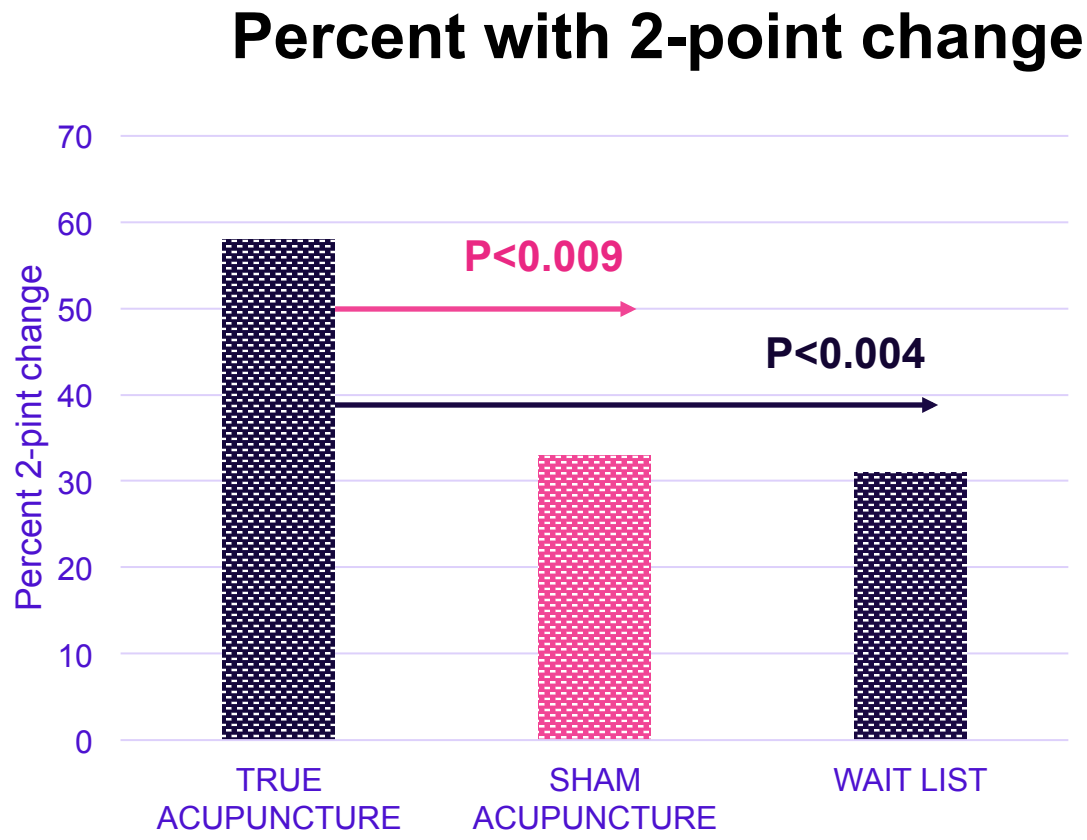
PATIENT CHARACTERISTICS

	Total (n=226)		True Acupuncture (n=110)		Sham Acupuncture (n=59)		Waitlist Control (n=57)	
Age, years								
Median	60.7		60.8		57.0		60.6	
Hispanic, N (%)	21	7%	11	10%	7	12%	3	5%
Race, N (%)								
White	193	88%	88	83%	54	93%	51	91%
Black	10	5%	6	6%	2	3%	2	4%
Asian	15	7%	11	10%	2	3%	2	4%
Prior Chemotherapy, N (%)	111	49%	56	51%	31	53%	24	42%
AI Therapy (median yrs)	1.1		1.0		1.1		1.1	
Prior Acupuncture, N (%)	44	19%	19	17%	13	22%	12	21%
Baseline Score – BPI WP			6.84		6.55		6.48	

6-WEEK RESULTS - WORST PAIN (BPI)

WORST PAIN	Fitted Difference*	P-value
True v. Sham	0.92 (0.20-1.65)	.01
True v. Waitlist	0.96 (0.24-1.67)	.01
Sham v. Waitlist	0.05 (-0.81-0.90)	.92

* Corrected for baseline score and study site



RESULTS - Other 6 Week Endpoints

BPI AVERAGE PAIN	Fitted Difference	P-value
True v. Sham	0.60 (0.03, 1.17)	.04
True v. Waitlist	0.71 (0.15, 1.28)	.01
Sham v. Waitlist	0.08 (-0.51, 0.68)	.79

WOMAC	Fitted Difference	P-value
True v. Sham	9.27 (3.73, 14.82)	.001
True v. Waitlist	12.18 (6.76, 17.59)	<.0001
Sham v. Waitlist	3.01 (-2.75, 8.78)	0.31

BPI STIFFNESS	Fitted Difference	P-value
True v. Sham	1.00 (0.19, 1.81)	.02
True v. Waitlist	1.09 (0.26, 1.92)	.01
Sham v. Waitlist	0.17 (-0.62, 0.96)	.67

M-SACRAH	Fitted Difference	P-value
True v. Sham	6.23 (0.92, 11.55)	.02
True v. Waitlist	9.40 (4.52, 14.28)	.0002
Sham v. Waitlist	4.26 (-1.32, 9.84)	.14

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ADVERSE EVENTS

	True Acupuncture (n=106) Grade				Sham Acupuncture (n=55) Grade			
ADVERSE EVENTS	0	1	2	3	0	1	2	3
Bruising	**56**	**50**	0	0	**41**	**14**	0	0
Dizziness	101	5	0	0	55	0	0	0
Ear pain	105	1	0	0	54	1	0	0
Hematoma	105	1	0	0	55	0	0	0
Bleeding at injection site	103	3	0	0	53	2	0	0
Pain in extremity	105	1	0	0	55	0	0	0
Presyncope	105	0	1	0	54	0	1	0

Grade 1 bruising (47% vs. 25%) p=.01

- Patients on true acupuncture were more likely to believe they were receiving true acupuncture 6 weeks (68% vs. 36%, p<.0001).
- The intervention effect did not differ between those believing vs. not believing they were receiving true acupuncture at either 6 weeks (p=.16) using interaction tests.

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CONCLUSIONS

- We have shown consistently, with multiple measures assessing pain and stiffness, that true acupuncture generated better outcomes than either control group in a large multicenter randomized controlled trial.
- Transitioning from twice-a-week to once-a-week acupuncture maintained the effect of the intervention.
- The intervention effects persisted 12 weeks following completion of the intervention.
- The toxicity of the intervention was minimal and limited to grade 1 bruising.

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CLINICAL IMPLICATIONS

- Acupuncture provides a non-pharmacologic option that can improve symptoms and possibly increase AI adherence + subsequent BC outcomes.
- For patients reluctant to take a prescription medication, that can result in other side effects, acupuncture provides a safe and effective alternative.
- Identification of non-opioid options for pain control is a public health priority.
- The cost of the 12-week (18 session) intervention was ~ $1,250 ($65-$75/session) and we feel there is now sufficient evidence to support insurance coverage of acupuncture for AI arthralgia.

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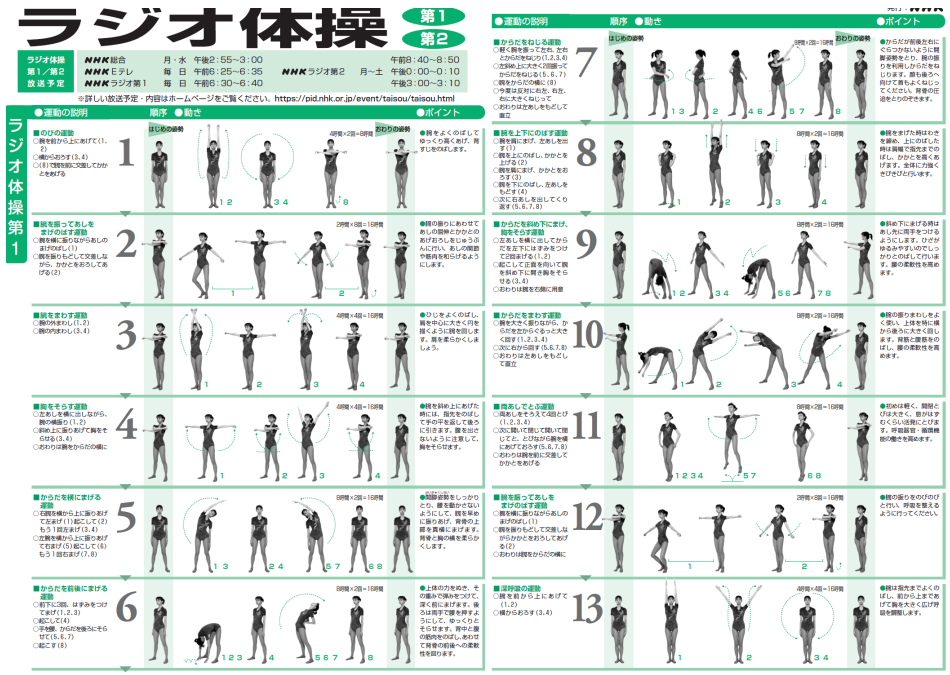
Final results of the randomized trial of exercise intervention vs. usual care for breast cancer patients with aromatase inhibitor to prevent and improve the aromatase inhibitor induced arthralgia

Kentaro Tamaki, Mutsuyo Takaesu, Sayaka Nagamine, Shigeharu Terukina, Yoshihiko Kamada, Kano Uehara, Naoko Takigami, Miwa Arakaki, Kazuko Yamashiro, Minoru Miyashita, Takanori Ishida, Keely May McNamara, Nobumitsu Tamaki, Hironobu Sasano
Nahanishi Clinic Okinawa, JAPAN

- 3 forms of exercises:
  - 120-150 min per week walking or running
  - Gentle calisthenics
  - Going up stairs and performing other daily activities



- **There was improvement in pain**
- **There was a statistically significant difference of AIs adherence between the exercise intervention group (99%) and the usual care group (92%) (P= . 030)**

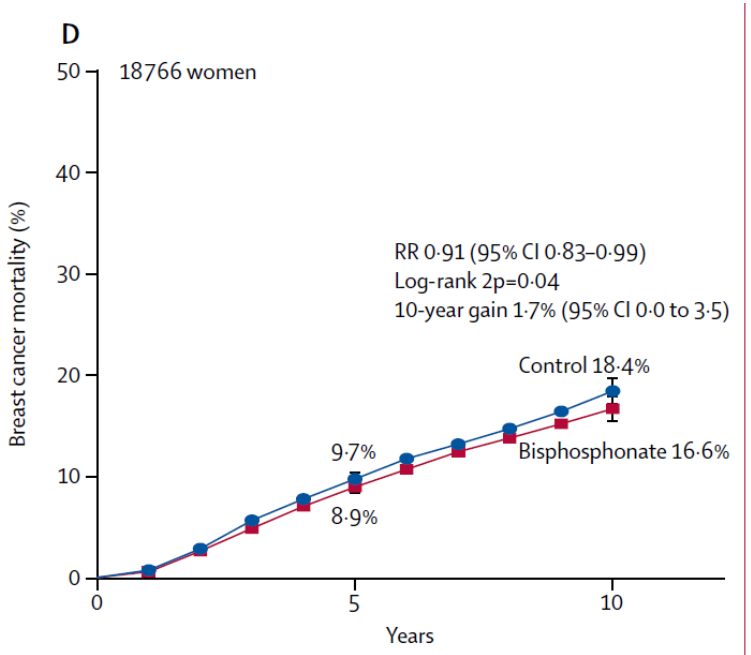
Extended adjuvant bisphosphonate treatment over five years in early breast cancer does not improve disease-free and overall survival compared to two years of treatment: Phase III data from the SUCCESS A study

Wolfgang Janni, Thomas WP Friedl, Tanja Fehm, Volkmar Mueller, Werner Lichtenegger, Jens Blohmer, Ralf Lorenz, Helmut Forstbauer, Emanuel Bauer, Visnja Fink, Inga Bekes, Jens Huober, Julia Jückstock, Andreas Schneeweiss, Hans Tesch, Sven Mahner, Sara Y Brucker, Georg Heinrich, Lothar Häberle, Peter A. Fasching, Matthias W Beckmann, Robert Coleman, Brigitte Rack

Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials

Lancet 2015; 386: 1353–61

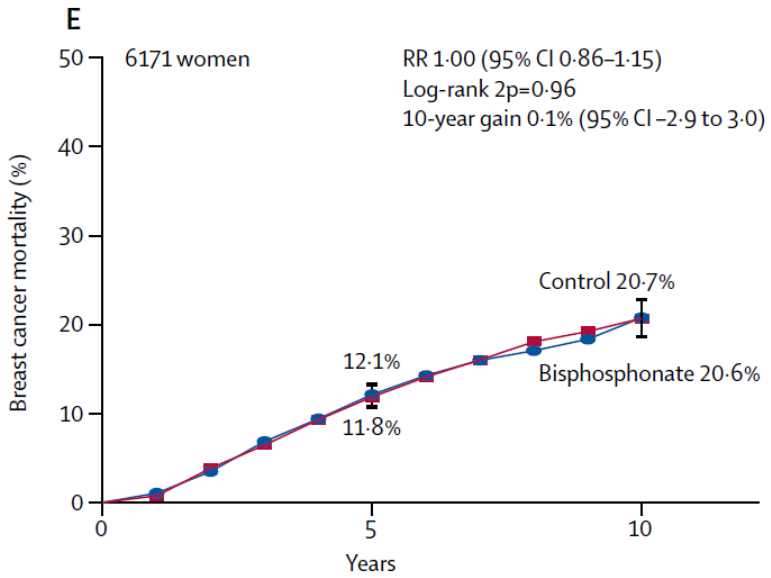
*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**



Death rates (%/year: total rate minus rate in women without recurrences) and log-rank statisti

Allocation	Years 0–4	Years 5–9	Years ≥10
Bisphosphonate	1·83 (1·70–1·97)	1·81 (1·59–2·03)	1·21 (0·72–1·69)
Control	1·98 (1·84–2·12)	1·97 (1·75–2·20)	1·69 (1·12–2·25)
Rate ratio (95% CI)	0·91 (0·81–1·01)	0·92 (0·75–1·10)	0·66 (0·18–1·15)
from (O–E)/V	–30·5/321·7	–9·5/121·0	–4·5/10·9

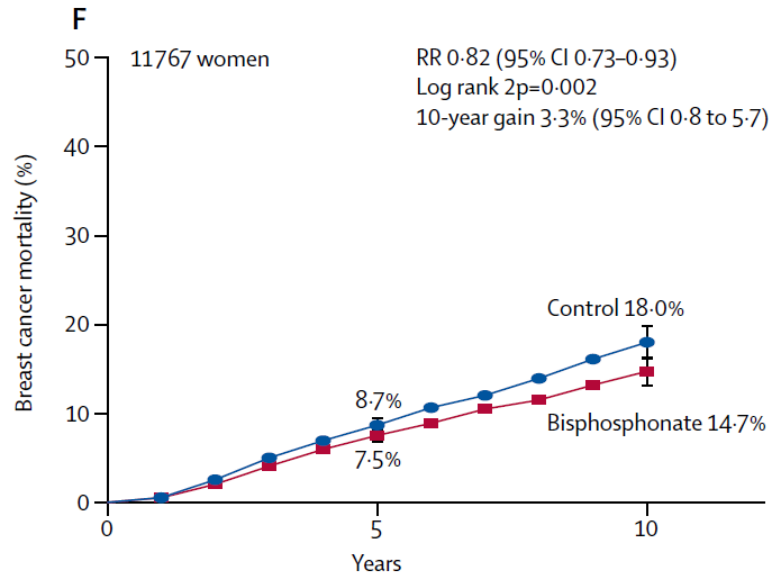
Breast Cancer Mortality ALL



Death rates (%/year: total rate minus rate in women without recurrence) and log-rank statistics

Allocation	Years 0–4	Years 5–9	Years ≥10
Bisphosphonate	2·43 (2·16–2·69)	2·26 (1·84–2·67)	1·13 (0·58–1·68)
Control	2·50 (2·22–2·79)	2·03 (1·65–2·40)	1·29 (0·71–1·88)
Rate ratio (95% CI)	0·97 (0·81–1·14)	1·10 (0·81–1·40)	0·71 (0·34–1·50)
from (O–E)/V	–3·3/130·6	5·0/50·0	–2·3/6·9

Breast Cancer Mortality Premenopausal



Death rates (%/year: total rate minus rate in women without recurrence) and log-rank statistics

Allocation	Years 0–4	Years 5–9	Years ≥10
Bisphosphonate	1·56 (1·41–1·72)	1·57 (1·30–1·84)	1·30 (0·34–2·26)
Control	1·74 (1·58–1·91)	2·04 (1·74–2·35)	2·73 (1·30–4·16)
Rate ratio (95% CI)	0·86 (0·72–0·99)	0·76 (0·55–0·97)	0·52 (0·18–1·44)
from (O–E)/V	–27·1/174·9	–18·0/65·0	–2·4/3·6

Breast Cancer Mortality Post menopausal

Category	Events/women		Bisphosphonate events		Ratio of annual event rates bisphosphonate : control	Rate ratio (CI)
	Allocated bisphosphonate	Allocated control	Log-rank O–E	Variance of O–E		
(a) Age, years (trend χ^2_1=4·9; 2p=0·03)						
<45	164/2475 (6·6%)	151/2141 (7·1%)	−0·3	71·3		1·00 (0·79–1·26)
45–54	152/3532 (4·3%)	173/3224 (5·4%)	−14·2	74·3		0·83 (0·61–1·11)
55–69	168/3314 (5·1%)	196/3022 (6·5%)	−25·1	84·4		0·74 (0·56–0·98)
≥70	13/531 (2·4%)	22/521 (4·2%)	−5·1	7·1		0·49 (0·19–1·29)
Age unknown	0/4 (0·0%)	0/2 (0·0%)				
(b) Menopausal status (trend χ^2_1=3·5; 2p=0·06)						
Premenopausal	217/3296 (6·6%)	212/2875 (7·4%)	−7·9	96·4		0·92 (0·71–1·20)
Perimenopausal	28/461 (6·1%)	19/367 (5·2%)	2·0	8·8		
Postmenopausal	252/6099 (4·1%)	311/5668 (5·5%)	−42·1	128·0		0·72 (0·57–0·90)
(c) ER status (χ^2_1=0·6; 2p=0·4)						
ER negative	107/1964 (5·4%)	135/1684 (8·0%)	−15·7	56·4		0·76 (0·54–1·07)
ER unknown	42/637 (6·6%)	47/690 (6·8%)	1·2	20·9		1·06 (0·60–1·86)
ER positive	348/7255 (4·8%)	360/6536 (5·5%)	−26·9	169·1		0·85 (0·70–1·04)
(d) Nodal status (trend χ^2_1=0·5; 2p=0·5)						
N0/N–	70/2638 (2·7%)	68/2631 (2·6%)	0·6	32·3		1·02 (0·72–1·44)
N1–3	225/4323 (5·2%)	231/3352 (6·9%)	−24·0	104·1		0·79 (0·62–1·02)
N4+	160/1205 (13·3%)	183/1190 (15·4%)	−14·3	76·1		0·83 (0·62–1·11)
N other/unknown	42/1690 (2·5%)	60/1737 (3·5%)	−6·9	24·6		0·76 (0·45–1·27)
(e) Tumour grade (trend χ^2_1=0·4; 2p=0·5)						
Well differentiated	24/877 (2·7%)	26/793 (3·3%)	−1·6	10·9		
Moderately differentiated	196/3667 (5·3%)	203/3249 (6·2%)	−11·7	94·4		0·88 (0·68–1·15)
Poorly differentiated	156/2801 (5·6%)	174/2326 (7·5%)	−17·6	76·8		0·80 (0·59–1·07)
Grade unknown	121/2511 (4·8%)	139/2542 (5·5%)	−4·4	61·4		0·93 (0·67–1·29)
(f) Bisphosphonate type (χ^2_1=0·3; 2p=0·6)						
Clodronate	139/2514 (5·5%)	165/2539 (6·5%)	−16·7	67·5		0·78 (0·57–1·07)
Aminobisphosphonate	358/7342 (4·9%)	377/6371 (5·9%)	−27·9	169·7		0·85 (0·70–1·03)
(g) Bisphosphonate (χ^2_4=5·9; 2p=0·21)						
Clodronate	139/2514 (5·5%)	165/2539 (6·5%)	−16·7	67·5		0·78 (0·57–1·07)
Zoledronic acid	200/4642 (4·3%)	250/4648 (5·4%)	−24·1	108·7		0·80 (0·63–1·03)
(i) Bisphosphonate duration (trend χ^2_1=0·2; 2p=0·7)						
<1 year	4/277 (1·4%)	4/283 (1·4%)	0·8	1·7		
2 years	169/3081 (5·5%)	154/2091 (7·4%)	−18·5	68·6		0·76 (0·56–1·04)
>2 years	324/6498 (5·0%)	384/6536 (5·9%)	−26·9	166·9		0·85 (0·70–1·04)
(j) Chemotherapy (χ^2_1=0·3; 2p=0·6)						
Absence	39/1616 (2·4%)	53/1616 (3·3%)	−6·3	21·0		0·74 (0·48–1·14)
Presence	458/8240 (5·6%)	489/7294 (6·7%)	−38·3	216·2		0·84 (0·70–1·00)
(k) Follow-up period, years (trend χ^2_1=2·5; 2p=0·11)						
0–1	173/9856 (1·8%)	204/8910 (2·3%)	−25·0	85·0		0·75 (0·56–0·99)
2–4	218/8445 (2·6%)	237/7609 (3·1%)	−20·0	104·6		0·83 (0·64–1·06)
5–9	104/5711 (1·8%)	99/5614 (1·8%)	0·8	46·8		1·02 (0·73–1·31)
≥10	2/706 (0·3%)	2/758 (0·3%)	−0·4	0·9		
Total	**497/9856 (5·0%)**	**542/8910 (6·1%)**	**−44·6**	**237·1**		**0·829 (0·730–0·941)**
						2p=0·004

0 0·5 1·0 1·5 2·0

Bisphosphonate better Control better

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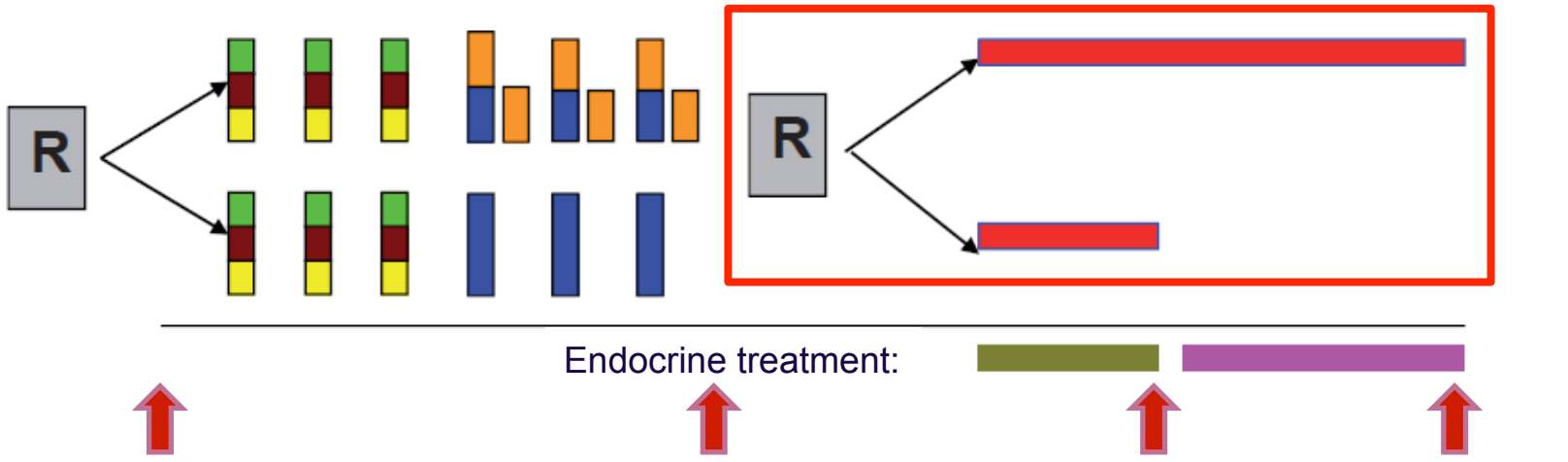
SUCCESS A – study design

(open-label, multicenter, 2x2 factorial design, randomized controlled Phase III study)



Blood sampling for CTC assessment

First randomization:
3 cycles FEC100 followed by 3 cycles docetaxel vs. 3 cycles FEC100 followed by 3 cycles docetaxel plus gemcitabine

Second randomization:
5 years vs. 2 years of zoledronate
(4 mg i.v. every 3 months for 2 years, followed by 4 mg i.v. every 6 months for 3 years vs. 4 mg i.v. every 3 months for 2 years)

5- FU 500 mg/m^2, Epirubicin 100 mg/m^2, Cyclophosphamide 500 mg/m^2 q3w

Docetaxel 100 mg/m^2 q3w

Docetaxel 75 mg/m^2, Gemcitabine 1.000 mg/m^2 d1,8 q3w

Tamoxifen 20 mg qid p.o. x 2a (plus Goserelin 3.6 mg depot x 2a in premenopausal pts

Anastrozole 1 mg qid p.o. x 3a in postmenopausal pts (Tam in premenopausal pts)

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Patient characteristics

- 3754 patients with high-risk early breast cancer (defined as pN1-3, or pT2-4, or G3, or hormone receptor negative, or age ≤ 35) randomized for SUCCESS A
- 3421 patients started with zoledronate treatment
- 434 patients with DFS event or loss to follow-up in the first two years after start of zoledronate treatment
- **2987** patients available for analysis

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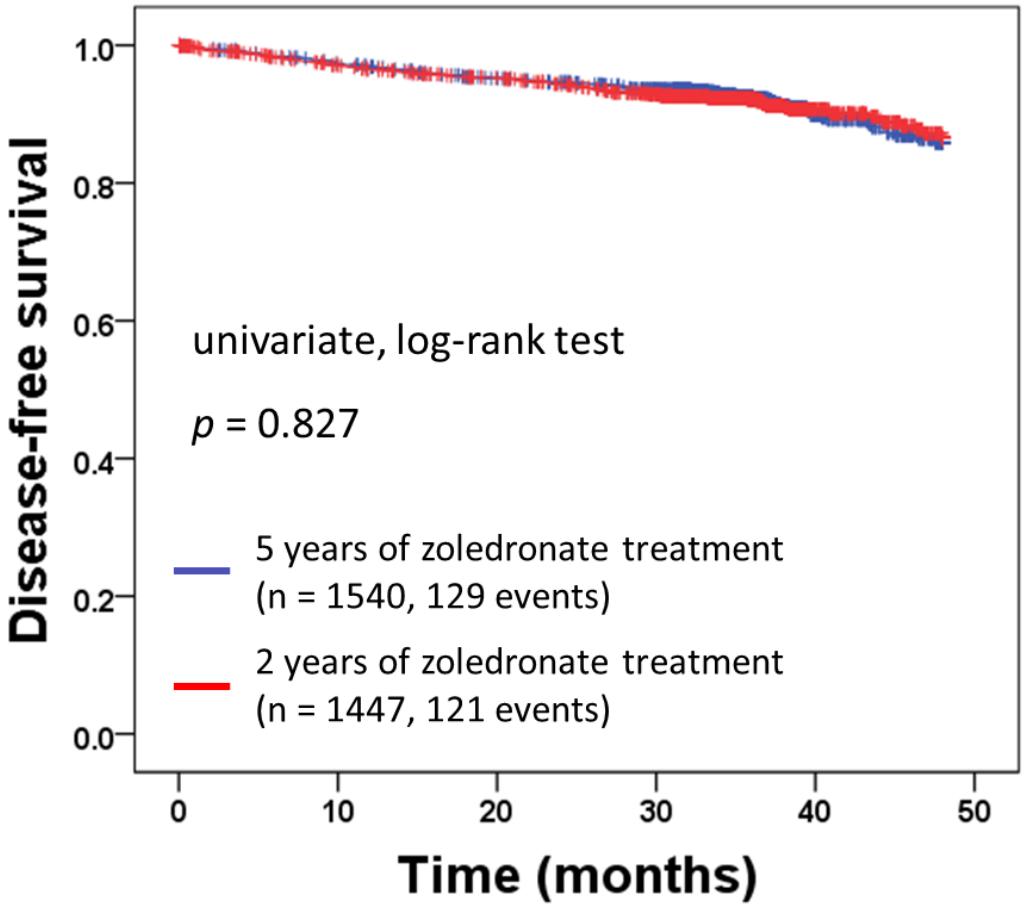
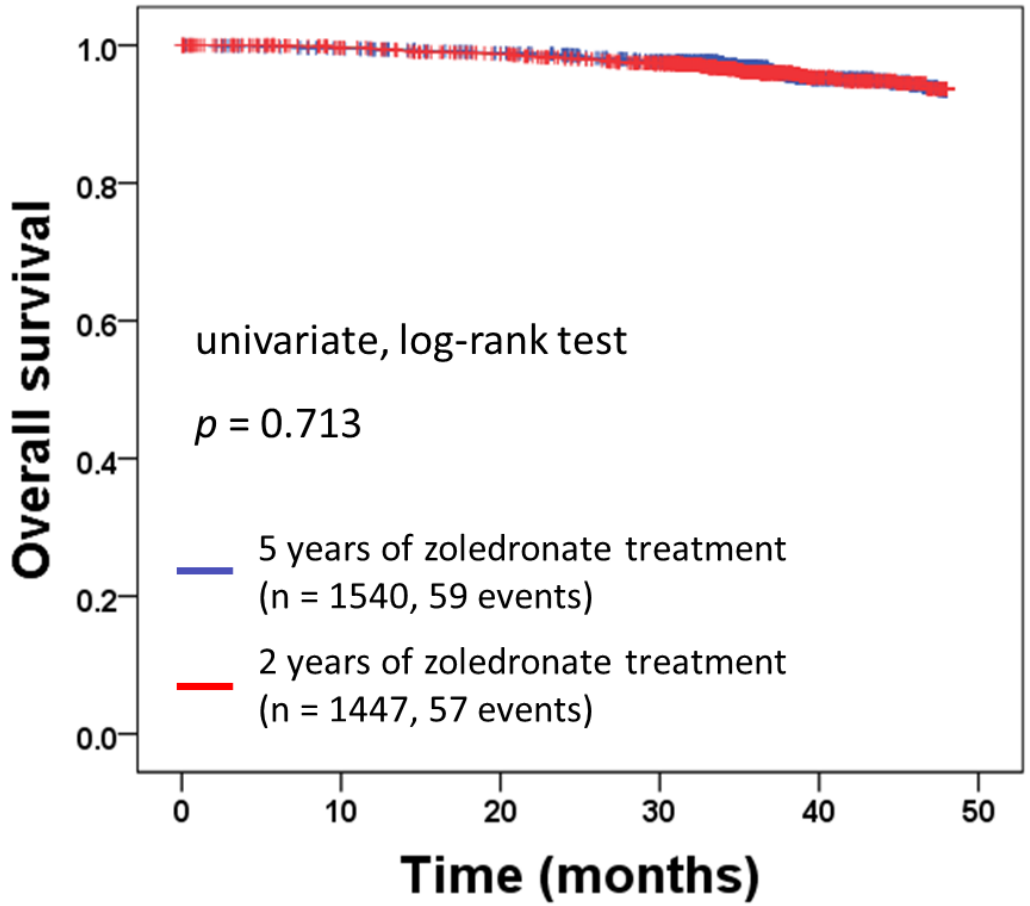
Adapted disease-free survival (DFS) and overall survival (OS) by zoledronate treatment arm





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Adverse events by zoledronate treatment arm
(as of 2 years after the start of zoledronate treatment)

Patient cohort	Number of adverse events observed (% of patients affected)	
	all grades	grade 3/4
Total	2845 (37.0%)	257 (6.4%)
5 years of zoledronate	1954 (46.2%)	159 (7.6%)
2 years of zoledronate	891 (27.2%)	98 (5.1%)

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Observed frequency (% of patients affected) of 10 most common adverse events

Adverse event	5 years of zoledronate		2 years of zoledronate	
	all grades	grade 3/4	all grades	grade 3/4
Bone pain	158 (8.3%)	9 (0.6%)	57 (3.7%)	5 (0.3%)
Arthralgia	96 (5.1%)	1 (0.1%)	50 (3.1%)	1 (0.1%)
Fatigue	78 (4.4%)	5 (0.3%)	34 (2.1%)	0 (0.0%)
Anemia	84 (4.4%)	1 (0.1%)	7 (0.5%)	1 (0.1%)
Neuropathy	47 (2.3%)	0 (0.0%)	32 (1.9%)	2 (0.1%)
Leukopenia	63 (3.6%)	0 (0.0%)	8 (0.6%)	3 (0.2%)
Hot flashes	41 (2.2%)	0 (0.0%)	25 (1.5%)	0 (0.0%)
Myalgia	39 (2.1%)	4 (0.3%)	17 (1.1%)	0 (0.0%)
SGPT (serum glutamic pyruvic transaminase) elevation	42 (2.5%)	1 (0.1%)	12 (0.7%)	0 (0.0%)
Headache	33 (1.8%)	4 (0.3%)	21 (1.2%)	0 (0.0%)

Key adverse events with regard to bisphosphonates

	5 years of zoledronate	2 years of zoledronate
Osteonecrosis of the jaw (ONJ)	11	5

Summary

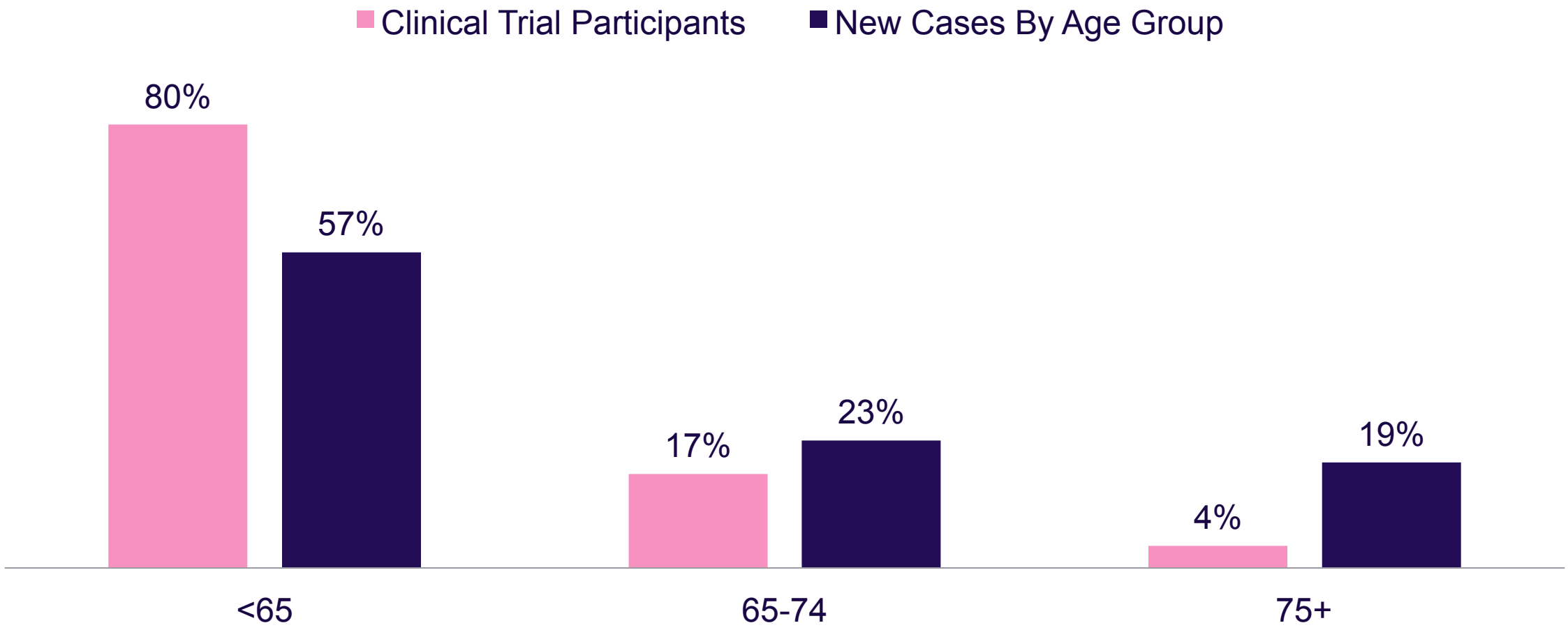
- No significant difference in DFS or OS between patients receiving 2 or 5 years of zoledronate treatment after adjuvant chemotherapy for early breast cancer
- Lack of benefit of extended zoledronate treatment independent from menopausal status
- 5 years of zoledronate treatment associated with increased frequency of adverse events compared to 2 years of zoledronate treatment
- Lack of significant difference with regard to prevalence of CTCs 5 years after adjuvant chemotherapy in accordance with survival analysis

U.S. Food and Drug Administration pooled analysis of outcomes of older women with hormone-receptor positive metastatic breast cancer treated with a CDK4/6 inhibitor as initial endocrine based therapy

- **Harpreet Singh, Lynn Howie, Erik Bloomquist, Suparna Wedam,**
- **Laleh Amiri-Kordestani, Shenghui Tang, Rajeshwari Sridhara,**
- **Amna Ibrahim, Kirsten Goldberg, Amy McKee, Julia A. Beaver, Richard Pazdur**

- **Office of Hematology and Oncology Products**
- **U.S. Food and Drug Administration**

Older Adults with Breast Cancer Enrolled on FDA Registration Trials Compared with New Cases by Age Group



FDA Registration Trials 2005-2015
SEER 18 2010-2014, All Races, Females

Methods

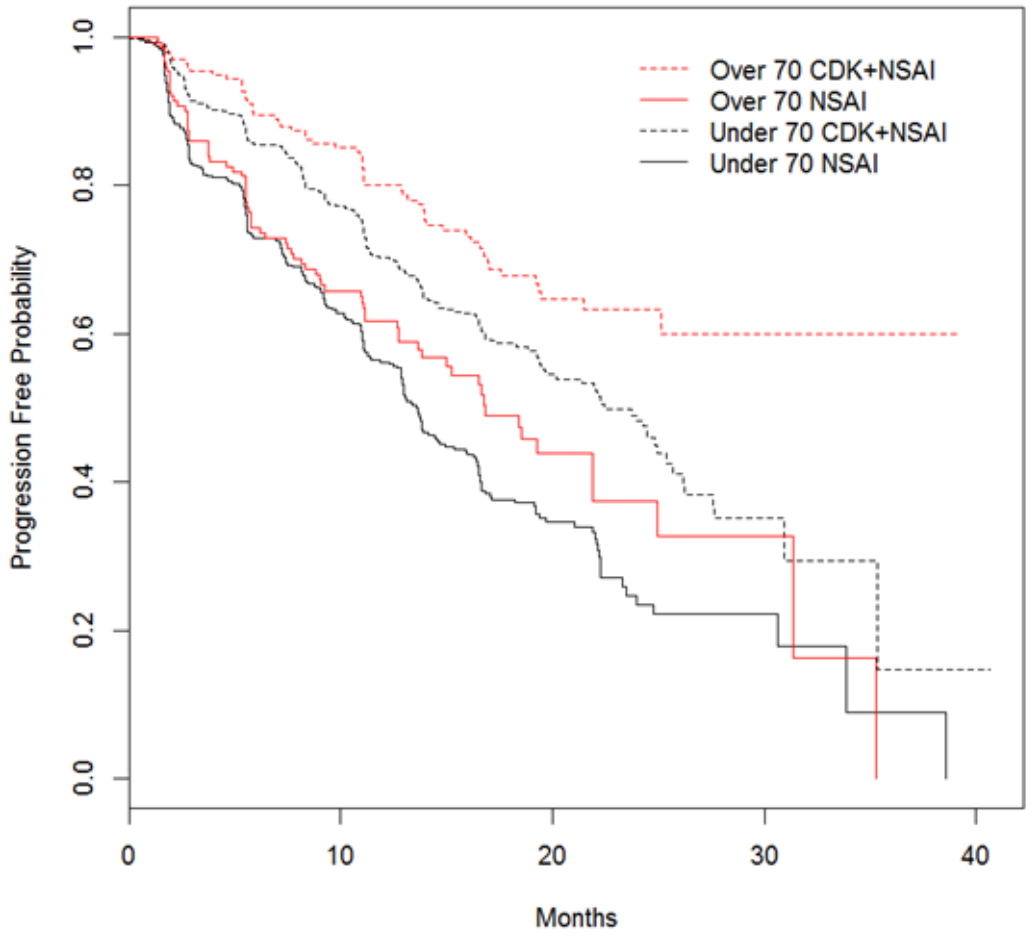
Pooled retrospective subgroup analysis

- Eligible patients
  - Enrolled on registration trials submitted to FDA for CDK 4/6 inhibitors in combination with an aromatase inhibitor for initial endocrine based therapy for advanced or metastatic breast cancer
  - Efficacy Population: ITT population (n=1992)
  - PFS evaluated in patients age ≥ 70 in treatment and control groups

Baseline Characteristics

	Age <65 N=716	Age ≥65 N=555	Age ≥70 N=329
ECOG			
0	446 (62)	299 (54)	162 (49)
1	264 (37)	253 (46)	164 (50)
2	6 (1)	3 (1)	3 (1)
Site of Disease			
Visceral	349 (49)	265 (48)	141 (43)
Bone Only	162 (23)	120 (22)	95 (29)
Prior therapy			
(Neo)Adjuvant chemotherapy	335 (47)	163 (29)	74 (22)
(Neo)Adjuvant endocrine therapy	342 (54)	224 (40)	126 (38)
Initial Stage			
Stage IV	292 (41)	267 (48)	171 (52)

Efficacy of CDK4/6 Inhibitors in Patients ≥ 70



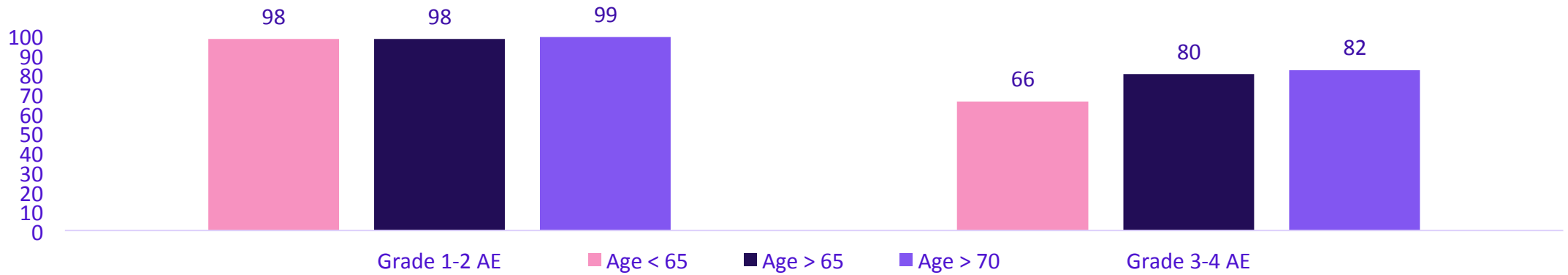
	Median PFS (95% CI)
Age≥70 CDK4/6 (n=280)	NR (25.1 months, NR)
Age <70 CDK4/6 (n=826)	23.75 months (21.9, 25.4)
Age ≥70 AI only	16.8 months (13.7, 21.9)
Age <70 AI only	13.8 months (12.9, 14.7)

HR 0.54 95% CI (0.47, 0.62)

No treatment difference across age subgroups.
Similar results with alternate age cut offs (>65, >75, etc)

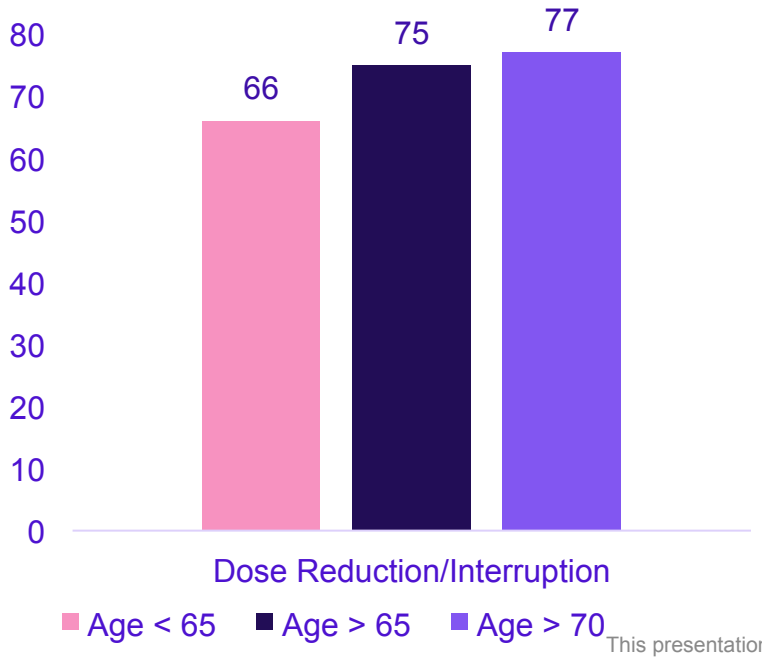
Pooled Adverse Events: Severity

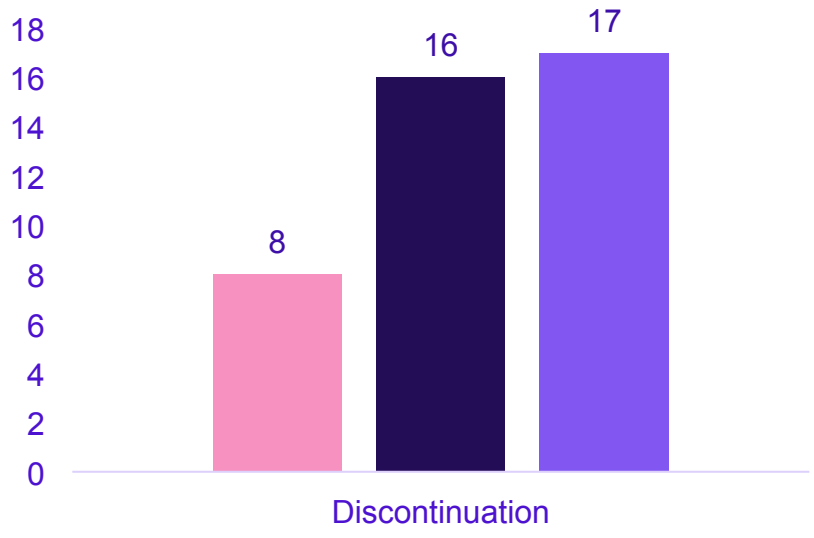
	Age < 65 years N = 625 (%)	Age ≥ 65 years N = 479(%)	Age ≥ 70 years N = 280 (%)
Grade 1-2 Adverse Events	610 (98)	470 (98)	277 (99)
Grade 3-4 Adverse Events	417 (66)	385 (80)	229 (82)
Grade 5 Adverse Events	7 (1)	11 (2)	8 (3)

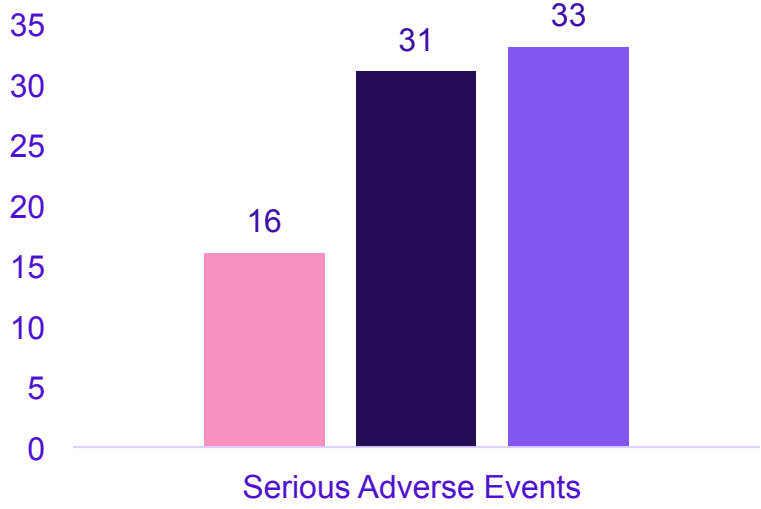


Pooled Adverse Events: Tolerability

	Age < 65 years N = 625 (%)	Age ≥ 65 years N = 479 (%)	Age ≥ 70 years N = 280 (%)
AE leading to dose reduction and/or interruption	411 (66)	360 (75)	216 (77)
AE leading to discontinuation	50 (8)	76 (16)	48 (17)
Serious Adverse Events	103 (16)	147 (31)	93 (33)







Selected Adverse Events

	Age <65 yrs N= 625 (%)	Age ≥ 65 yrs N= 479 (%)	Age ≥ 70 yrs N= 280 (%)
Neutropenia			
All Grades	**414 (66)**	**318 (66)**	**184 (66)**
Grade 3-4	**326 (52)**	**263 (55)**	**155 (55)**
Infections			
All Grades	**258 (41)**	**230 (48)**	**139 (50)**
Hepatotoxicity			
All Grades	**115 (18)**	**78 (16)**	**51 (18)**
Grade 3-4	**43 (7)**	**29 (6)**	**20 (7)**
Fatigue			
All Grades	**258 (41)**	**221 (46)**	**133 (48)**
Grade 3	**14 (2)**	**14 (3)**	**10 (4)**
Diarrhea			
All Grades	**201 (32)**	**235 (49)**	**142 (51)**
Grade 3	**18 (3)**	**23 (5)**	**14 (5)**

Conclusions

- Older patients with breast cancer benefit from treatment with CDK4/6 inhibitors as initial endocrine based therapy for HR positive, HER2 negative, metastatic breast cancer
- Severity of adverse events and rates of dose modifications and interruptions higher in ≥65, ≥70
- Rates of selected adverse events similar across pooled trials

Conclusions

- Individuals not compliant with screening more likely to not be compliant with treatment
- GnRH agonists during adjuvant chemotherapy improve fertility preservation
- Obesity can lead to more complications during adjuvant therapy
- Weight loss may decrease risk of breast cancer
- Exercise and acupuncture can improve symptoms and adherence to Ais
- 5 years of adjuvant bisphosphonates equivalent to 2 with more toxicity
- Adverse events from CDK4/6 inhibitors worse in older women but benefit the same

Overall survival results of a randomized trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment (NCT00578006) ASCO 2017

Study Design

Patients receiving chemotherapy for metastatic breast, lung, GU, GYN cancer at MSKCC

RANDOMIZE

INTERVENTION ARM
Self-report 12 common symptoms
- Prior to / between visits, by web
- Weekly email reminders to patients
- Alerts to nurses (by email)
- Reports to oncologists (at visits)

CONTROL ARM
"Standard" symptom monitoring

Outcomes
- QOL
- ER visits
- Survival

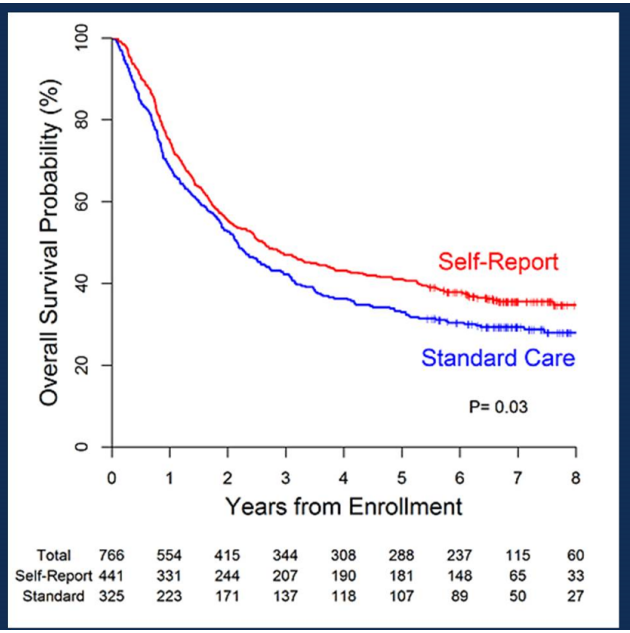
Stratified by level of prior computer use
Randomized 2:1 for those w/o prior use

Treatment discontinuation, withdrawal, hospice, death

Alternative: Systematic Symptom Monitoring

Overall Survival

- Compared to standard care, median survival was 5 months longer among patients in the self-reporting arm (31.2 vs. 26.0 months) (*P=0.03*)
- Remained significant in multivariable analysis: Adjusted hazard ratio 0.832 (*95% CI; 0.696, 0.995*)



How would I use these results in clinic?

- Nurse navigators focus on patients with history of non-compliance
- Discuss GnRH agonists with all women interested in ovarian preservation
- Discuss weight control with EVERY patient and offer support
- Discuss exercise with EVERY patient
- Consider acupuncture for AI-related pain
- Check in with older women more frequently to assess side effects
- AND FINALLY……..

J Clin Oncol. 2016 Jul 1;34(19):2221-31. doi: 10.1200/JCO.2015.64.3171. Epub 2016 Apr 4.

Absolute Benefit of Adjuvant Endocrine Therapies for Premenopausal Women With Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Early Breast Cancer: TEXT and SOFT Trials.

Regan MM[1], Francis PA[2], Pagani O[2], Fleming GF[2], Walley BA[2], Viale G[2], Colleoni M[2], Láng I[2], Gómez HL[2], Tondini C[2], Pinotti G[2], Price KN[2], Coates AS[2], Goldhirsch A[2], Gelber RD[2].

STEPP分析

根据中位复发风险(Composite Risk)预测5年STEPPs的BCFI. 直观指导用药策略

根据风险复合评分#大于1.59患者为乳腺癌复发中高危人群

参考文献：Regan MM, et al. J Clin Oncol. 2016 Jul 1;34(19):2221–31.

开始评估

2018

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