Montefiore Einstein
Center for Cancer Care

Highlights 2018 San Antonio Breast Cancer Symposium: New Developments

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Acknowledgements and Topics for Discussion

Best of San Antonio 1/20/2019 NYC

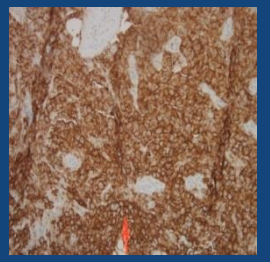
- Dr. Joseph Sparano(Montefiore)-tumor biology endocrine rx and genomic profile
- Dr. Sheldon Feldman(Montefiore)- axillary nodal Rx, decision making and quality of life
- Dr. Larry Solin(U of Penn)- radiation
- Dr. Francesco Esteva(NYU)- chemotherapy
- Dr. Charles Shapiro(Mt. Sinai)- survivorship

FERN FELDMAN ANOLICK

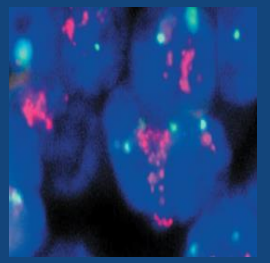
(1942-1979)

Precision Medicine:
Role of Biomarkers in Breast Cancer

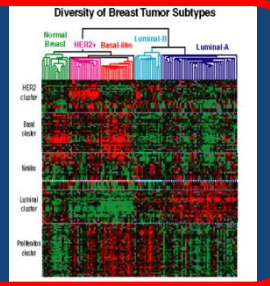
- 1st generation: protein expression ~ 1970
  - ER/PR IHC



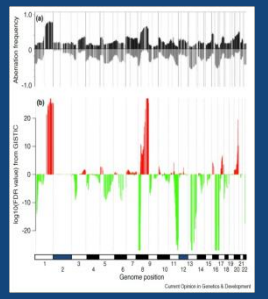
- 2nd generation: gene amplification ~ 1990
  - HER2/neu FISH



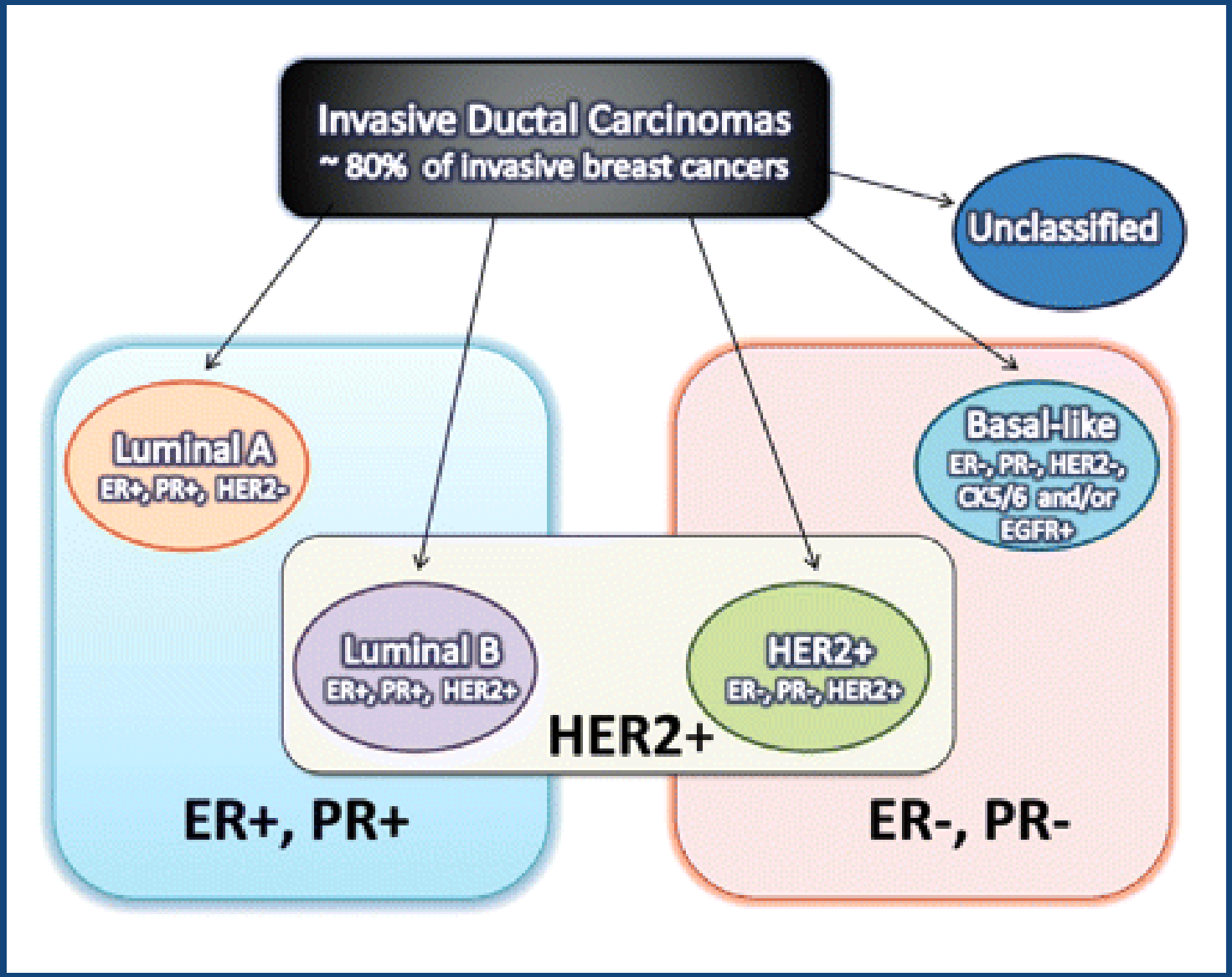
- 3rd generation: gene expression ~ 2004
  - Oncotype DX, Mammaprint, BCI
  - PAM50, Endopredict



- 4th generation: mutational profiling ~ 2010
  - Commercial and academic assays

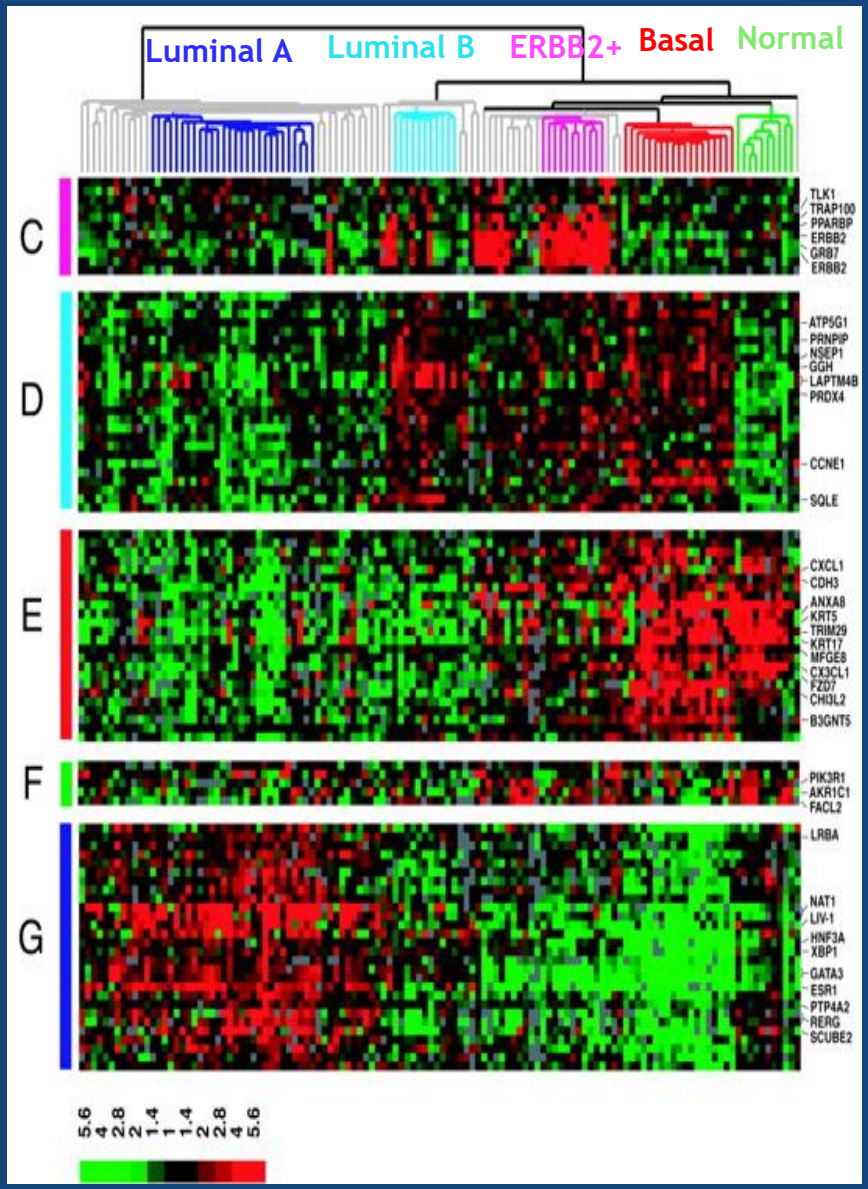


Breast Cancer Phenotypes



Gene Expression Profiling in Breast Cancer

- Breast cancer is heterogeneous
- Distinct subtypes
- Prognosis varies by subtype



PNAS 2003; 100(14): 8418–8423

Gene Expression Profiling in ER+/HER2- Breast Cancer: Prognosis and Prediction

# Genes	Assay	Regulatory Approval	Clinical Utility
21	Oncotype DX	CLIA	Prognostic – Node -/+ Predictive - chemotherapy benefit
70	MammaPrint	FDA	Prognostic – Node-/+ (clinical high risk)
50	Prosigna	FDA	Prognostic - Node -/+
7	Breast Cancer Index	CLIA	Prognostic –Node -/+ Predictive - extended

21-Gene Expression Recurrence Score Assay and Algorithm

Proliferation
Ki67
STK15
Survivin
CCNB1(cyclinB1)
MYBL2

HER2
GRB7
HER2

Estrogen
ER
PGR
BCL2
SCUBE2

Invasion
MMP11
CTSL2

GSTM1

CD68

BAG1

Reference
ACTB(B-actin)
GAPDH
RPLPO
GUS
TFRC

RS = +0.47 x HER2 Group Score
-0.34 x ER Group Score
+1.04 x Proliferation Score
+0.10 x Invasion Group Score
+0.05 x CD68
-0.08 x GSTM1
-0.07 x BAG1

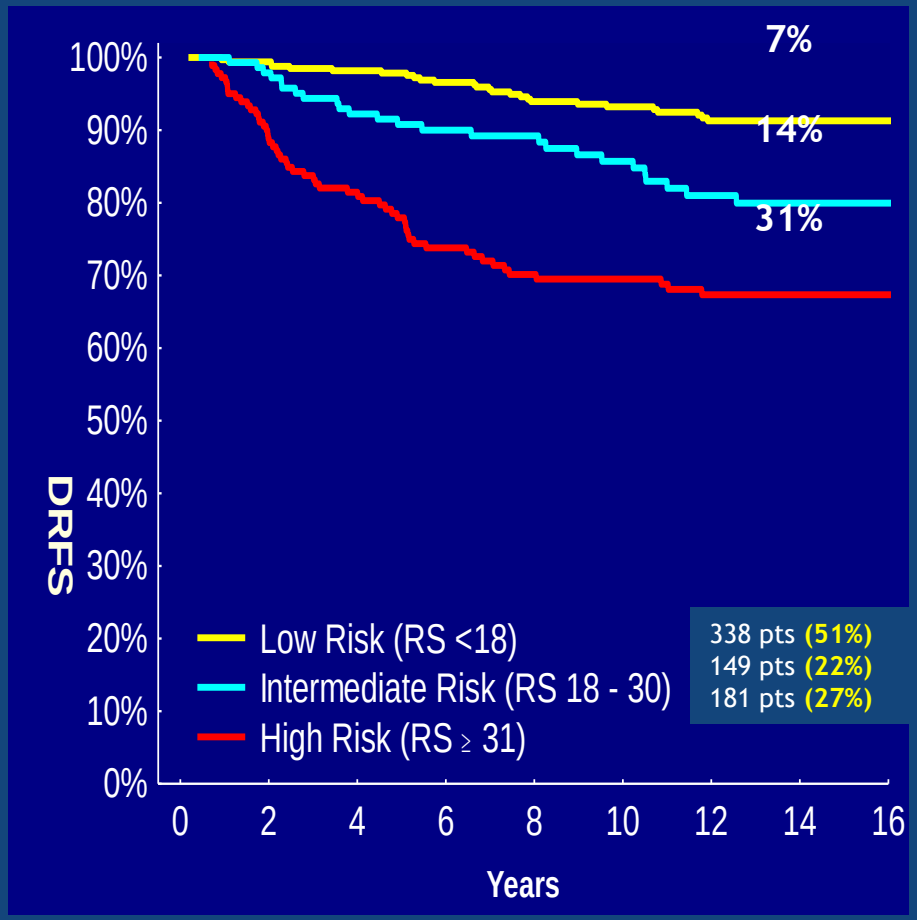
Category	Original	TAILORx
Low risk	0-17	0-10
Intermediate risk	18-30	11-25
High Risk	31-100	26-100

NEJM 2004; 351(27): 2817-26

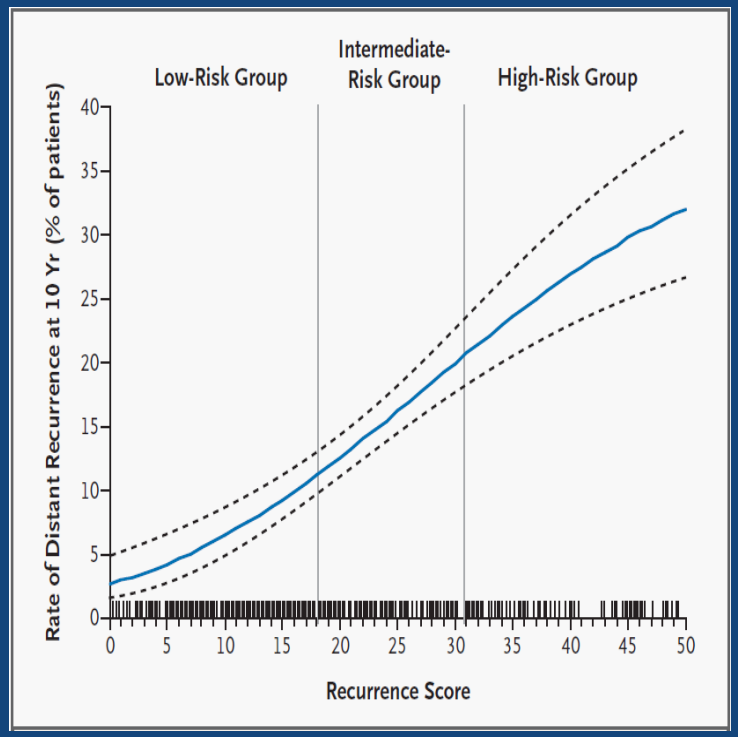
Prognosis: Prospective Validation of 21-Gene Assay (B14)

(N=668 ER+, node-neg - tamoxifen x 5 years enrolled between January, 1982- October 1988)

10-year Distant recurrence rate - RS group



10-year Distant recurrence rate - RS continuous



Multivariate cox model with distant recurrence as outcome revealed a statistically significant association for RS that was **independent of age and tumor size**

NEJM 2004; 351(27): 2817-26

TAILORx Methods: Treatment Assignment & Randomization

Accrued between April 2006 – October 2010

Key Eligibility Criteria
- Node-negative
- ER-pos, HER2-neg
- T1c-T2 (high-risk T1b)

Preregister - Oncotype DX RS (N=11,232)

↓

Register (N=10,273)

Statistical Design
- Non-inferiority - IDFS
- HR 1.332 (90 vs. 87% 5-yr DFS)
- Type I 10%, type II 5%
- Full info– 835 IDFS events

ARM A: Low RS 0-10
(N=1629 evaluable)
ASSIGN
Endocrine Therapy (ET)

Mid-Range RS 11-25
(N=6711 evaluable)
RANDOMIZE
Stratification Factors: Menopausal Status, Planned Chemotherapy, Planned Radiation, and RS 11-15, 16-20, 21-25

ARM D: High RS 26-100
(N=1389 evaluable)
ASSIGN
ET + Chemo

RS = 11 (B14 Study)
- 7.3% distant recurrence rate at 10 years
- 95% CI 5%, 10%

ARM B: Experimental Arm
(N=3399)
ET Alone

ARM C: Standard Arm
(N=3312)
ET + Chemo

RS= 25 (B14 Study)
- 16.1% distant recurrence rate at 10 years
- 95% CI 13%, 20%

RS 11-25 (B20 Study):
5% distant recurrence rate at 10 years

Sparano et al. *N Engl J Med* 2018

ECOG-ACRIN cancer research group
Reshaping the future of patient care

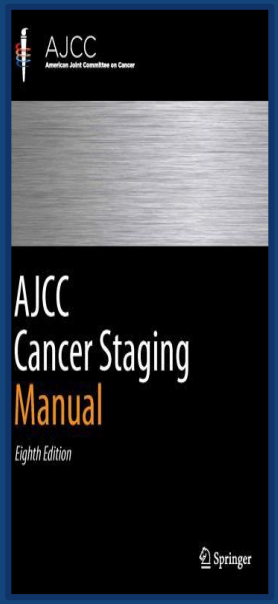
TAILORx Low Risk Registry: RS 0-10 – Endocrine Therapy Alone

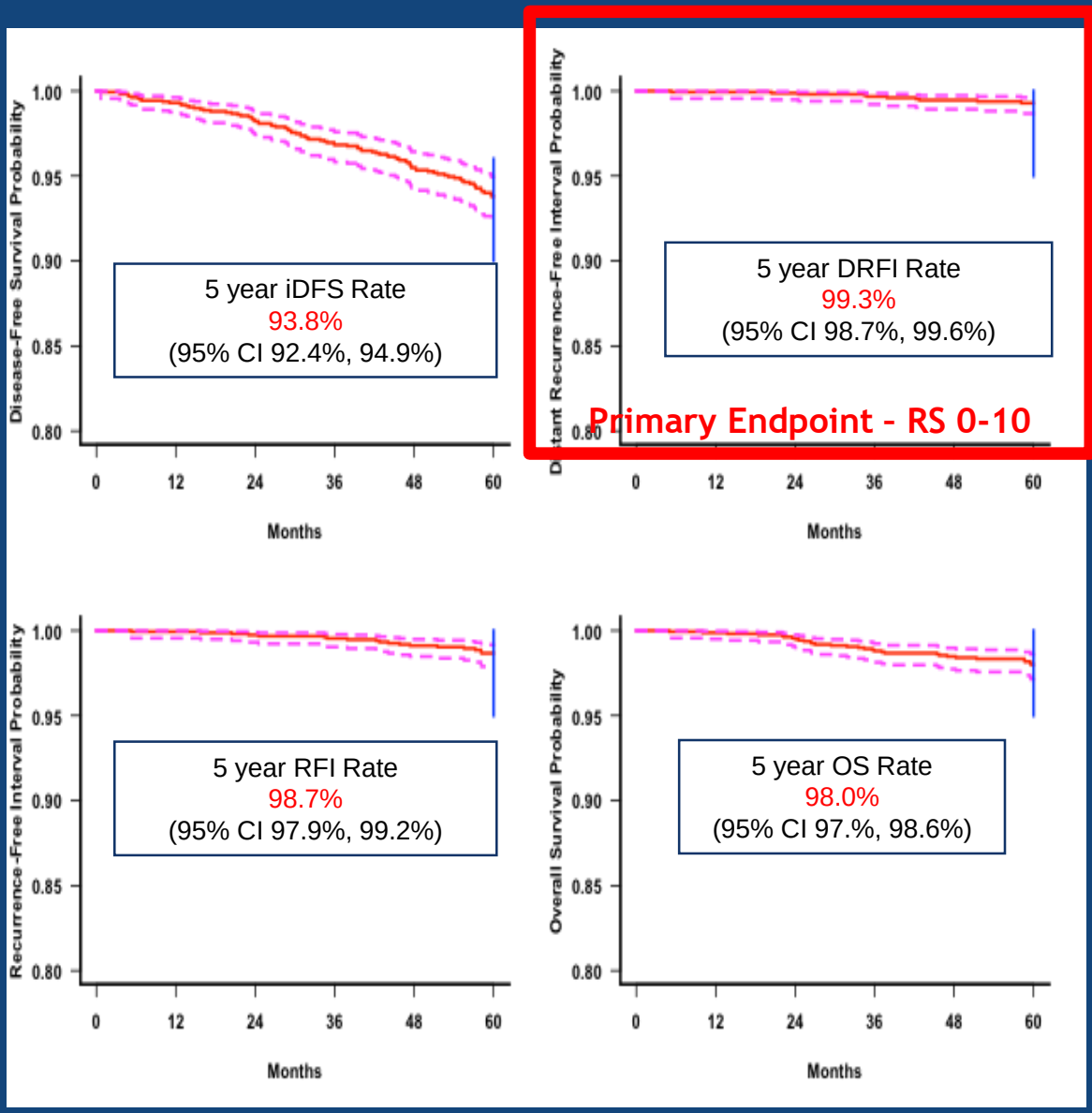
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prospective Validation of a 21-Gene Expression Assay in Breast Cancer

J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, E.A. Perez, J.A. Olson, J.A. Zujewski, T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.N. Atkins, J.L. Berenberg, and G.W. Sledge





Sparano et al. N Eng J Med 2015

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ECOG-ACRIN cancer research group

Reshaping the future of patient care

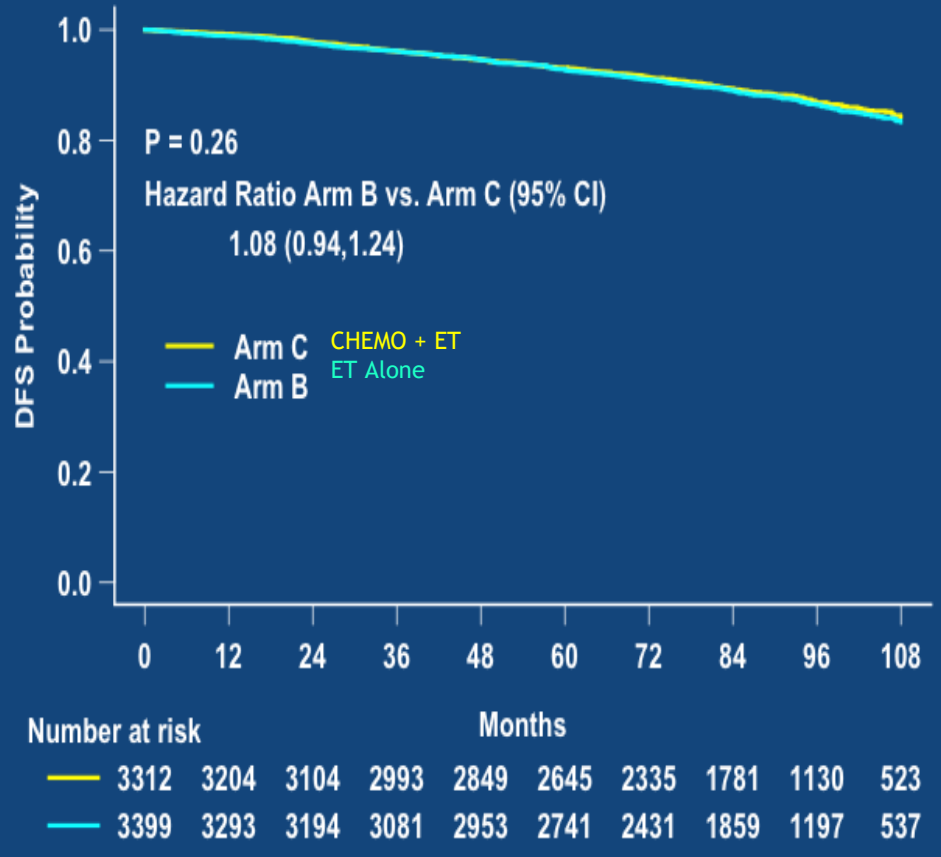
Research Advocacy Network

Sparano et al. *N Engl J Med* 2018

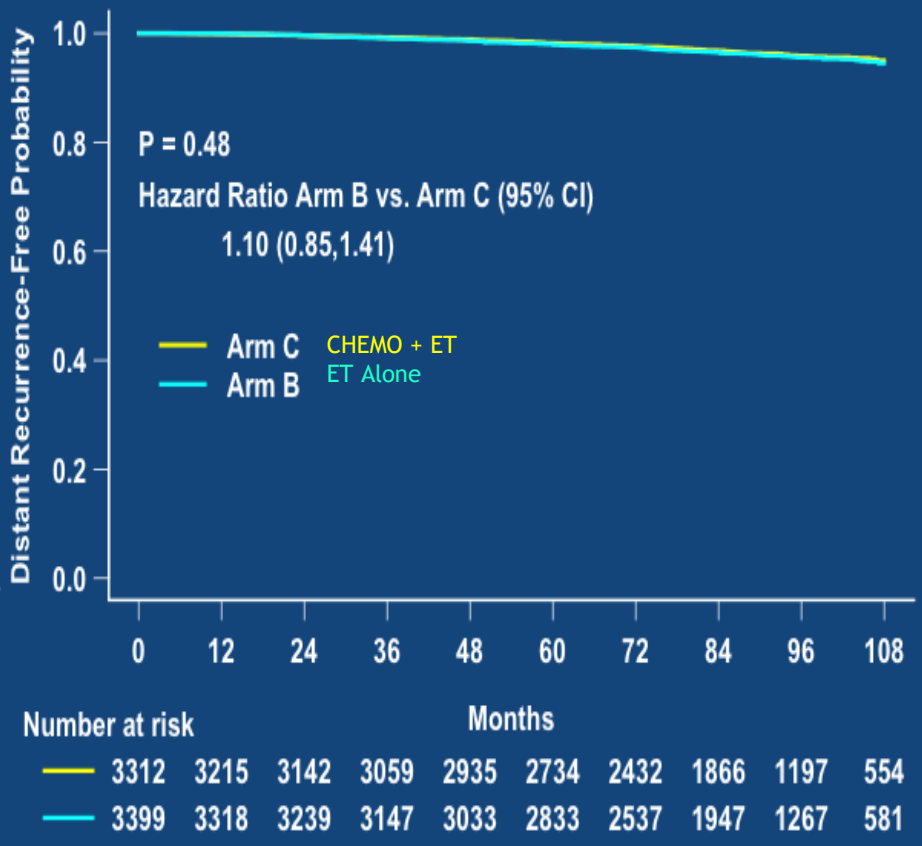
TAILORx Results - ITT Population: RS 11-25 (Arms B & C)

836 IDFS events (after median of 7.5 years), including 338 (40.3%) with recurrence as first event, of which 199 (23.8%) were distant

Primary Endpoint
Invasive Disease-Free Survival



Secondary Endpoint
Distant Relapse-Free Interval



Sparano et al. *N Engl J Med* 2018

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TAILORx Subgroup Analysis - 50 or Younger:

Chemotherapy Associated with Fewer Earlier & Later Distant Recurrences within RS 16-25 Range (Especially 21-25)

Freedom from recurrence of breast cancer at a distant site	5 Years		9 Years
Score of ≤10, endocrine therapy	99.7±0.3		98.5±0.8
Score of 11–15, endocrine therapy	98.8±0.6		97.2±1.0
Score of 11–15, chemoendocrine therapy	98.5±0.7		98.0±0.8
Score of 16–20, endocrine therapy	98.1±0.7	Δ 1.6%	93.6±1.4
Score of 16–20, chemoendocrine therapy	98.9±0.5		95.2±1.3
Score of 21–25, endocrine therapy	93.2±1.7	Δ 6.5%	86.9±2.9
Score of 21–25, chemoendocrine therapy	96.4±1.2		93.4±2.3
Score of ≥26, chemoendocrine therapy	91.1±1.6		88.7±2.1

Δ 0.8% (between 16–20 endocrine therapy and 16–20 chemoendocrine therapy)

Δ 3.2% (between 21–25 endocrine therapy and 21–25 chemoendocrine therapy)

Sparano et al. N Engl J Med 2018

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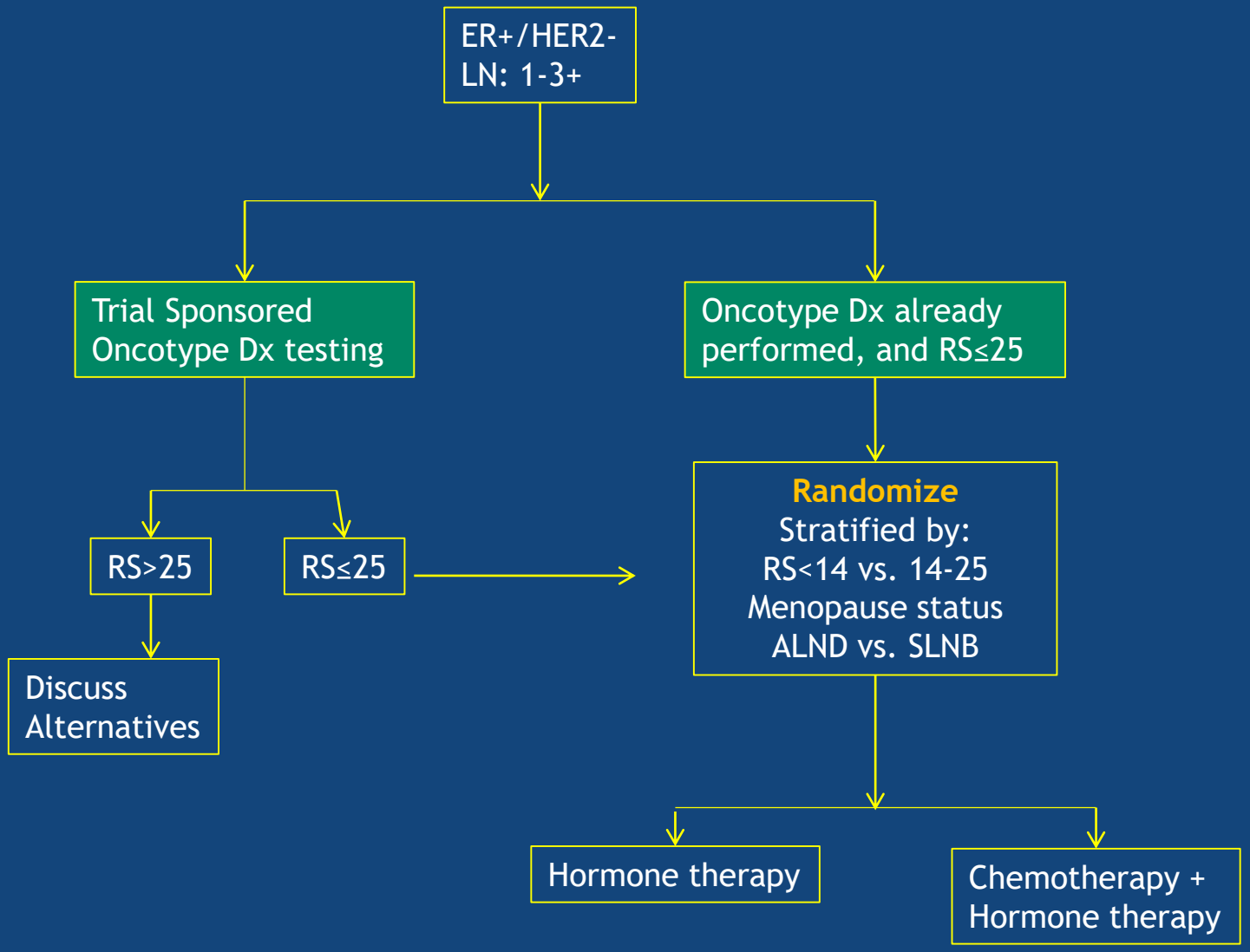
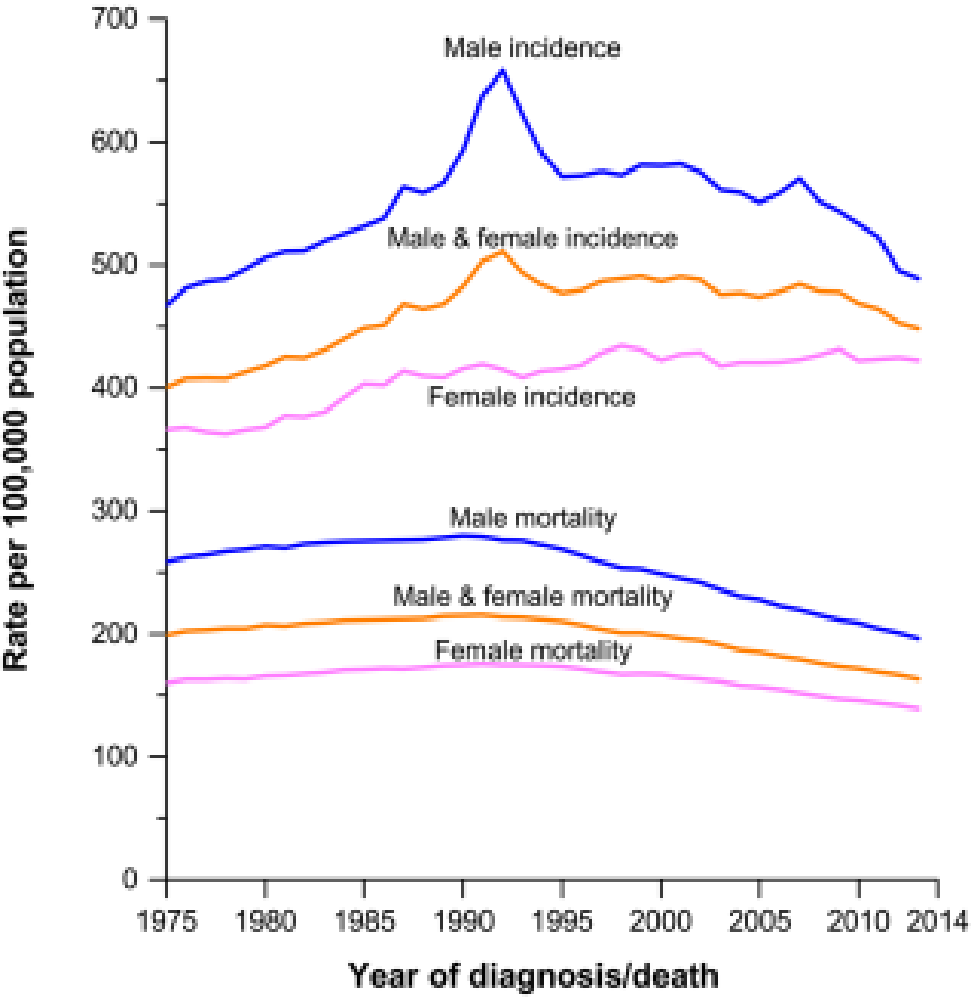
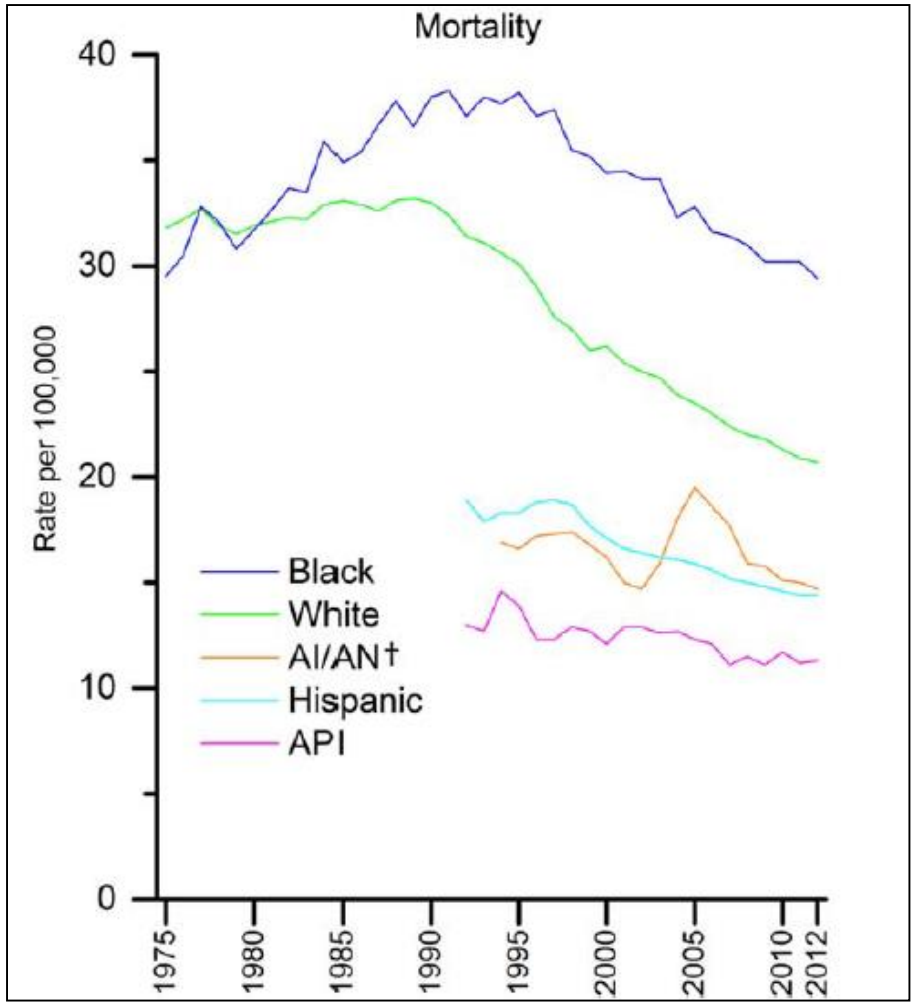
RxPONDER Trial
(Accrual completed, awaiting results)



Cancer Mortality Declining in U.S.



Cancer Incidence and Mortality



Breast Cancer Mortality by Year

Siegel, Miller, Jemal. Cancer Statistics 2017; DeSantis et al. Cancer Statistics, 2015

Breast Cancer Symptoms/Diagnosis/Philosophy

- Over 80% of patients with breast cancer are asymptomatic when diagnosed
- Typically diagnosis made on screening mammogram or noticing a new lump
- Needle biopsy of the lump confirms the diagnosis and leads to a specific treatment plan for that particular type of breast cancer
- Important that we strive for **Minimally Effective not Maximally Tolerated treatment**
- Goal for patients to be cured of cancer while avoiding side effects from treatment
- You cannot improve on being asymptomatic from a disease!!!!!

Sequelae of Breast Cancer Treatment

The benefits of current treatment strategies are effective, many cancer survivors are at risk for developing physiologic and psychological late effects of cancer treatment that might lead to premature mortality and morbidity and compromise their quality of life. Psychological symptoms include anxiety, depression, fatigue, difficulty sleeping, and loss of self-esteem. Physiologic changes include pain, numbness, cognitive impairment, weight gain, loss of sexual interest, spontaneous menopause, and peripheral neuropathy. LYMPHEDEMA is a major QOL issue!!

National Lymphedema Network

Arm symptoms after axillary lymph node surgery

- Pain
- Numbness
- Weakness
- Limitation of range of movement
- Seroma
- Cording(axillary web syndrome)
- Swelling: LYMPHEDEMA

WHAT IS LYMPHEDEMA?

- Lymphedema is a chronic lymphatic disease that results in disfiguring swelling in one or more parts of the body. It can be hereditary (Primary Lymphedema) or it can occur after a surgical procedure, infection, radiation or other physical trauma (Secondary Lymphedema). **In breast cancer, for example, it can appear in the arm on the same side as the cancer, after lymph nodes are removed from the armpit region for cancer staging.** Primary Lymphedema often occurs in the lower extremities. Lymph is the protein-rich body fluid that accumulates when the lymphatic system for fluid transport is damaged

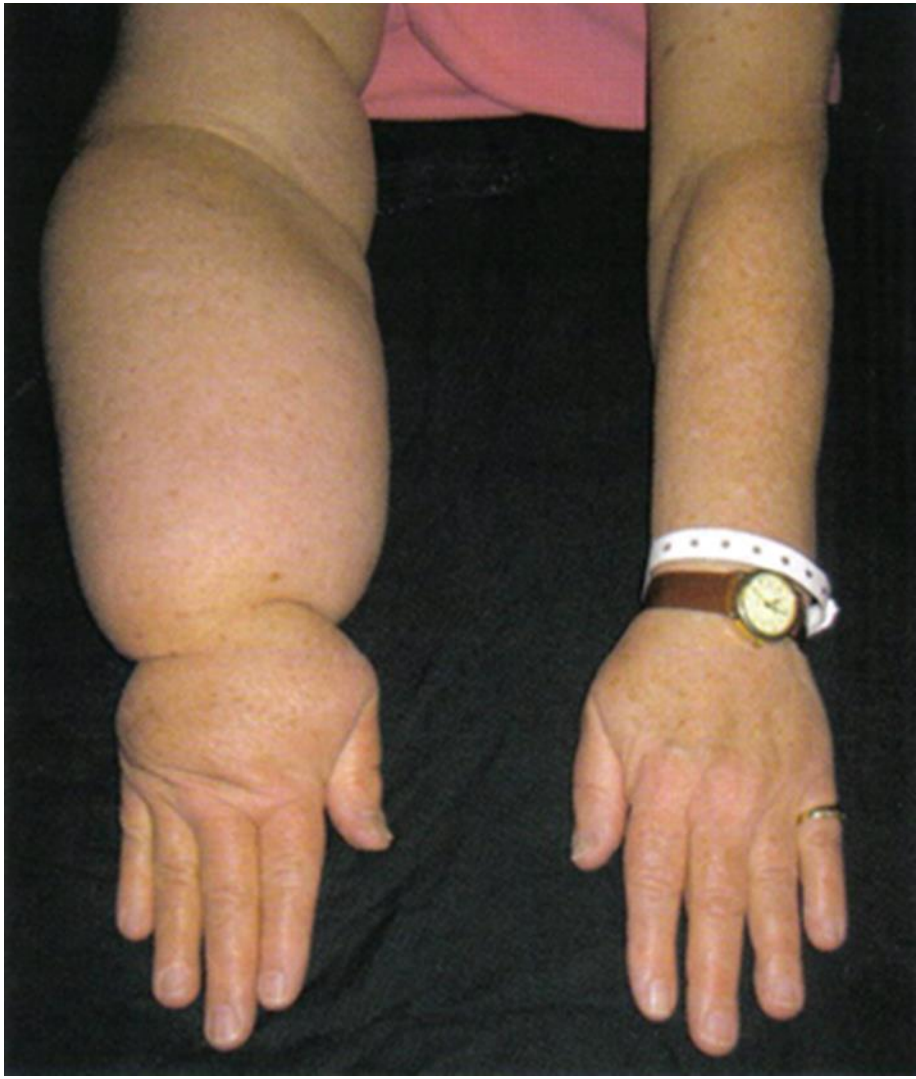
Lymphatic Research and Education Network Website

PATIENT'S POINT OF VIEW

"LYMPHEDEMA WORSE THAN MASTECTOMY"

"I FEAR LYMPHEDEMA MORE THAN CANCER"

"LYMPHEDEMA REMINDS ME I HAVE CANCER EVERY DAY"



LYMPHEDEMA: SCOPE OF THE PROBLEM

- 3.1M breast cancer survivors in the US, (NCI estimates >4M by 2024)
- Worldwide: 1.7M women dx with breast cancer annually
- Lymphedema rates

SLNB:5-7%

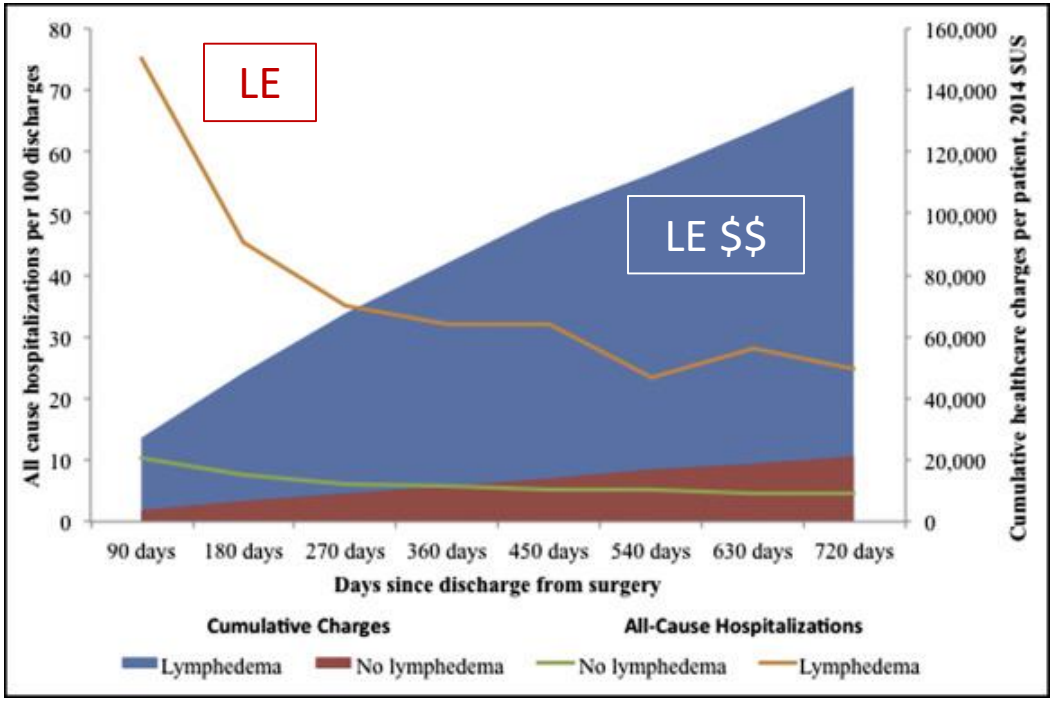
ALND: 15-20%

ART: 10-15%

ALND +XRT: 24-40%

Complicated breast cancer–related lymphedema: health care resource utilization and associated costs of management

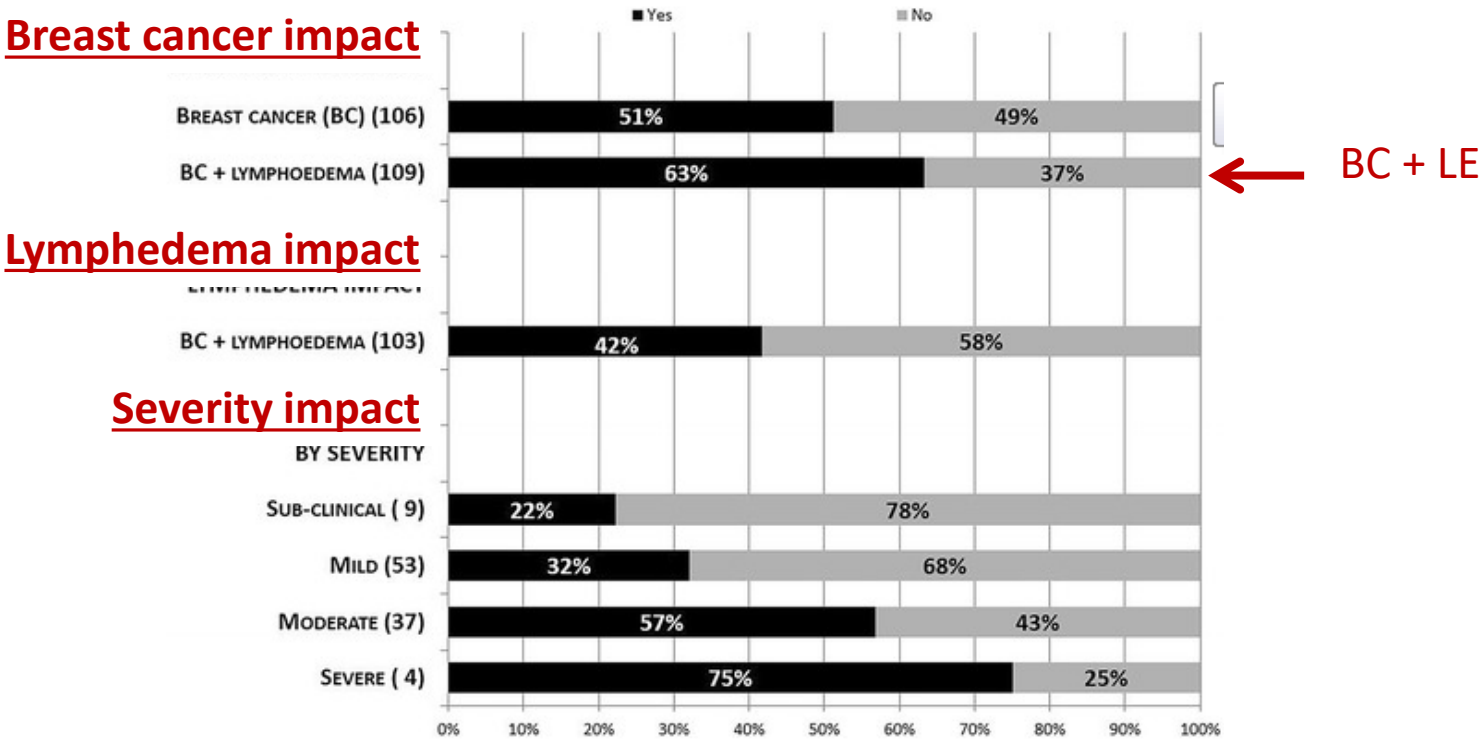
- 56,075 women
- IRR for admission if LE: 5.02 (4.76 to 5.29)
- Health care charges: $58,088 vs $31,819, p<0.001



Two-year standardized all-cause hospitalizations cumulative per patient charges ($) with and without complicated lymphedema.

Basta M et al. Am J Surg 2016

Impact of LE on work and career after breast cancer



- Annual number of days off work for subclinical/mild vs moderate/severe LE: 1.4 vs 8.1 (p=0.003)

Boyages et al. SpringerPlus 2016

OVERVIEW OF LYMPHEDEMA ISSUE

- Major morbidity of breast cancer treatment
- Impacts quality of life and survivorship
- Often life long chronic therapy
- Many patients poorly controlled- infectious complications and secondary malignancy
- Risk factors; number nodes removed, BMI>30 radiation, advanced age, limited ROM, taxol
- Incidence 40% high risk group

Is lymph node removal important?

- Overall survival-NO
- Disease free survival: loco-regional control
- Prognosis TNM staging
- Guide for systemic treatment-LESS SO
- Complications: lymphedema, chronic pain, shoulder mobility, nerve injury

Rationale for Cancer Staging

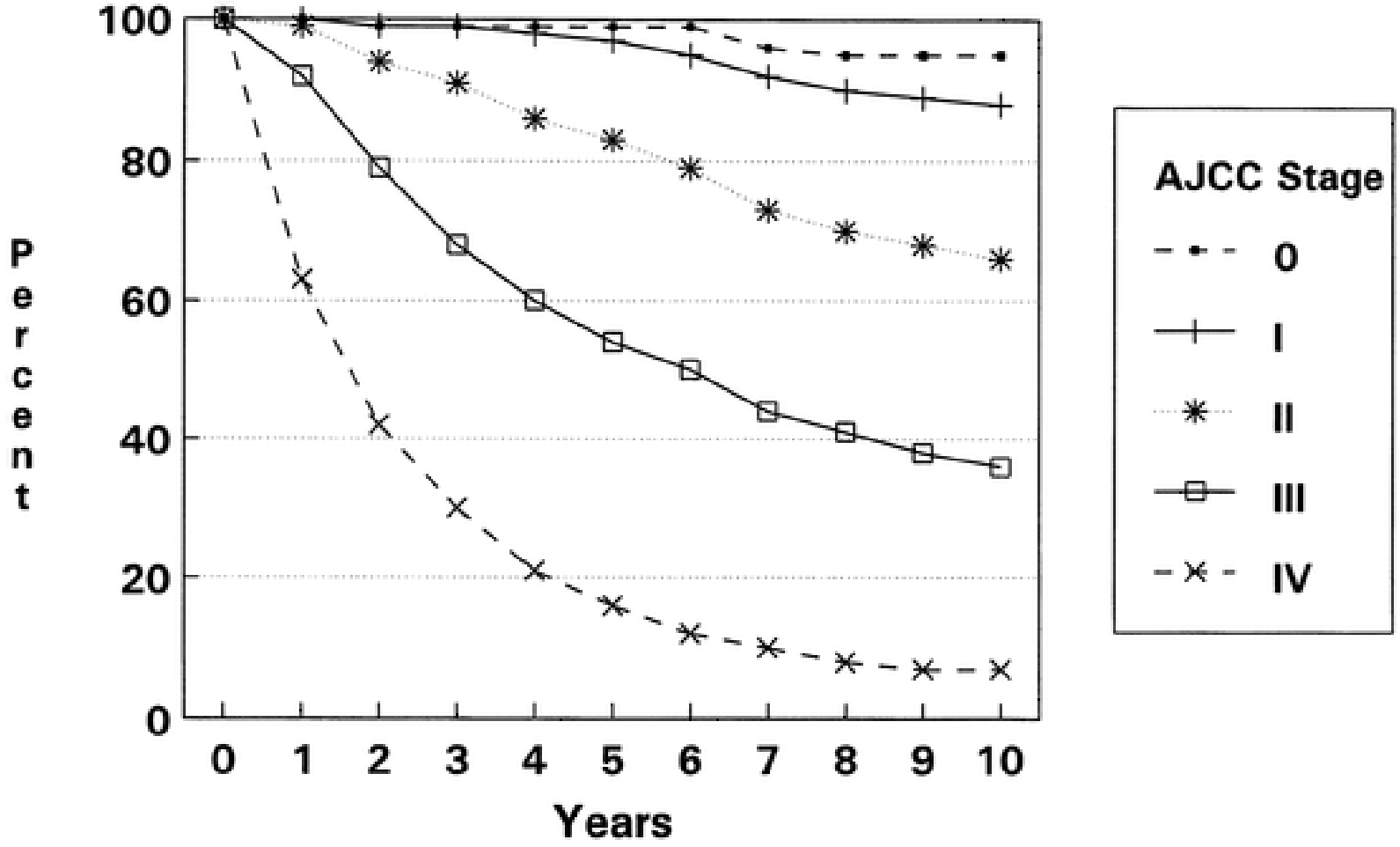
CLINICAL CARE

- Define extent and prognosis of cancer
- Guide appropriate treatment
- Basis for guidelines(NCCN and others)

COMMUNICATION ABOUT PATIENT GROUPS

- Population impact of cancer; changes over time
- Group similar cases for clinical trials

Anatomic stage is a key predictor of cancer outcome; 10 year data NCDB (cancer vol 83,1988)



Montefiore Einstein Center for Cancer Care

Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

AJCC 8th Edition-Breast Cancer

ANATOMIC STAGE

CLINICAL

PATHOLOGICAL

TNM

Still can used when biomarkers and genomic scores are not available

PROGNOSTIC STAGE (PREFERRED)

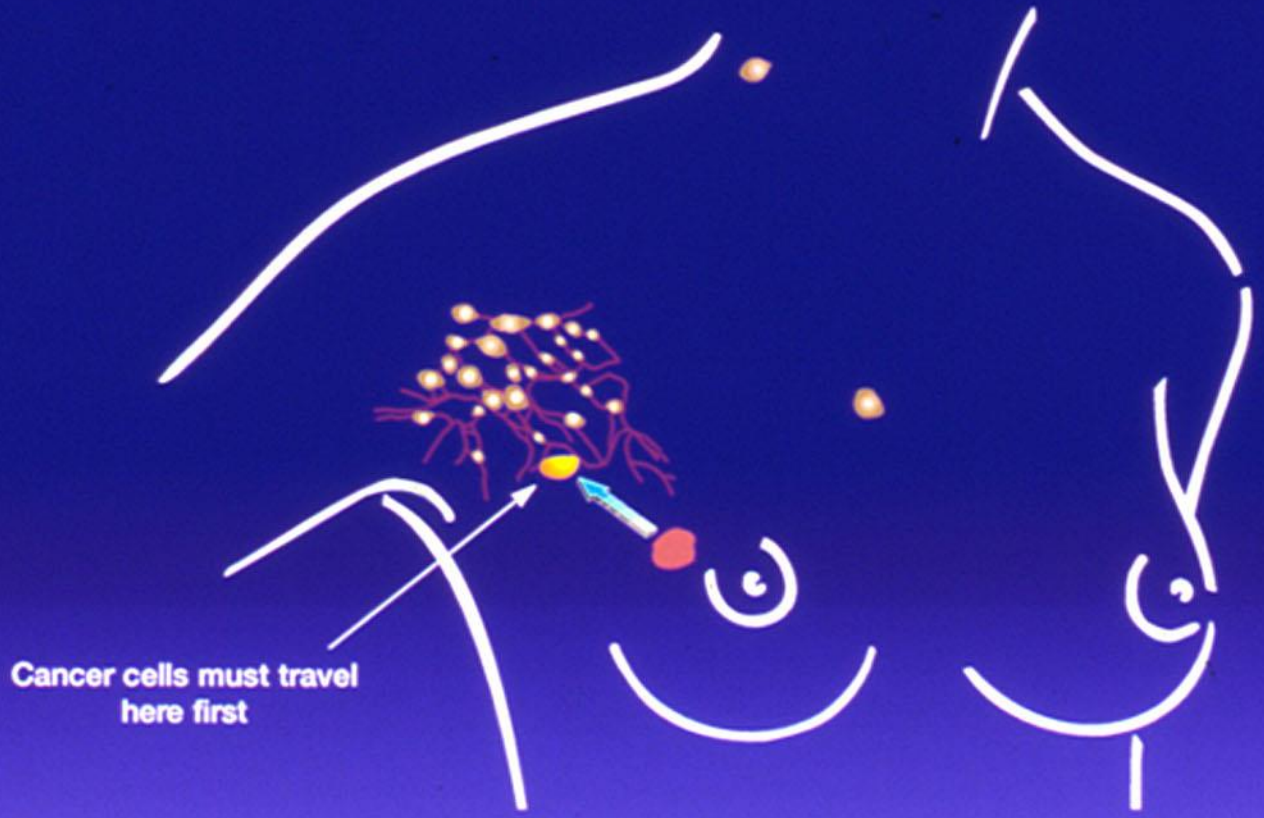
- BASED ON PATIENTS TREATED WITH ENDOCRINE AND OR SYSTEMIC CHEMOTHERAPY
- TNM
- BIOMARKERS - ER, PR,HER2
- TUMOR GRADE
- GENOMIC SCORE – ONCOTYPE DX

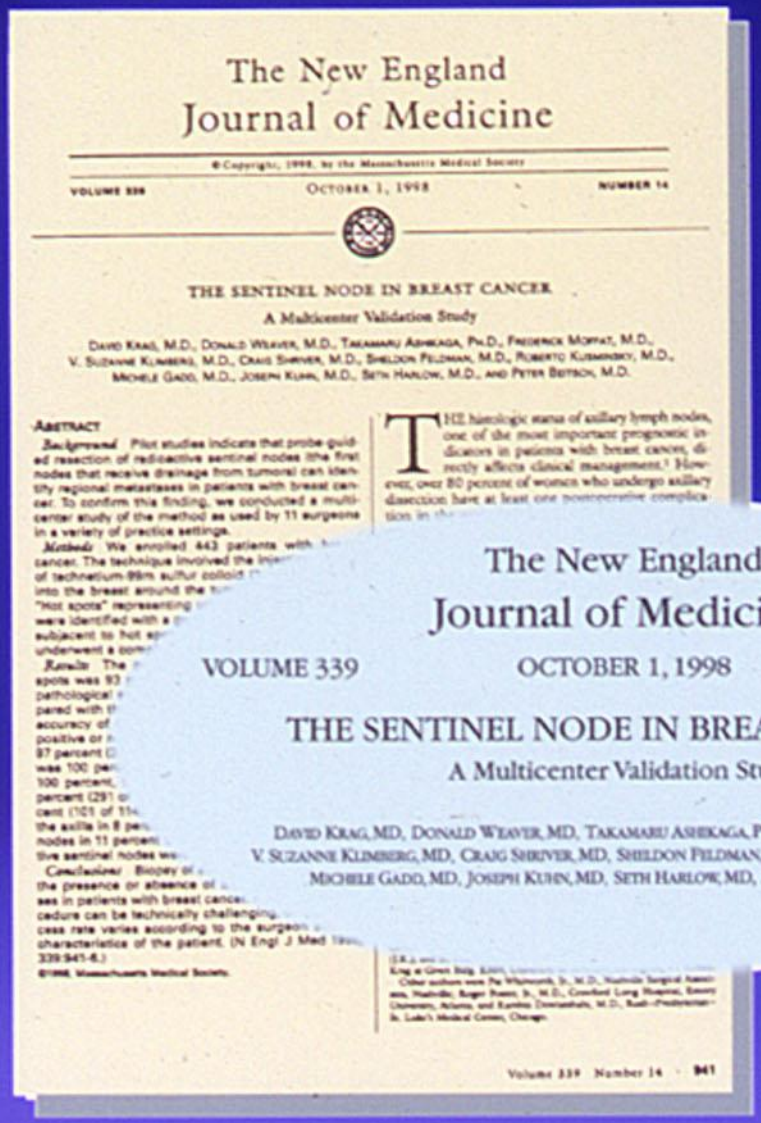
AJCC 8th Edition- NODE POSITIVE- HR+

T	N	M	G	HER2	ER	PR	PROGNOSTIC STAGE	AJCC 7TH
T2	N1	M0	1	-	+	+	1B	2B
T2	N1		2	+	+	+	1B	2B
T0-2	N2		1-2	+	+	+	1B	3A
T3	N1-2		1-2	+	+	+	1B	3A
T0-2	N2		1	-	+	+	2A	3A
Any	N3		1	-	+	+	3A	3C
T2	N1		3	-	+	+	3B	2B
T0-2	N2		3	-	+	-	3C	3A
T0-2	N2		3	-	-	+/-	3C	3A
T3	N1-2		3	-	+	-	3C	3A
T3	N1-2		3	-	-	+/-	3C	3A

NOTE: IMPACT OF GRADE AND HER 2 NEU on Prognostic Stage T3N2 Grade 3 TP= 1B

Sentinel (Primary) Lymph Node Concept
–Breast Cancer–




The New England
Journal of Medicine

VOLUME 339 OCTOBER 1, 1998 NUMBER 14

THE SENTINEL NODE IN BREAST CANCER

A Multicenter Validation Study

DAVID KRAG, M.D., DONALD WEAVER, M.D., TAKAMARU ASHIKAGA, PH.D., FREDERICK MOFFAT, M.D., V. SUZANNE KLIMBERG, M.D., CRAIG SHRIVER, M.D., SHELDON FELDMAN, M.D., ROBERTO KUSMINSKY, M.D., MICHELE GADD, M.D., JOSEPH KUHN, M.D., SETH HARLOW, M.D., AND PETER BEITSCH, M.D.

ABSTRACT

Background Pilot studies indicate that probe-guided resection of radioactive sentinel nodes (the first nodes that receive drainage from tumors) can identify regional metastases in patients with breast cancer. To confirm this finding, we conducted a multicenter study of the method as used by 11 surgeons in a variety of practice settings.

Methods We enrolled 443 patients with [illegible] cancer. The technique involved the injection of technetium-99m sulfur colloid [illegible] into the breast around the [illegible] "hot spots" representing [illegible] were identified with a [illegible] subjacent to hot spots [illegible] underwent a complete [illegible]

Results The [illegible] spots was 93 [illegible] pathological [illegible] pared with [illegible] accuracy of [illegible] positive or [illegible] 97 percent [illegible] was 100 per[illegible] 100 percent, [illegible] percent (291 of [illegible] cent (101 of 11[illegible] the axilla in 8 per[illegible] nodes in 11 percent [illegible] tive sentinel nodes we[illegible]

Conclusions Biopsy of [illegible] the presence or absence of [illegible] ses in patients with breast cancer. [illegible] cedure can be technically challenging, [illegible] cess rate varies according to the surgeon [illegible] characteristics of the patient. (N Engl J Med [illegible] 339:941-6.)

©1998, Massachusetts Medical Society.

THE histologic status of axillary lymph nodes, one of the most important prognostic indicators in patients with breast cancer, directly affects clinical management.[1] However, over 80 percent of women who undergo axillary dissection have at least one postoperative complication [illegible]

[illegible]

Volume 339 Number 14 · 941

The New England
Journal of Medicine

VOLUME 339 OCTOBER 1, 1998 NUMBER 14

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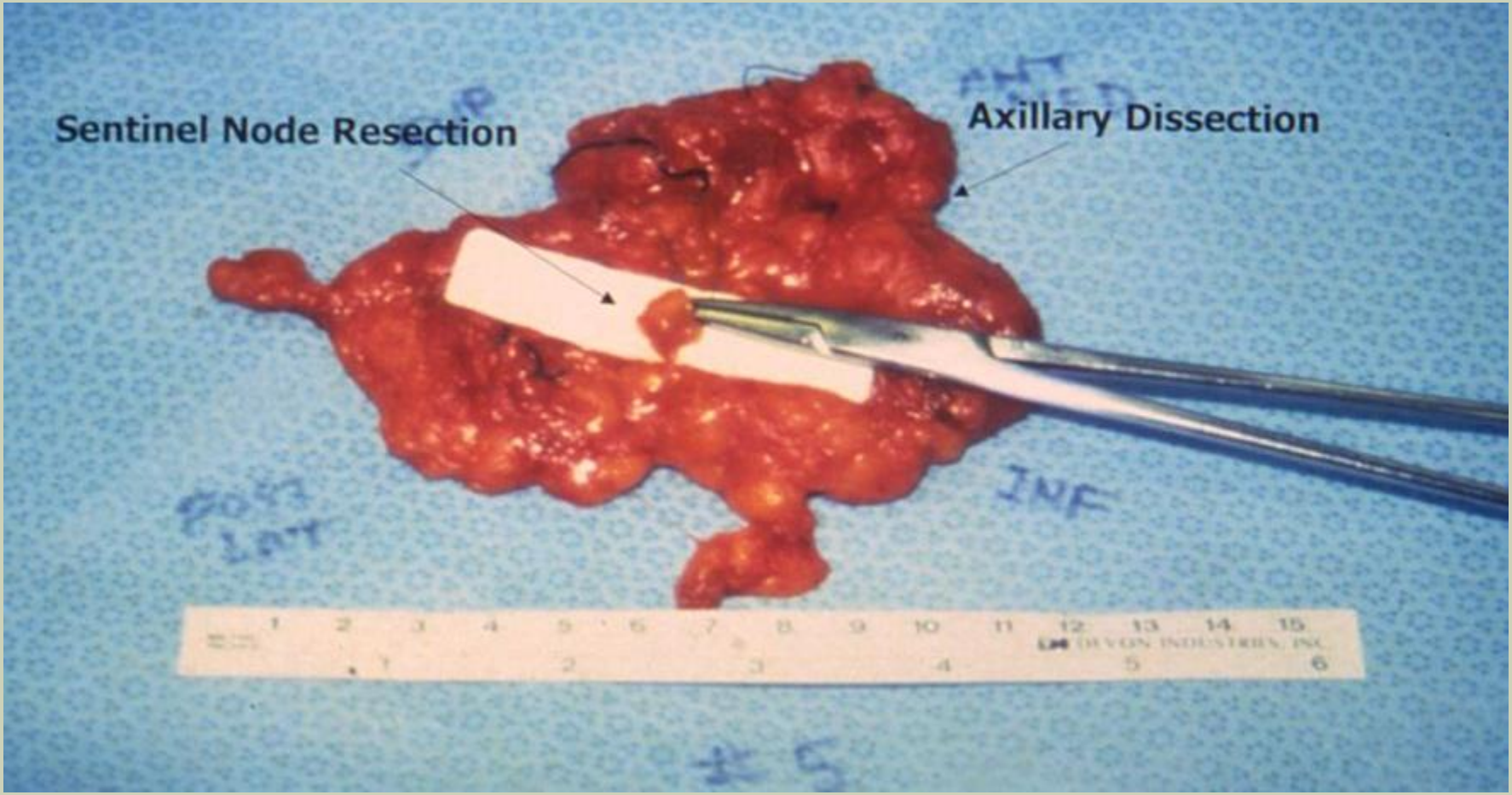
The Sentinel Node in Breast Cancer

A Multicenter Study

The New England Journal of Medicine,
October 1, 1998, Vol. 339, No. 14.

SENTINEL NODE VS ALND

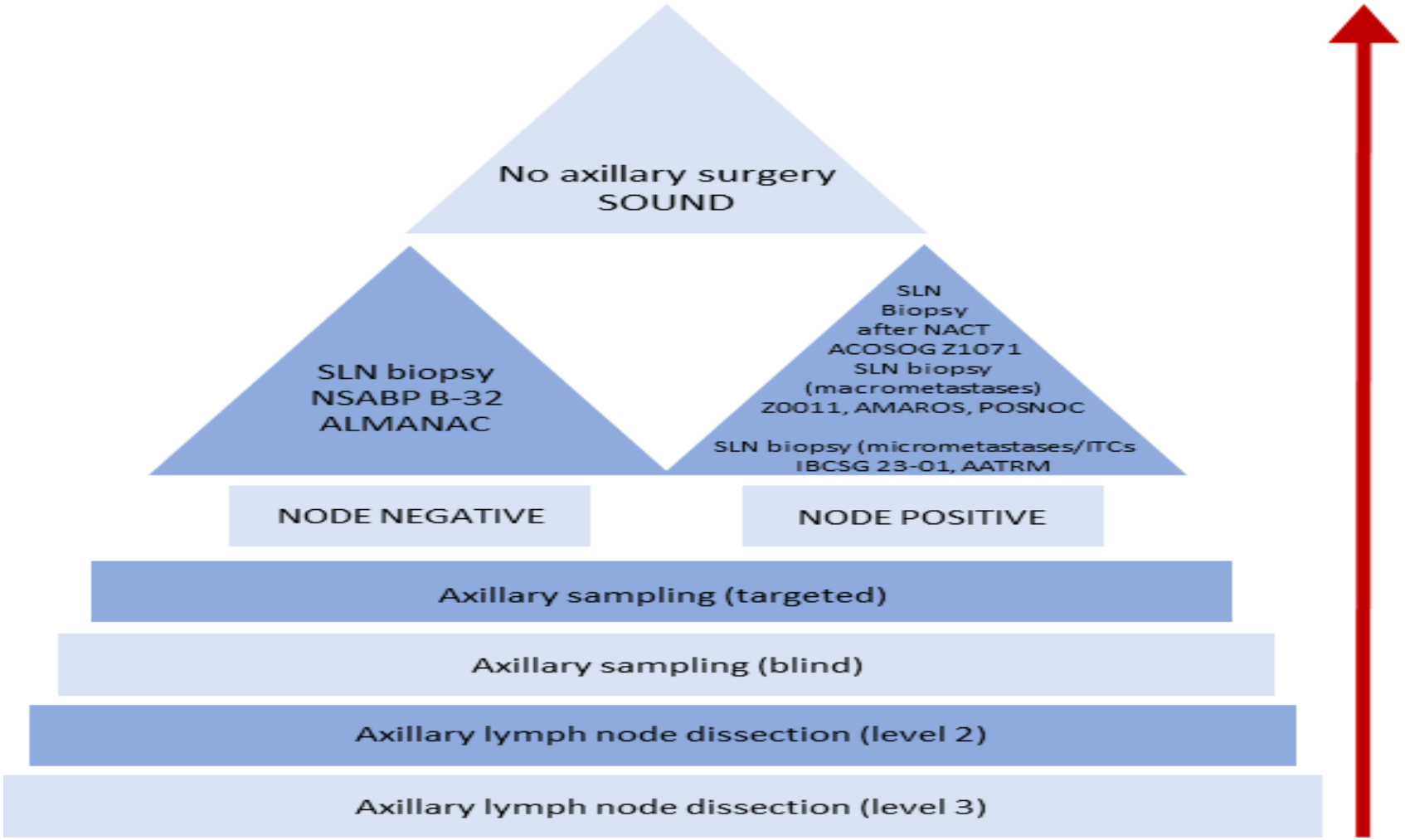


Dr. BLAKE CADY

LYMPH NODE METASTASES; "INDICATORS NOT GOVERNORS OF SURVIVAL" Arch Surg 1984

"Biology is King; selection of cases is Queen, and the technical details of surgical procedures are princes and princesses of the realm who frequently try to overthrow the powerful forces of the King and Queen, usually to no long-term avail, although with some temporary apparent victories." 1997

DE-ESCALTION OF AXILLARY SURGERY



Montefiore Einstein
Center for Cancer Care

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

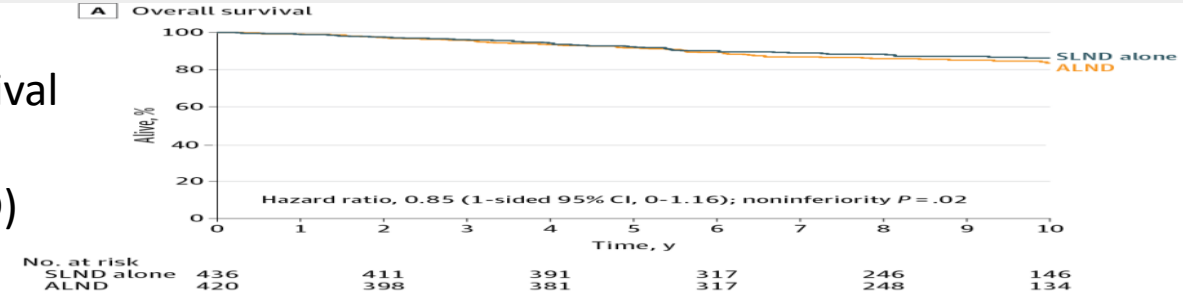
Sentinel Node Biopsy; Major Improvement!

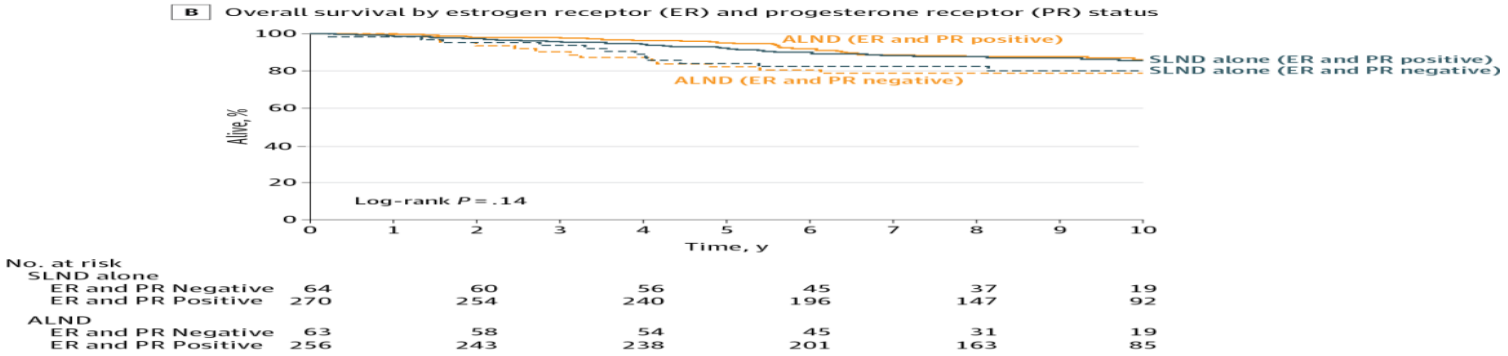
- Replaces ALND for pts with healthy sent node
- Marked reduction BCRL(5-7%)
- ACOSOG Z11 study: not necessary to do ALND if limited cancer involvement of sent node when pts have lumpectomy surgery since will receive radiation and systemic therapy. 27% of patients have additional lymph nodes with cancer that were not removed and no difference in survival
- NOT yet proven to avoid ALND in patients having mastectomy-since the number of lymph nodes involved with cancer determine the benefit of post-mastectomy radiation

From: **Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node MetastasisThe ACOSOG Z0011 (Alliance) Randomized Clinical Trial**

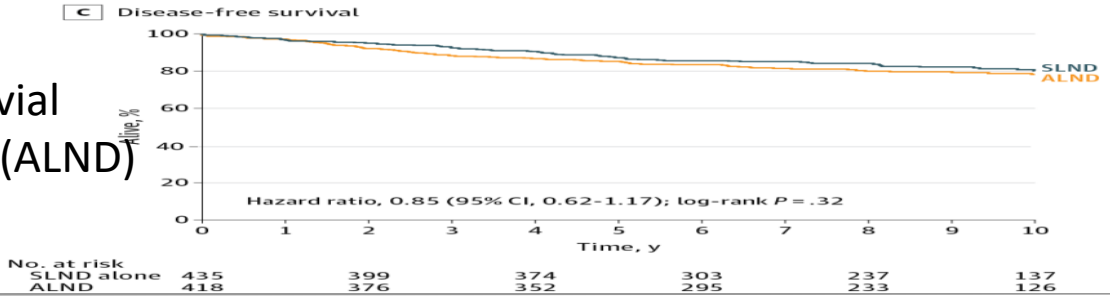
JAMA. 2017;318(10):918-926. doi:10.1001/jama.2017.11470

Overall survival
86.3(SN) vs
83.6%(ALND)





Disease free survivial
80.2(SN) vs 78.2%(ALND)



Axillary Surgery Options

- SO PATIENTS MUST UNDERSTAND THAT IF THEY CHOOSE MASTECTOMY OVER LUMPECTOMY THEY ARE INCREASING THE LIKELIHOOD THAT THEY WILL UNDERGO AN ALND WITH AN INCREASED RISK OF DEVELOPING LYMPHEDEMA
- Very relevant point of discussion since mastectomy rates have been increasing among patient who are eligible for breast conservation surgery(lumpectomy)

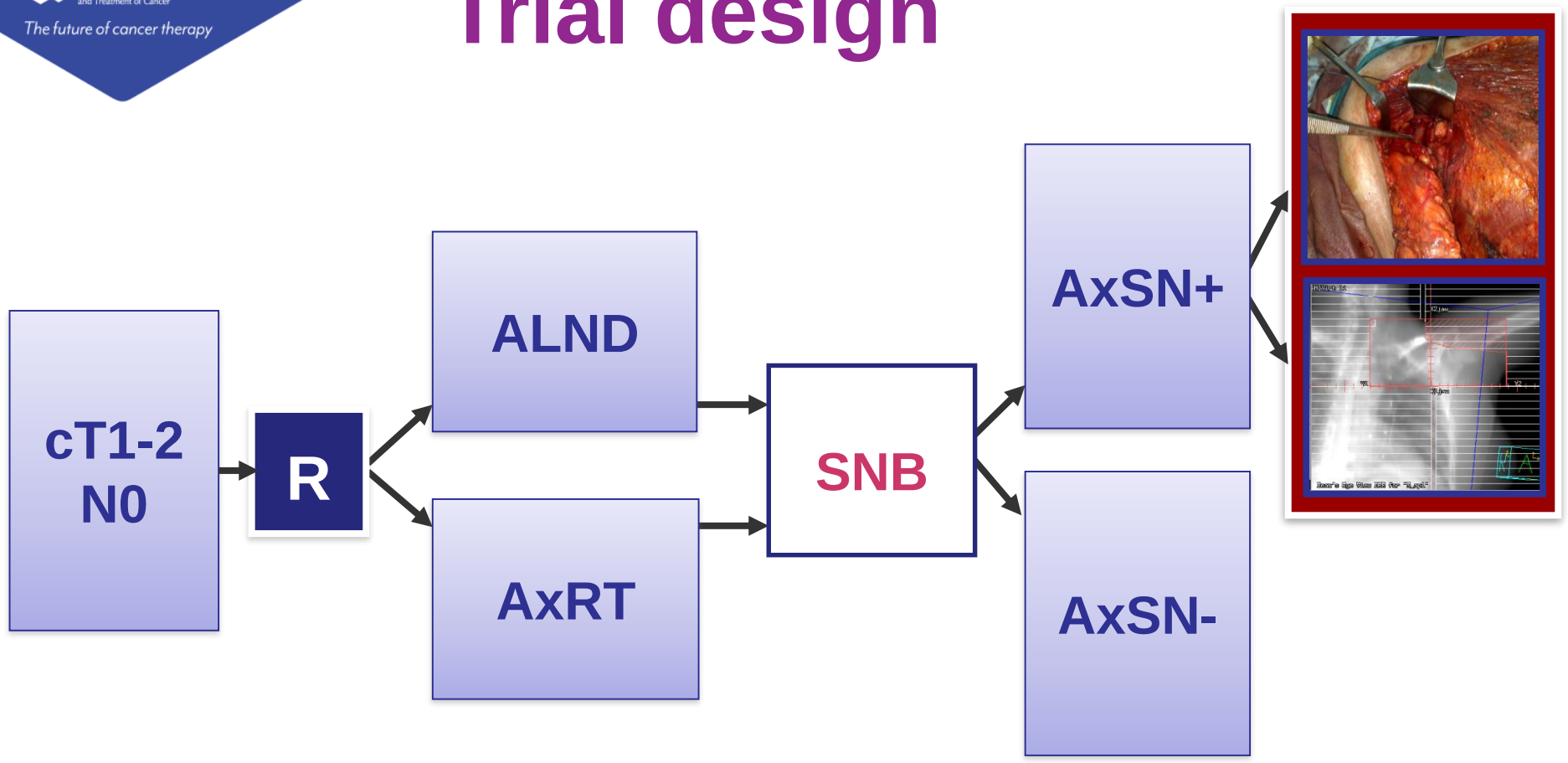
Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients: 10-year results of the EORTC AMAROS trial

By the EORTC Breast Cancer Group and Radiation Oncology Group
In collaboration with the Dutch BOOG Group and ALMANAC Trialists' Group

Emiel J Rutgers
The Netherlands Cancer Institute,
Amsterdam

Clinical trial information: NCT00014612

Trial design



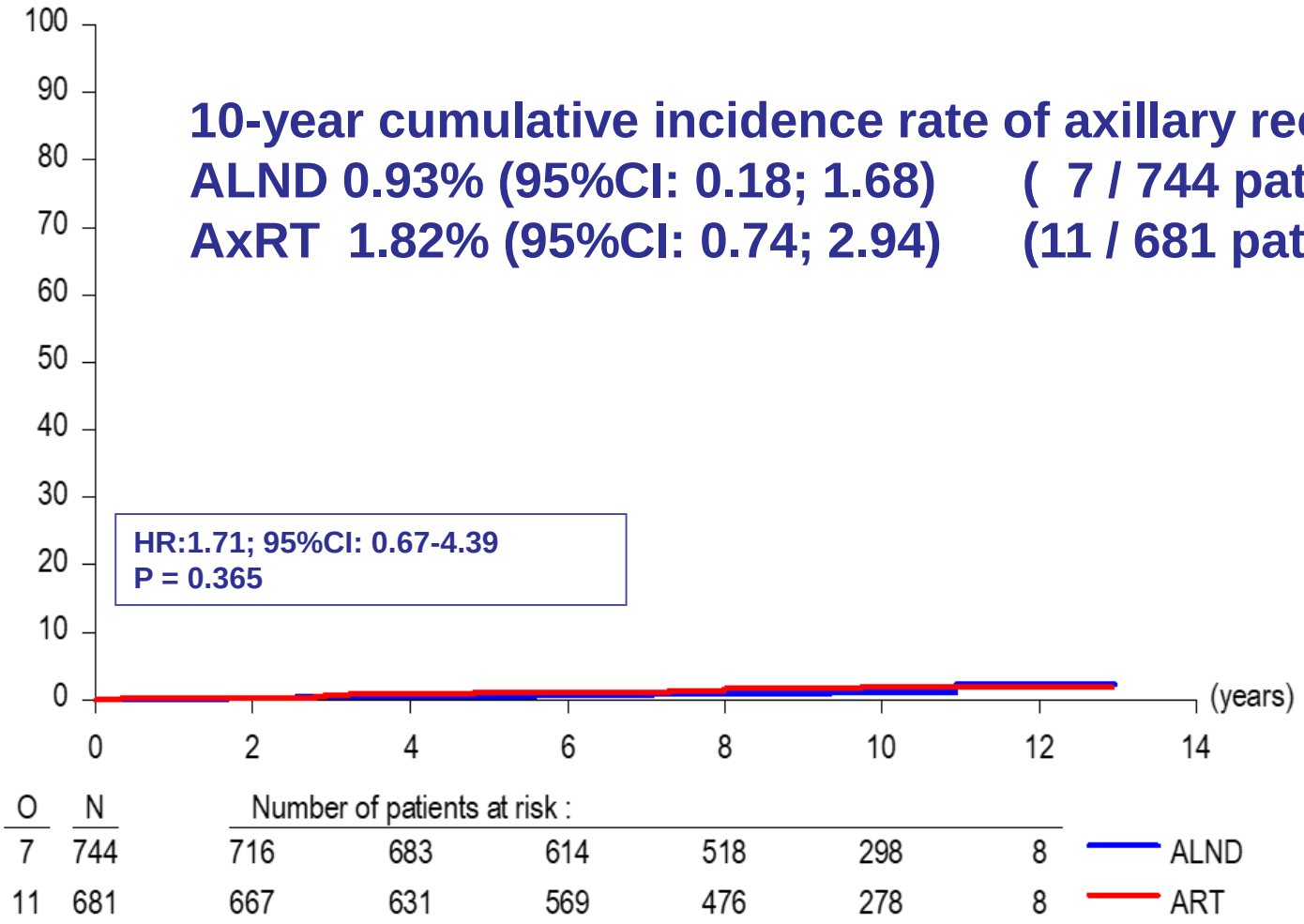
Stratification: institution
Adjuvant systemic therapy by choice

EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

Axillary recurrence rate

AxSN+ ITT population

10-year cumulative incidence rate of axillary recurrence:
ALND 0.93% (95%CI: 0.18; 1.68) (7 / 744 patients)
AxRT 1.82% (95%CI: 0.74; 2.94) (11 / 681 patients)



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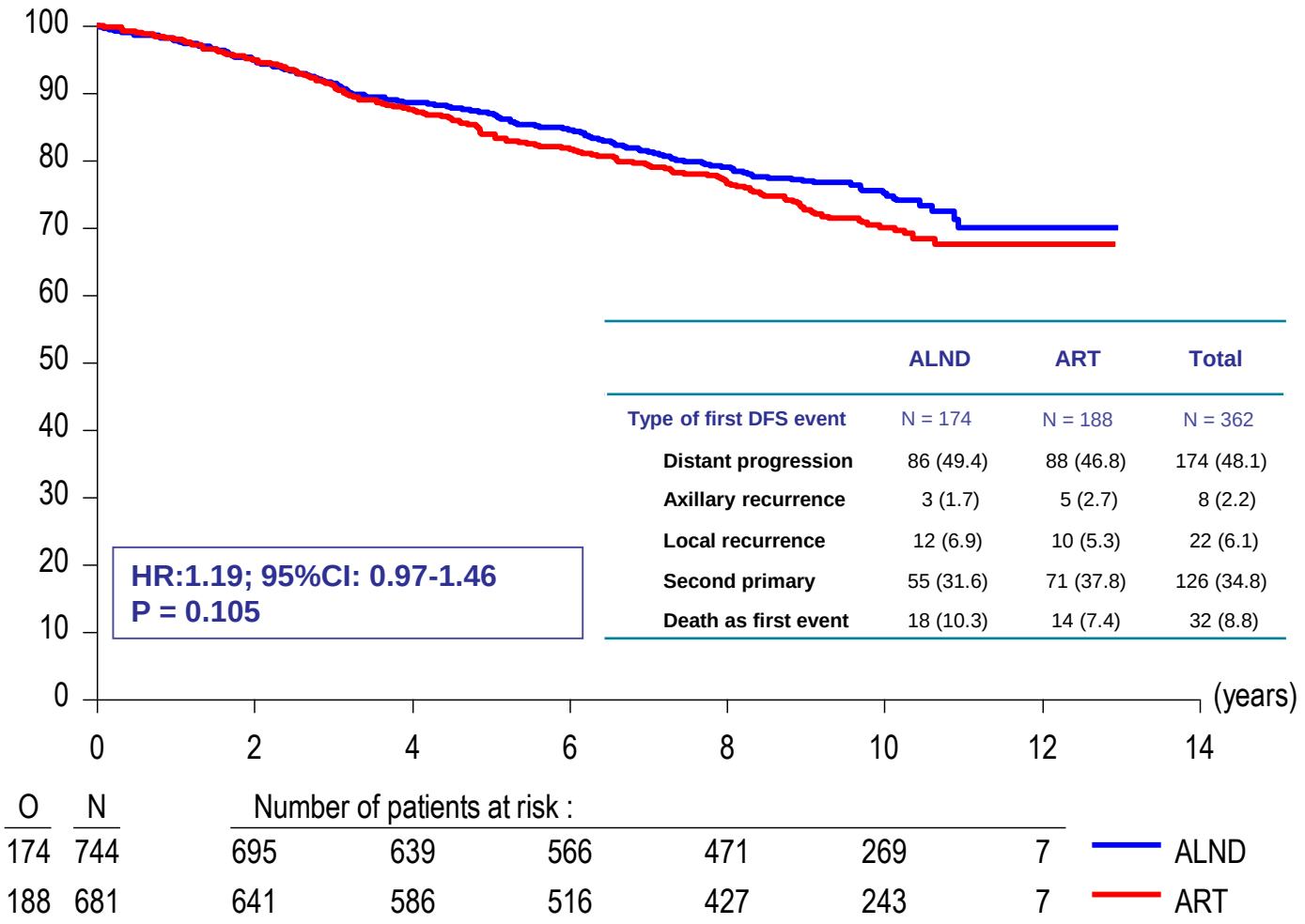
Cumulative incidence analysis considers death as a competing risks. HR and Wald p-value based on Fine & Gray model

Disease-free survival

AxSN+ ITT population

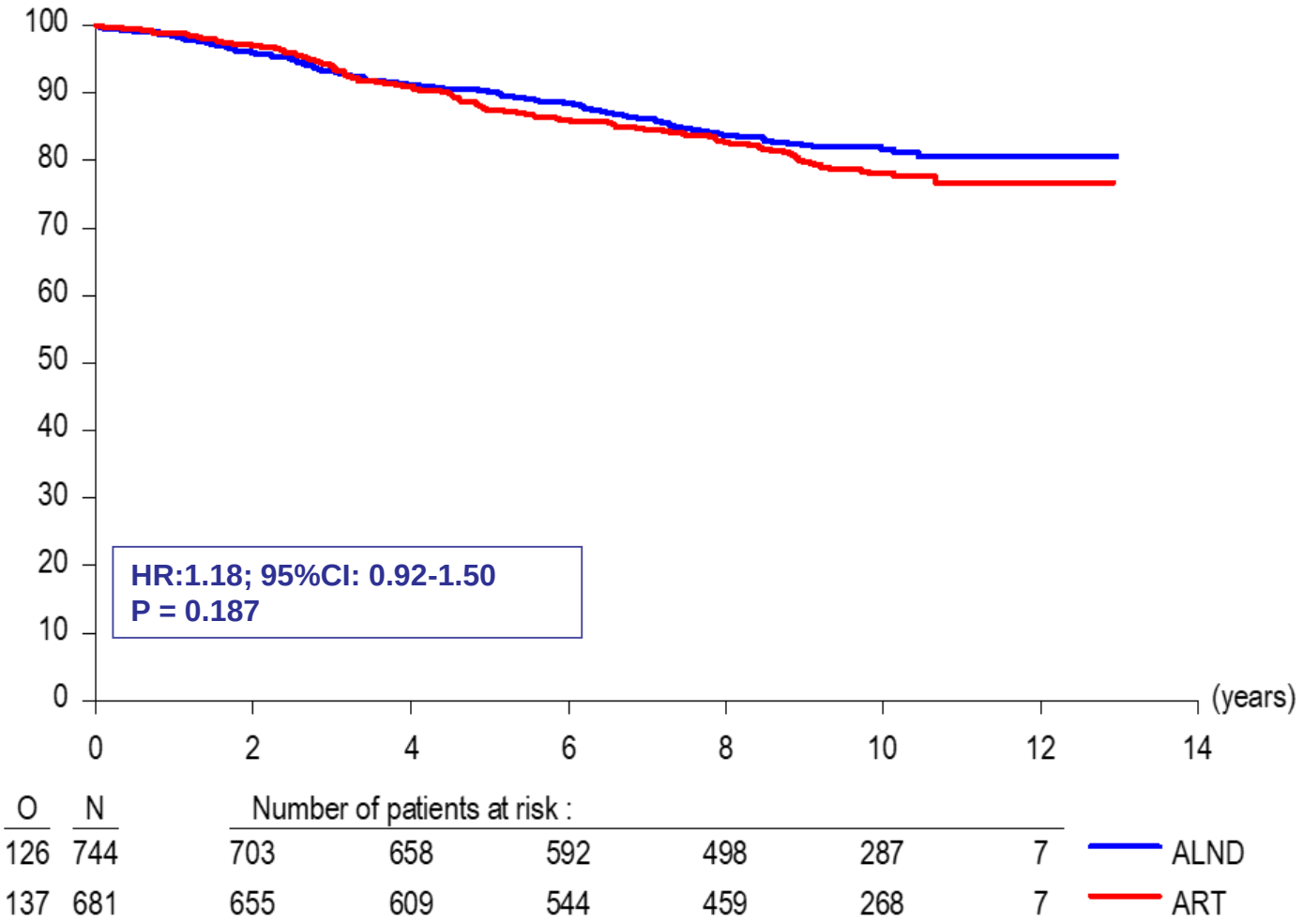


	ALND	ART	Total
Type of first DFS event	N = 174	N = 188	N = 362
Distant progression	86 (49.4)	88 (46.8)	174 (48.1)
Axillary recurrence	3 (1.7)	5 (2.7)	8 (2.2)
Local recurrence	12 (6.9)	10 (5.3)	22 (6.1)
Second primary	55 (31.6)	71 (37.8)	126 (34.8)
Death as first event	18 (10.3)	14 (7.4)	32 (8.8)

Events : local recurrence (incl. ipsilateral DCIS), axillary recurrence, distant metastasis, second primary (including contralateral DCIS), death. If multiple events occurred within a 1-month time window, the following prioritization was applied: distant progression, axillary recurrence, local recurrence, second primary, death. HR and Wald p-value based on Cox proportional hazard model

Distant metastasis free survival

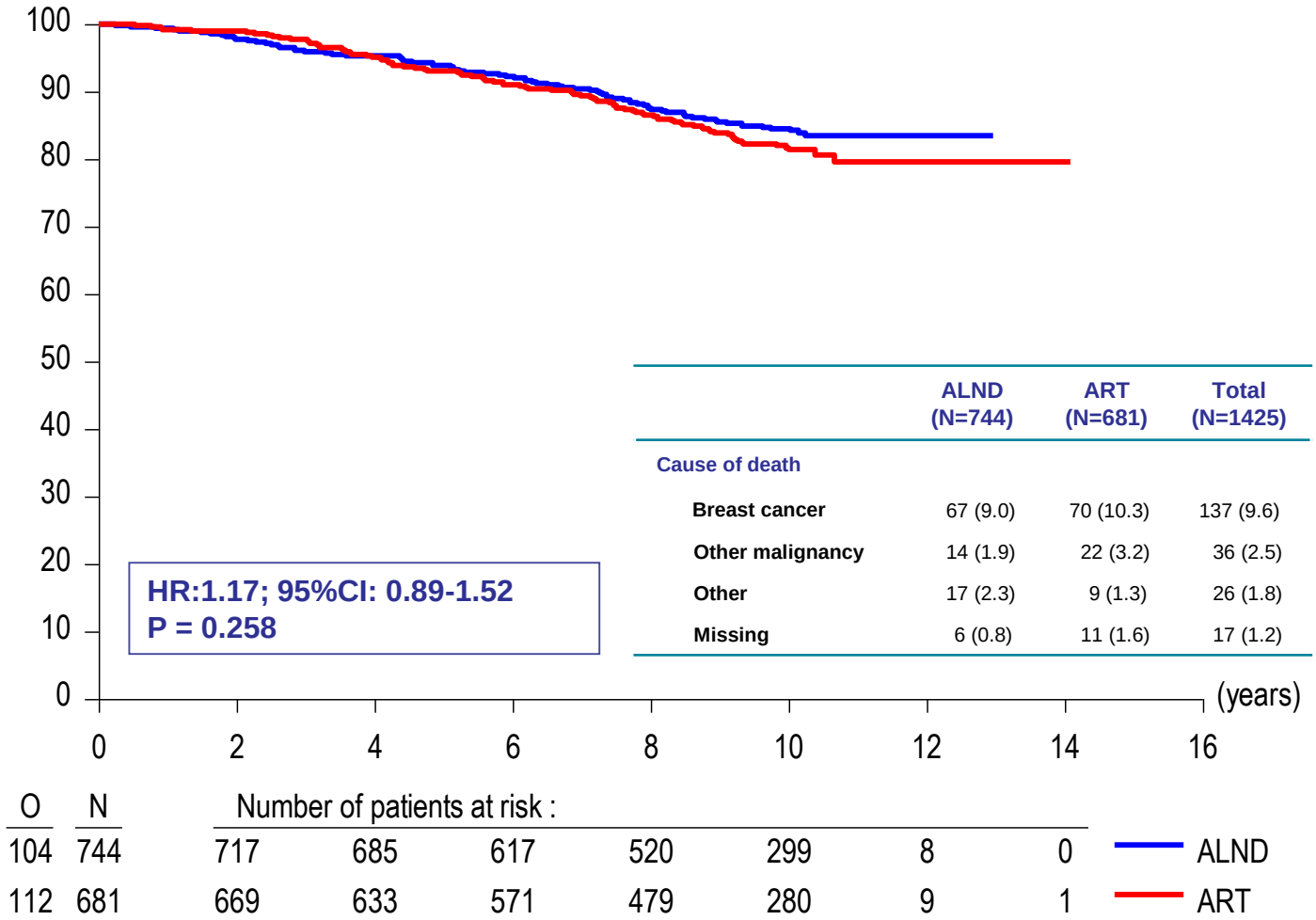
AxSN+ ITT population



Events : distant metastasis, death. HR and Wald p-value based on Cox proportional hazard model

Overall survival

AxSN+ ITT population



	ALND (N=744)	ART (N=681)	Total (N=1425)
Cause of death			
Breast cancer	67 (9.0)	70 (10.3)	137 (9.6)
Other malignancy	14 (1.9)	22 (3.2)	36 (2.5)
Other	17 (2.3)	9 (1.3)	26 (1.8)
Missing	6 (0.8)	11 (1.6)	17 (1.2)

HR and Wald p-value based on Cox proportional hazard model

Lymphedema of the arm

Measured: 1, 3 and 5 years after treatment

Items:

1. Clinical observation
2. Measurement

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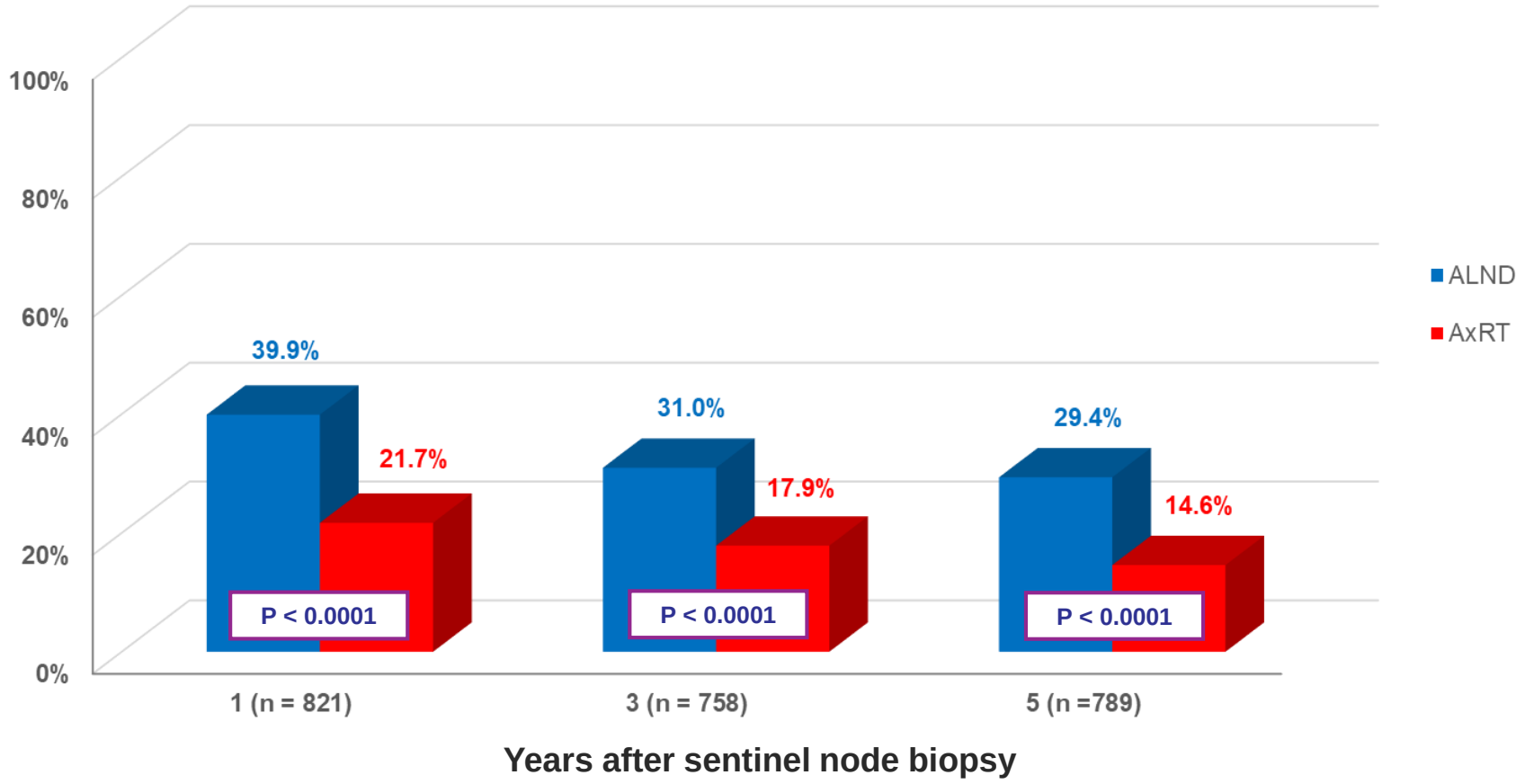
Lymphedema: clinical observation and/or treatment



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P-value from exact Fisher's test

Conclusion

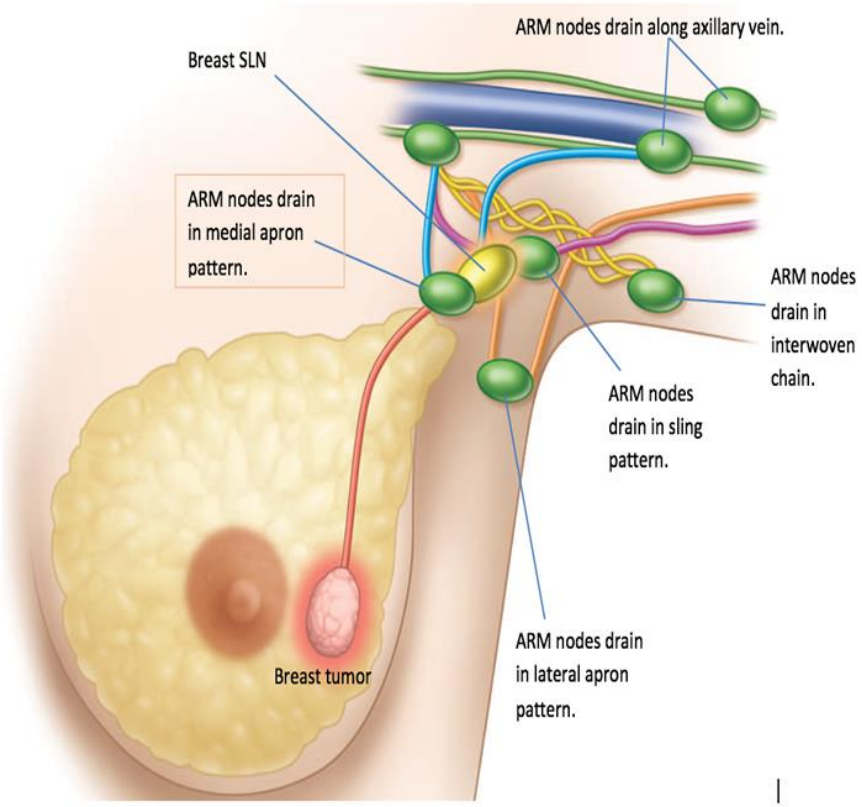
- Both ALND and AxRT provide excellent and comparable locoregional control in AxSN+ patients after 10 years, and no differences in DFS and OS
- Diagnosis of axillary lymph node recurrence after 5 yrs is a very rare event
- Significantly less lymphedema after AxRT after 5 years

Conclusion

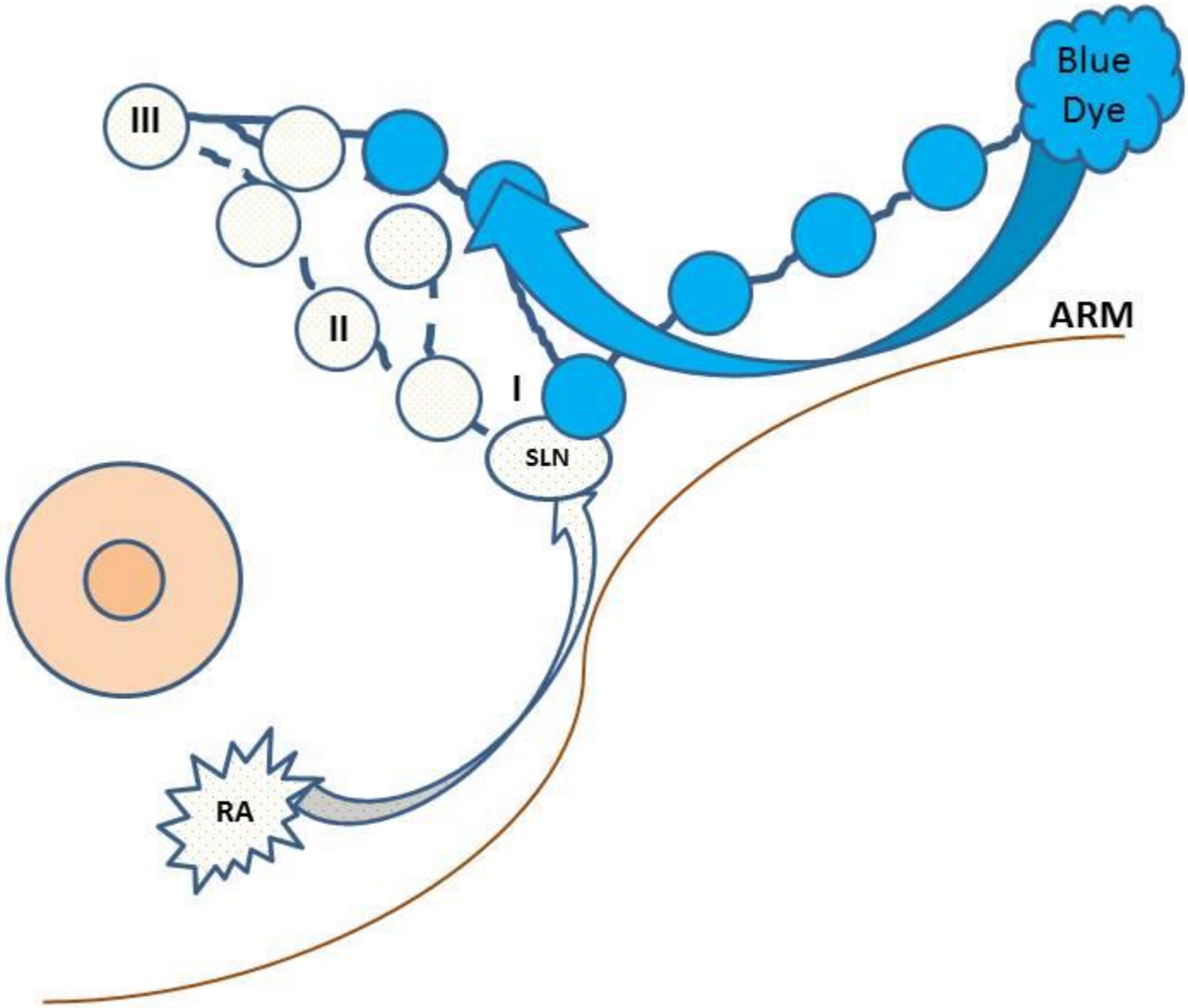
- AxRT can be considered standard treatment for patients with Amaros eligibility criteria
- Too few mastectomy patients for statistical significance but likely applies
- Radiation fields used more extensive than current approach

The concept of axillary reverse mapping(ARM)

- Involves mapping the lymphatic drainage form the upper extremity, determine anatomic variation and ensure preservation
- Reverse mapping – blue dye, radioisotope or ICG
-

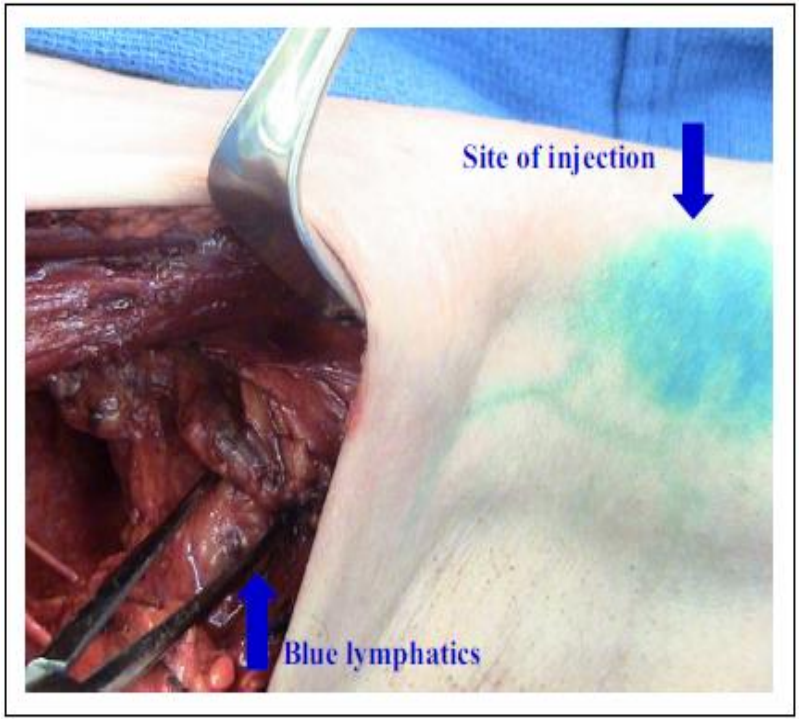


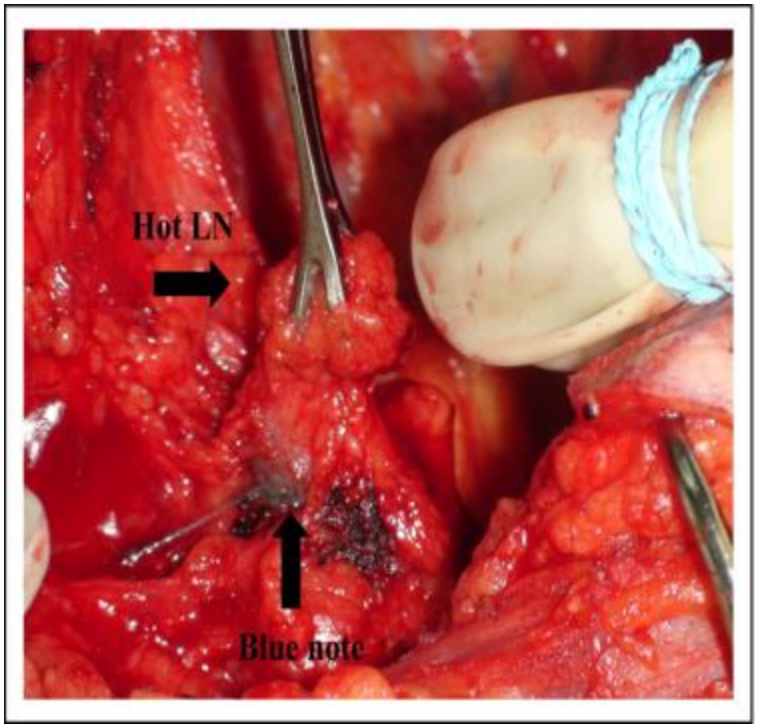
Five variations in upper extremity lymphatic drainage as demonstrated by Axillary Reverse Mapping (ARM) and their relationship to the breast sentinel lymph node (SLN).



Courtesy Klimberg

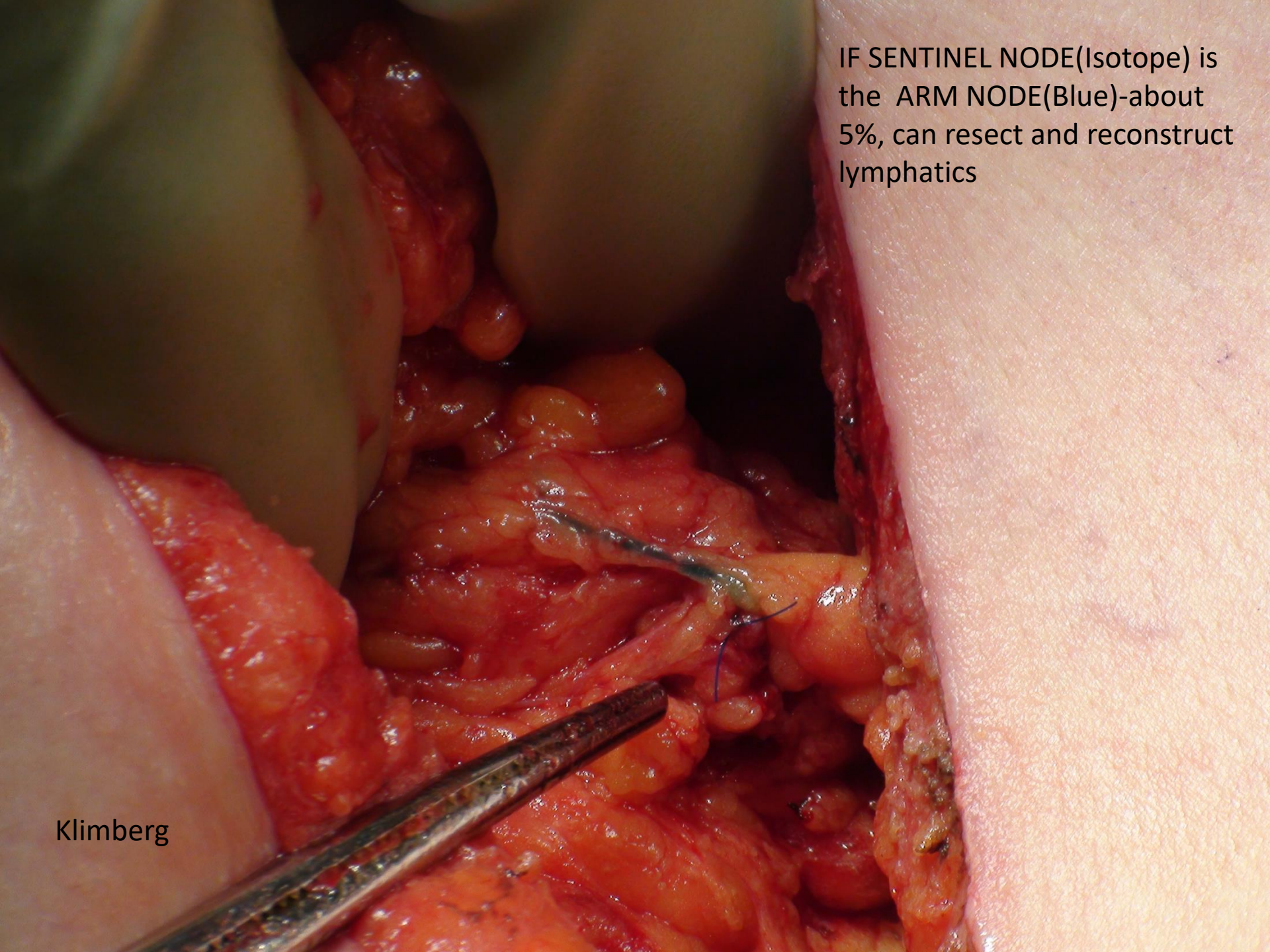
Axillary Reverse Mapping





- ARM, preserves upper extremity lymphatics
- Avoid inadvertent injury to arm related nodes

Courtesy Klimberg


IF SENTINEL NODE(Isotope) is the ARM NODE(Blue)-about 5%, can resect and reconstruct lymphatics
Klimberg

EVOLUTION OF LYMPHA

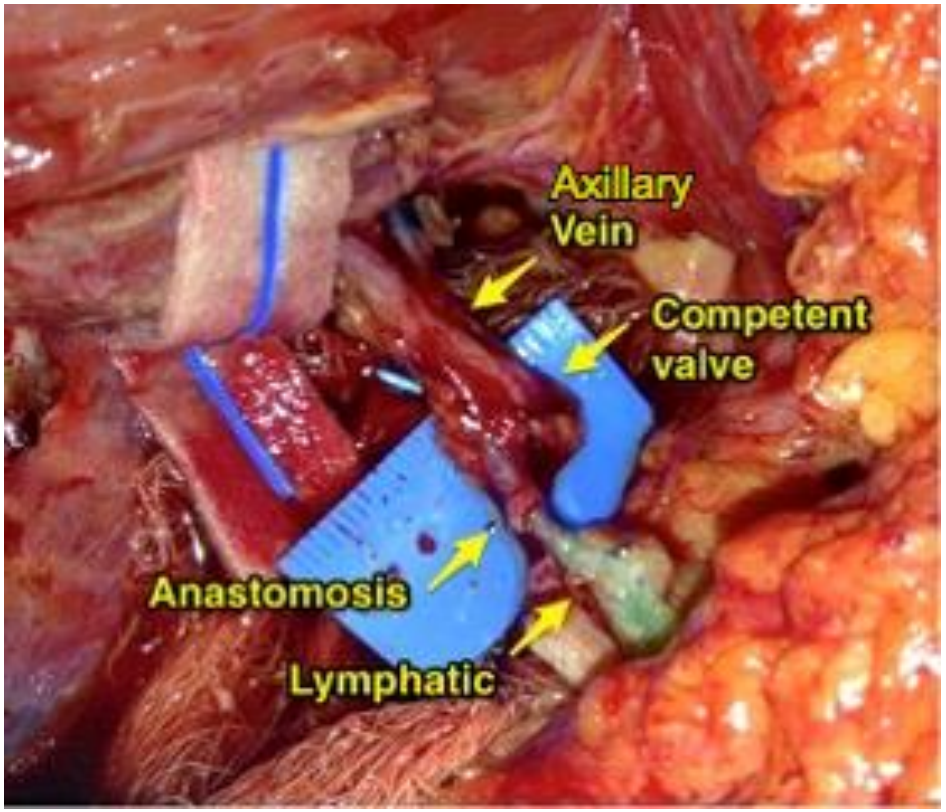
Single Institution Experience with Lymphatic Microsurgical Preventive Healing Approach (LYMPHA) for the Primary Prevention of Lymphedema

Sheldon Feldman, MD[1], Hannah Bansil, MD[1], Jeffrey Ascherman, MD[2], Robert Grant, MD[2], Billie Borden, BA[3], Peter Henderson, MD[2], Adewuni Ojo, MD[1], Bret Taback, MD[1], Margaret Chen, MD[1], Preya Ananthakrishnan, MD[1], Amiya Vaz, BA[1], Fatih Balci, MD[1,5], Chaitanya R. Divgi, MD[4], David Leung, MD[4], and Christine Rohde, MD[2]

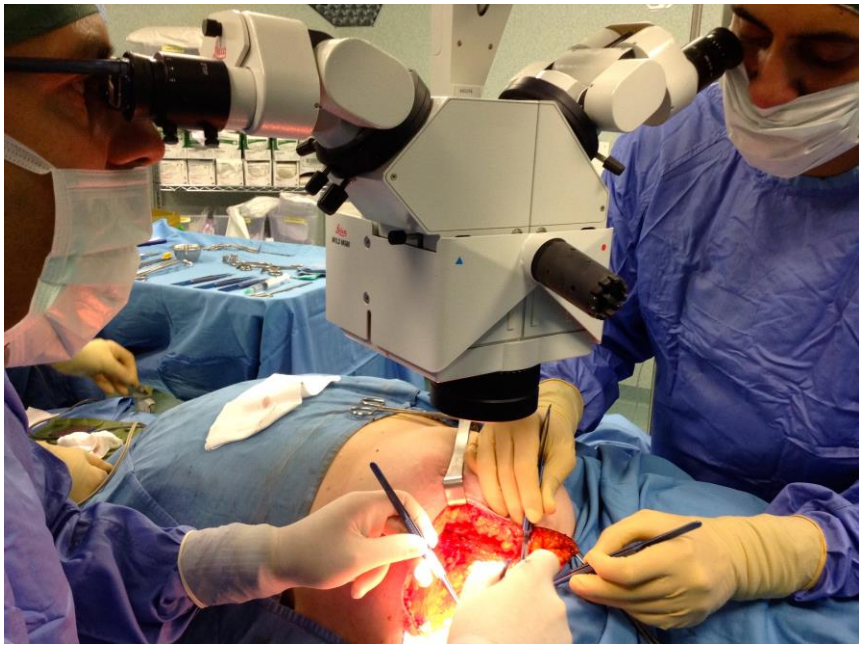
[1]Division of Breast Surgery, Columbia University Medical Center, New York-Presbyterian Hospital, Columbia University, New York, NY; [2]Division of Plastic Surgery, Columbia University Medical Center, New York-Presbyterian Hospital, Columbia University, New York, NY; [3]Columbia University College of Physicians and Surgeons, New York, NY; [4]Department of Radiology, Columbia University Medical Center, New York-Presbyterian Hospital, Columbia University, New York, NY; [5]Department of Surgery, Atakent Hospital, Acibadem University, Istanbul, Turkey

2015 – **Feldman, Bansil, et. al.** report Columbia's experience with LYMPHA in the *Annals of Surgical Oncology*.[25]

LYMPHA Procedure



- Average diameter of anastomosed vessels was 1-2 mm. Average 1.5 lymphatics



- LYMPHA added about 45 minutes of OR time.
- No LVA-related complications.

FIRST COLUMBIA LYMPHA PATIENT:

74yo Woman(Nun) Stage 2B Left Invasive Lobular Carcinoma. Left Modified Radical Mastectomy with Implant: Feb 2013

Severe arthritis- ambulates with walker. Major concern mobility issues if developed lymphedema. Arm measurements and 18 month f/u lymphoscintigram normal

Sequence of treatment decision

- Essentially all patients with breast cancer require local therapy(surgery-lumpectomy or mastectomy), axillary nodal evaluation and possible radiation
- Essentially all patients with invasive breast cancer require systemic therapy with anti-estrogen medicine and/or chemotherapy to treat cancer cells that may be spread to organs outside the breast
- KEY QUESTION WHICH GOES FIRST??

Sequence of treatment decision(cont)

- Based on the subtype of the cancer, size of tumor and lymph node involvement, many patients benefit from systemic therapy prior to surgery (neoadjuvant) for the following reasons:

a. Tumor gets smaller or disappears(complete response) so can remove less breast tissue- more normal breast appearance

b. Cancer containing axillary lymph nodes can become cancer free allowing avoidance of ALND

c. Can assess the effectiveness of the medical treatment

Complete pathological response by subtype after neoadjuvant chemotherapy

TABLE 1. Axillary Pathologic Complete Response Rates in Patients With Biopsy-Proven Axillary Lymph Node Metastases After Neoadjuvant Systemic Therapy

References	No. of Patients	SLNB Success Rate (%)	Axillary pCR (%)	Molecular Subtype (%)			
				ER+ HER2−	ER+ HER2+	ER- HER2+	ER- HER2−
Mamtami et al[13]	195	98	49	21	70	97	47
Park et al[14]	178	95	41	24	52	52	59
Dominici et al[15]	109	—	—	—	67	79	—
Boughey et al[16]	689	93	40	—	—	—	—
Yagata et al[17]	95	85	33	—	—	—	—
Newman et al[18]	54	98	32	—	—	—	—
McVeigh et al[19]	78	—	37	—	—	—	—
Total [n/N (%)]	—	1067/1144 (93)	497/1236 (40)	33/148 (22)	71/111 (64)	96/125 (77)	46/89 (52)

pCR indicates pathologic complete response; ER; estrogen receptor; HER2, human epidermal growth factor receptor 2; SLNB, sentinel lymph node biopsy.

Current approach lymphedema prevention:

- Less axillary surgery- sentinel node bx, preop chemotherapy for node + patients
- No sentinel node bx if will not effect systemic Rx, SSO choosing wisely- pts >age 70
- Preserve arm nodes with Axillary Reverse mapping technique
- LYMPHA procedure if extensive residual disease requiring complete axillary dissection
- Monitor for pre-clinical volume increase with bioimpedence spectroscopy(L-Dex)
- Patient education and awareness key
- Early physical therapy
- Multidisciplinary team to evaluate patients refractory to conservative management-LVA,LNT,Liposuction

POSNOC TRIAL-opened 7/2014

- POSITIVE SENTINEL NODE-ADJUVANT THERAPY ALONE VS ADJUVANT THERAPY PLUS AXILLARY CLEARANCE OR AXILLARY RADIATION
- PATIENT HAVING BREAST CONSERVATION WITH 2 OR LESS MACROMETS IN SENTINEL NODE
- ELUCIDATE VALUE OF AXILLARY SPECIFIC TREATMENT IN SETTING OF SYSTEMIC THERAPY

San Antonio Breast Cancer Symposium, December 4-8, 2018

Surgical treatment after neoadjuvant systemic therapy in young women with breast cancer: Results from a prospective cohort study

Hee Jeong Kim [1,2], Laura Dominici[1,3], Shoshana Rosenberg[1], Linda Ma Pak[1,3], Phillip D. Poorvu[1], Kathryn Ruddy[4], Rulla Tamimi[3], Lidia Schapira[5], Steven Come[6], Jeffrey Peppercorn[7], Virginia Borges[8], Ellen Warner[9], Hilde Vardeh[6], Laura Collins[6], Rachel Gaither[1], Tari King[1,3], Ann H. Partridge[1]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Asan Medical Center, Seoul, South Korea; [3]Brigham and Women's Hospital, Boston, MA; [4]Mayo Clinic, Rochester, MN; [5]Stanford University, Palo Alto, CA; [6]Beth Israel Deaconess Medical Center, Boston, MA;[7] Massachusetts General Hospital, Boston, MA; [8]University of Colorado Cancer Center, Aurora, CO; [9] Sunnybrook Health Science center, Toronto, ONT

DANA-FARBER CANCER INSTITUTE

ASAN Medical Center

Background

- Randomized controlled trials (RCTs) have demonstrated that eligibility for breast conserving surgery (BCS) can be increased after neoadjuvant chemotherapy (NAC)

- Despite eligibility for BCS, analyses from large pre-operative RCTs have revealed many women are undergoing mastectomy:
  - 76% of BCS eligible patients had mastectomy in CALGB 40601 (HER2+)
  - 69% of BCS eligible patients had mastectomy in CALGB 40603 (TNBC)

Background

- Young women are more likely to present with large tumors and may benefit from a neoadjuvant systemic approach
- Recent data suggest that response rates, including pathologic complete response (pCR), are higher in women <40 years than in older women
- Little is known about how response to NAC influences surgical decision making in young women

Objectives

- To describe the use of and response to NAC among young women with breast cancer
- To evaluate choice of surgical procedure considering:
  - Before- and after- NAC eligibility for BCS
  - Clinical and pathological response to NAC
- To evaluate reasons for not undergoing BCS when BCS eligible after NAC

Methods

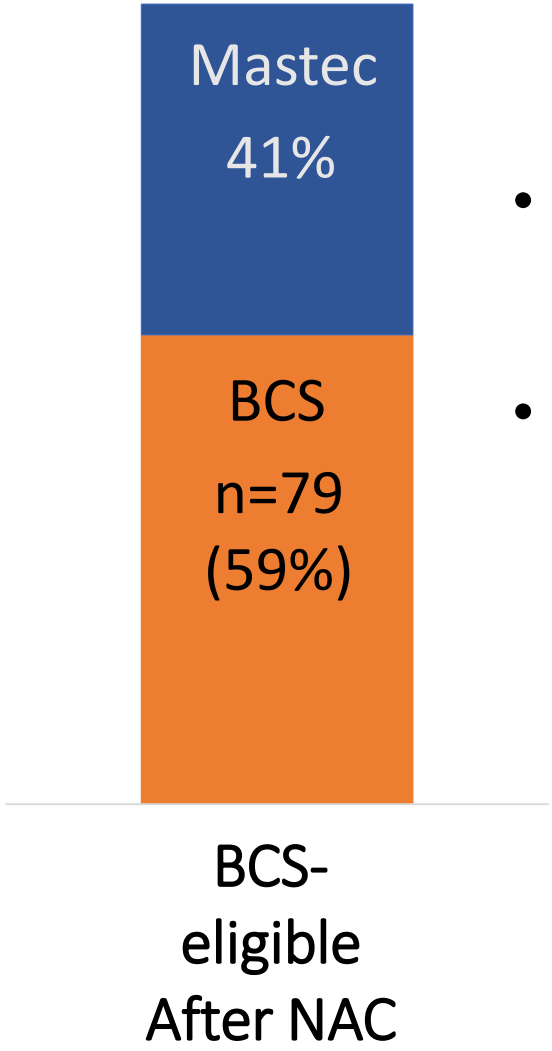
- The Young Women`s Breast Cancer Study (
  - Multicenter prospective cohort
  - Women age ≤40 at diagnosis of breast cancer identified through pathology record review
  - 12 participating hospitals (academic and community)
  - 1302 women enrolled from October 2006 to June 2016

- The study was established to explore biological, medical and psychosocial issues in young breast cancer patients

Methods

- BCS eligibility before and after NAC and clinical response to NAC were abstracted from the medical records by two trained surgeons and reviewed by a third investigator in instances of discrepancy

Initial surgical procedure among BCS-eligible patients after NAC (N=133)



- 41% of BCS-eligible patients after NAC chose mastectomy
- The proportion of patients with BCS as first surgical procedure was not influenced by response to NAC
  - 42% of BCS-eligible patients with clinical CR chose mastectomy and 35% had a pCR

Reasons for choosing mastectomy in BCS-eligible patients (N=55)

- The most common documented reason that BCS-eligible patients chose mastectomy was patient preference (53%)
- 40% chose mastectomy because of carrying a BRCA 1 or 2, or p53 mutation or having a strong family history
- 75% who chose mastectomy underwent bilateral mastectomy
- Among BCS-eligible patients with cCR and/or ultimately pCR who chose mastectomy, these reasons were similar

Conclusions and Implications

- NAC increased the proportion of young women with breast cancer who were eligible for BCS, yet 40% of eligible patients chose mastectomy regardless of response to NAC in a large multicenter cohort
  - Personal preference (without known high risk predisposition) was most common reason
- While rates of NAC have increased over time and response rates have improved, rate of BCS as first surgical procedure is not increasing
- Surgical decisions among young women with breast cancer appear driven by factors beyond the extent of disease and response to NAC
- Focused efforts to optimize surgical decision-making are needed

Local therapy and quality of life outcomes in young women with breast cancer

Laura Dominici, Jiani Hu, Tari King, Kathryn J. Ruddy, Rulla M. Tamimi, Jeffrey Peppercorn, Lidia Schapira, Virginia F. Borges, Steven E. Come, Ellen Warner, Ann Partridge, Shoshana Rosenberg

DANA-FARBER/BRIGHAM AND WOMEN'S CANCER CENTER

Background

- More than 13,000 women ≤40 years of age are diagnosed with breast cancer each year
  - ~7% of new breast cancers diagnosed in the United States

- Despite equivalent local regional control and survival with breast conservation and mastectomy, rates of (bilateral) mastectomy are increasing in young women
  - 3.6% in 1998 → 33% in 2011

Anders Semin Oncol 2009 Kurian JAMA 2014 Aalders JCO 2016

Background

- Previous studies of women of all ages treated for breast cancer found no clinically meaningful differences in QOL related to surgical procedure
  - Some QOL domains improved after CPM
- Young women are at increased risk for poorer psychosocial outcomes following a breast cancer diagnosis and in survivorship
- Little is known about the impact of surgery, particularly in the era of increasing bilateral mastectomy, on QOL in young survivors

Hwang JCO 2016
Koslow Ann Surg Onc 2013
Lebel Health Psychol

Objectives

- Using a multicenter prospective cohort of young women with breast cancer, we sought to:
  - Evaluate differences in QOL among women who had breast conserving surgery (BCS), unilateral mastectomy and bilateral mastectomy
  - Identify demographic and treatment-related factors that impact QOL

Methods

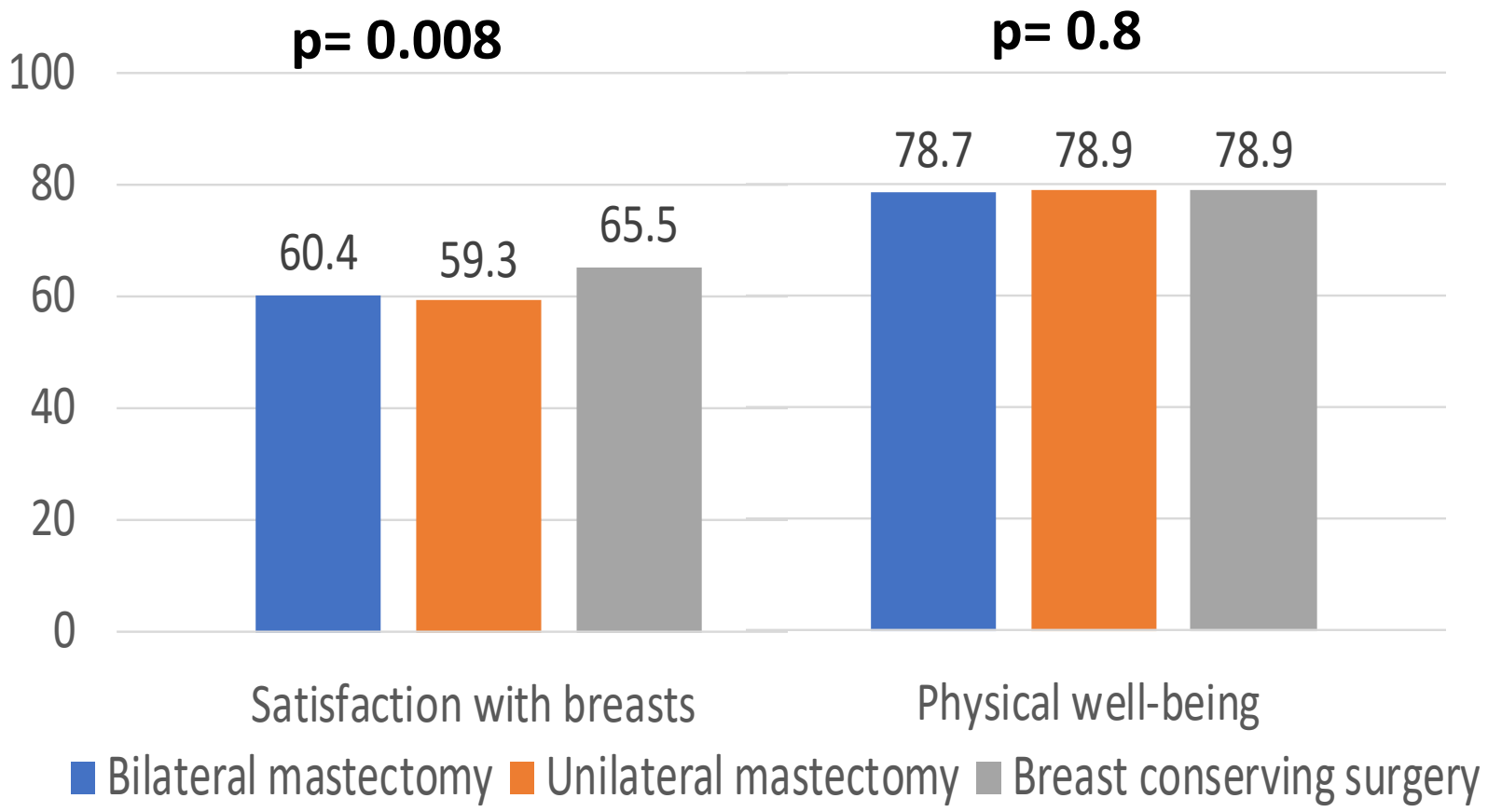
- This analysis used a cross-sectional study design
- BREAST-Q was administered to all eligible YWS participants in active follow-up in 2016-2017, either as a stand-alone survey or as part of their 10-year follow-up
- Median time from diagnosis to BREAST-Q completion: 5.8 (range: 1.9-10.4) years
- Demographics and treatment information were obtained from serial surveys and chart review.

BREAST-Q

- Six domains:
  - Satisfaction with breasts
  - Psychosocial well-being
  - Physical well-being
  - Sexual well-being
  - Overall outcome
  - Process of care

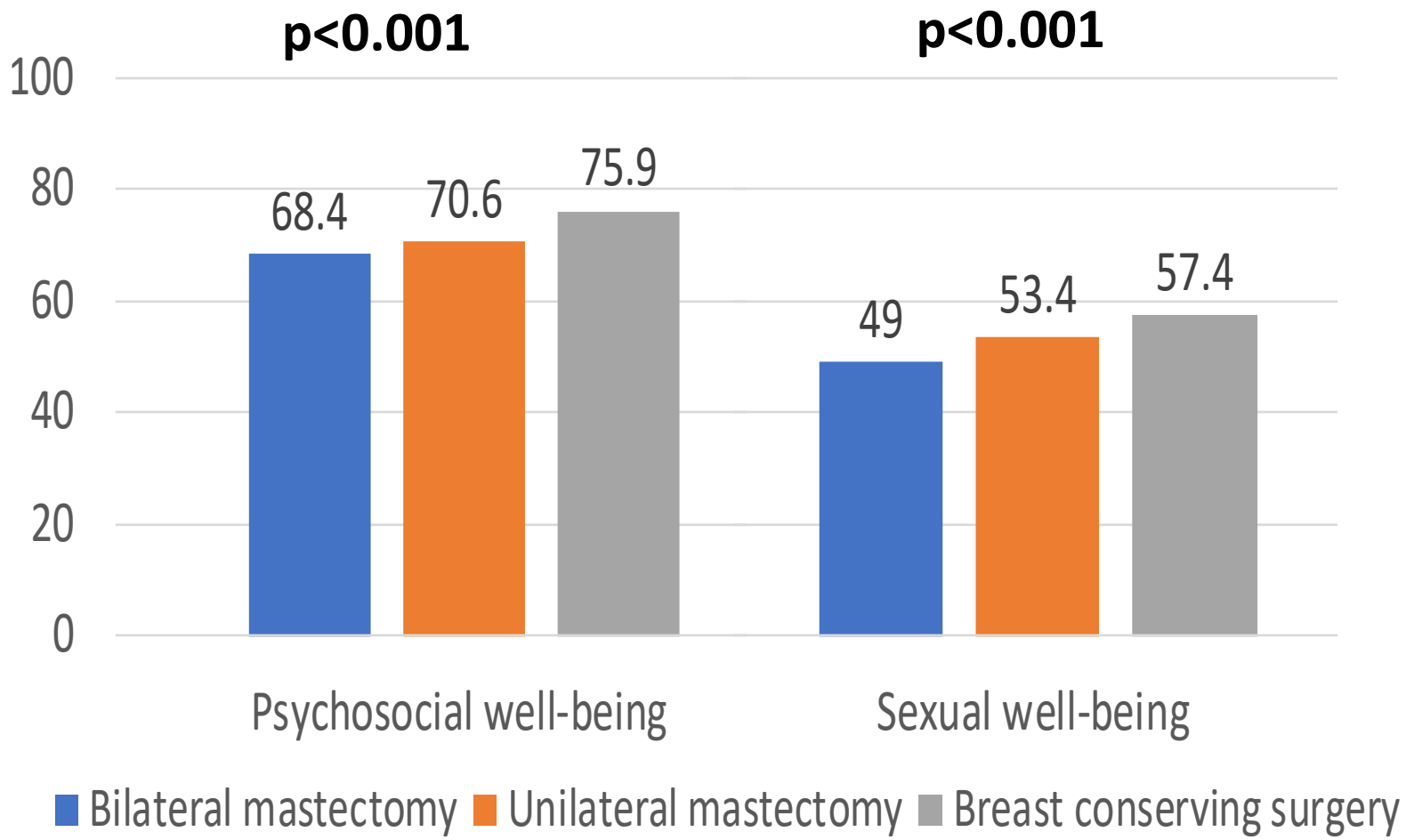
Pusic Plast Reconstr Surg 2009

BREAST-Q Mean Scores



Higher score = Better QOL

BREAST-Q Mean Scores



Higher score = Better QOL

Limitations

- One time survey of women enrolled in an observational cohort study
  - Preoperative QOL likely drives surgical choices
- Findings may have limited generalizability to more diverse populations
  - Majority of participants are white and of a high socio-economic status

Conclusions

- Local therapy decisions are associated with a persistent impact on QOL in young breast cancer survivors
- Compared to BCS, unilateral or bilateral mastectomy is associated with significant decreases in QOL domains for:
  - Satisfaction with breasts
  - Psychosocial well-being
  - Sexual well-being

San Antonio Breast Cancer Symposium®, December 4-8, 2018

Abs GS03-01. Randomized trial of low dose tamoxifen to prevent recurrence of breast intraepithelial neoplasia. Study TAM01

A.DeCensi*, M.Puntoni, A.Guerrieri Gonzaga, S.Caviglia, F.Avino, L.Cortesi, M.Donadio, M.Grazia Pacquola, F.Falcini, M.Gulisano, M.Digennaro, A.Carriello, K.Cagossi, G.Pinotti, M.Lazzeroni,D.Serrano, D.Branchi, S.Campora, M.Petrera, T.Buttiron Webber, L.Boni and B.Bonanni

Ente Ospedaliero Ospedali Galliera Genova
Ospedale di rilievo nazionale e di alta specializzazione

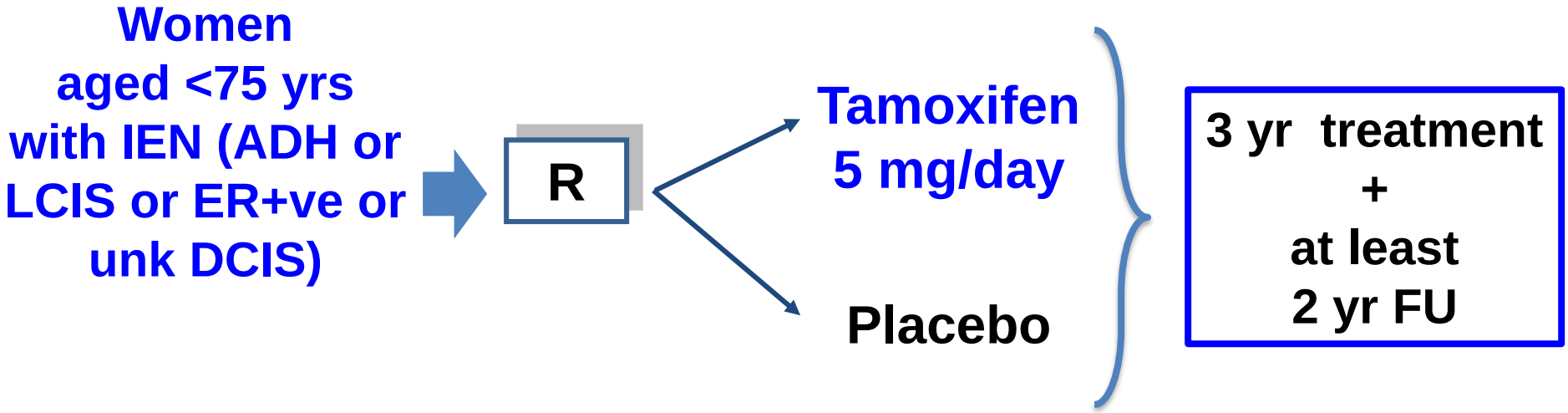
IEO Istituto Europeo di Oncologia

Queen Mary University of London

Barts and The London Queen Mary's School of Medicine and Dentistry

EudraCT Number
2007-007740-10
ClinicalTrials.gov
NCT01357772

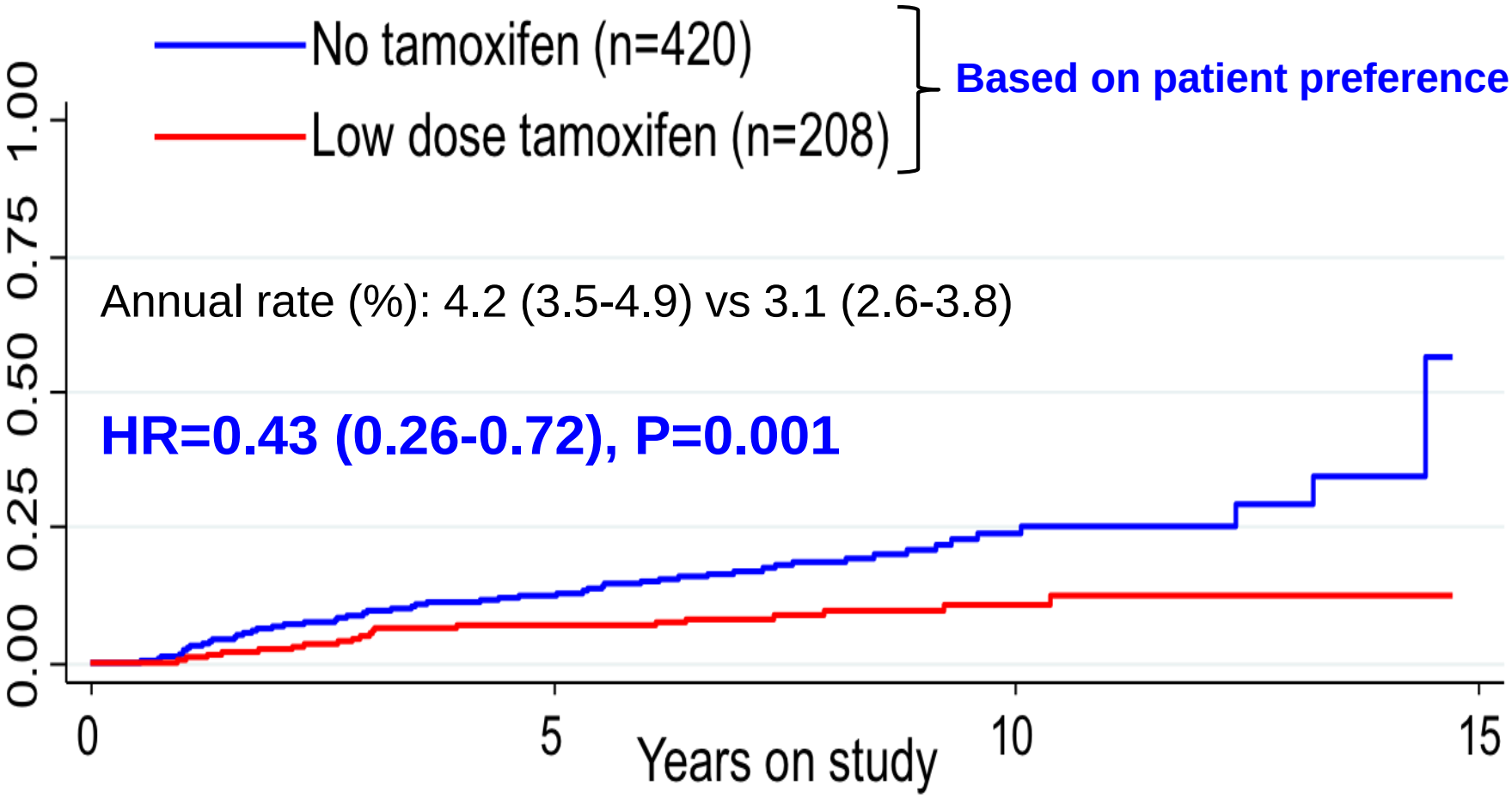
Study Design



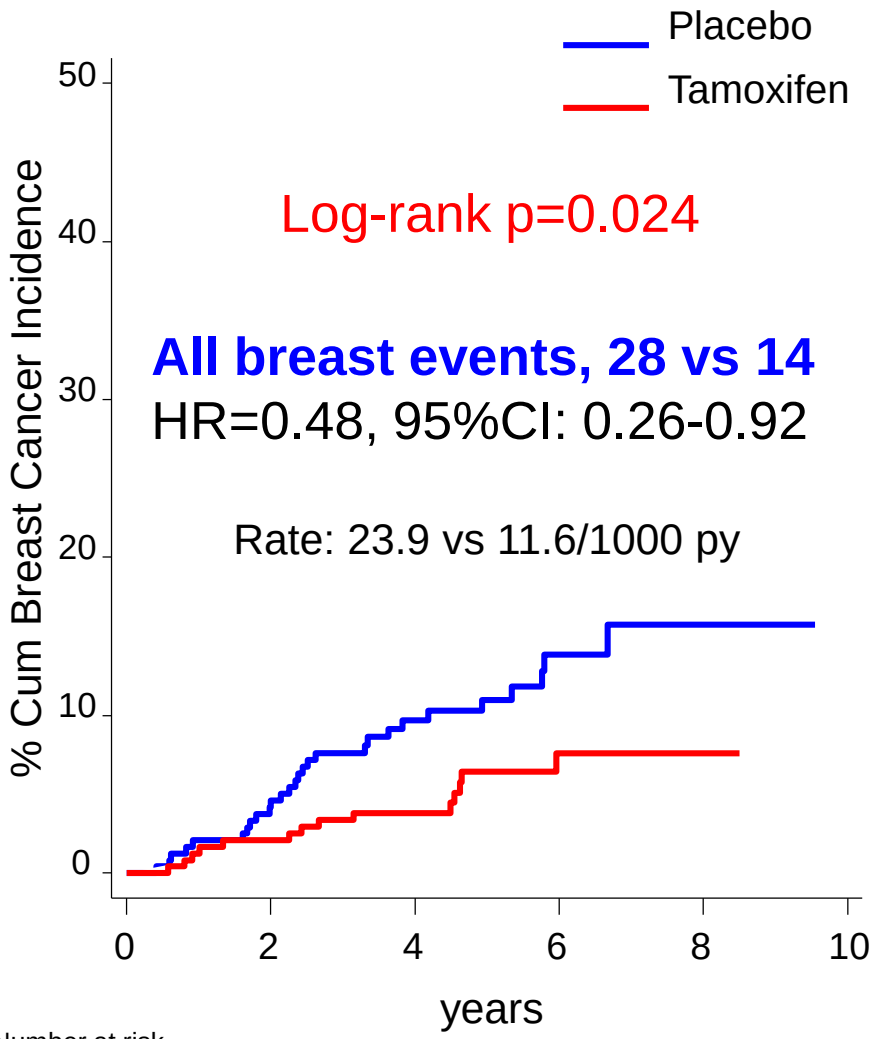
Primary endpoint: Incidence of invasive breast cancer or DCIS

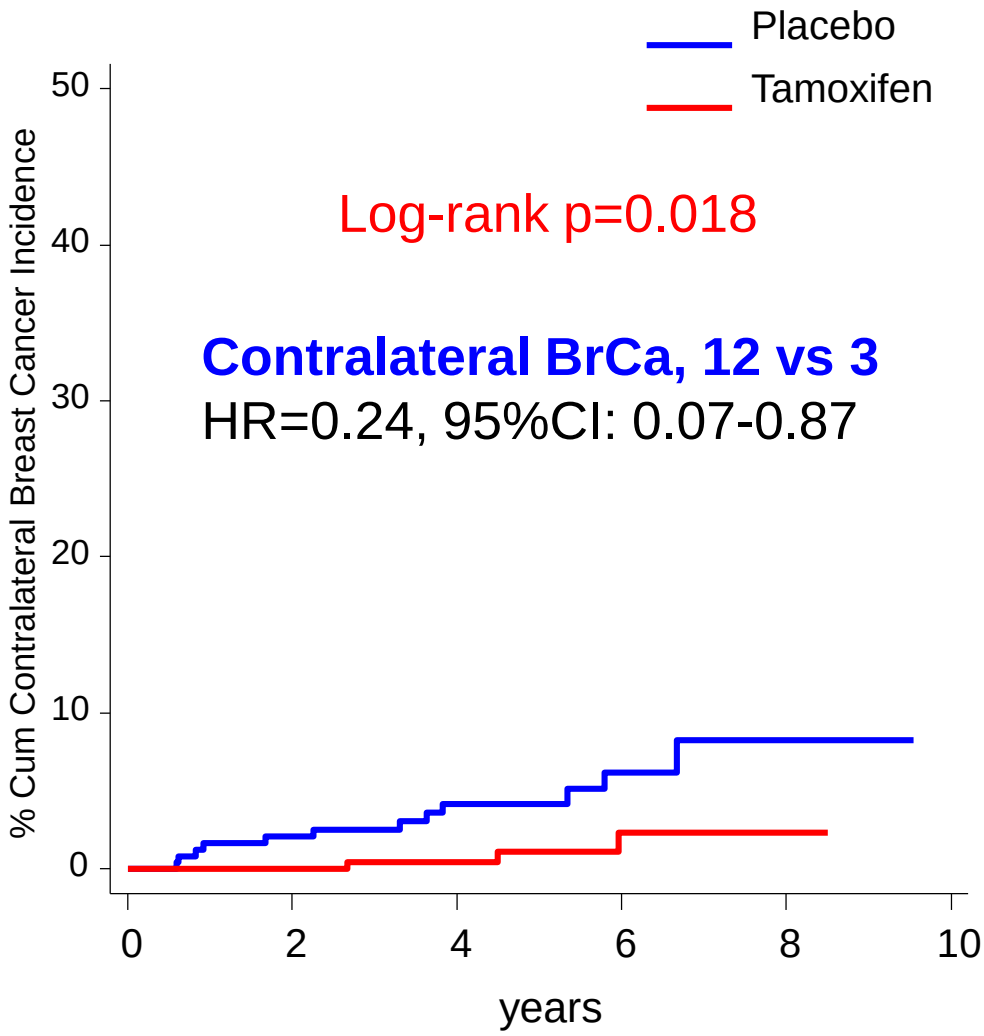
- 500 participants enrolled from 14 centers in Italy
- Visit and QoL every 6 months, Mx every year
- Median follow up = 5.1 years (IQR 3.9-6.3)
- Primary events: 42

Effect of 10 mg on alternate days on ipsilateral recurrence in high risk DCIS>50 yrs



Guerrieri Gonzaga et al. *Int J Cancer* 139:2127-34, 2016





Number at risk

Pla	247	225	161	78	4	0
Tam	253	234	172	76	3	0

247	225	161	78	4	0	
253	234	172	76	3	0	

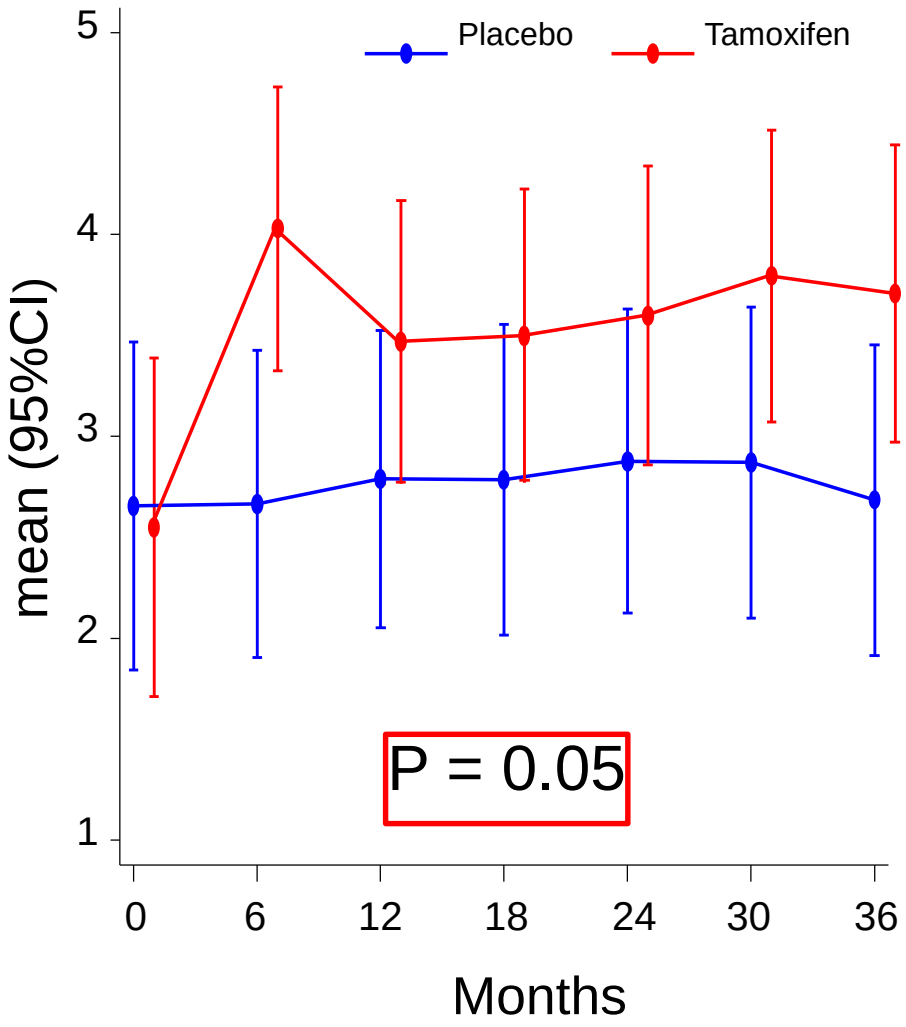
Serious adverse events

	Tamoxifen	Placebo
Endometrial cancer	1	0
DVT or PE	1	1
Other neoplasms	4	6
Coronary heart disease	2	2
Other	3	5
Death	1	2
Total	12	16

20 mg/d, expected Endometrial Cancer: **2.7**; DVT+PE: **2.4**[1]

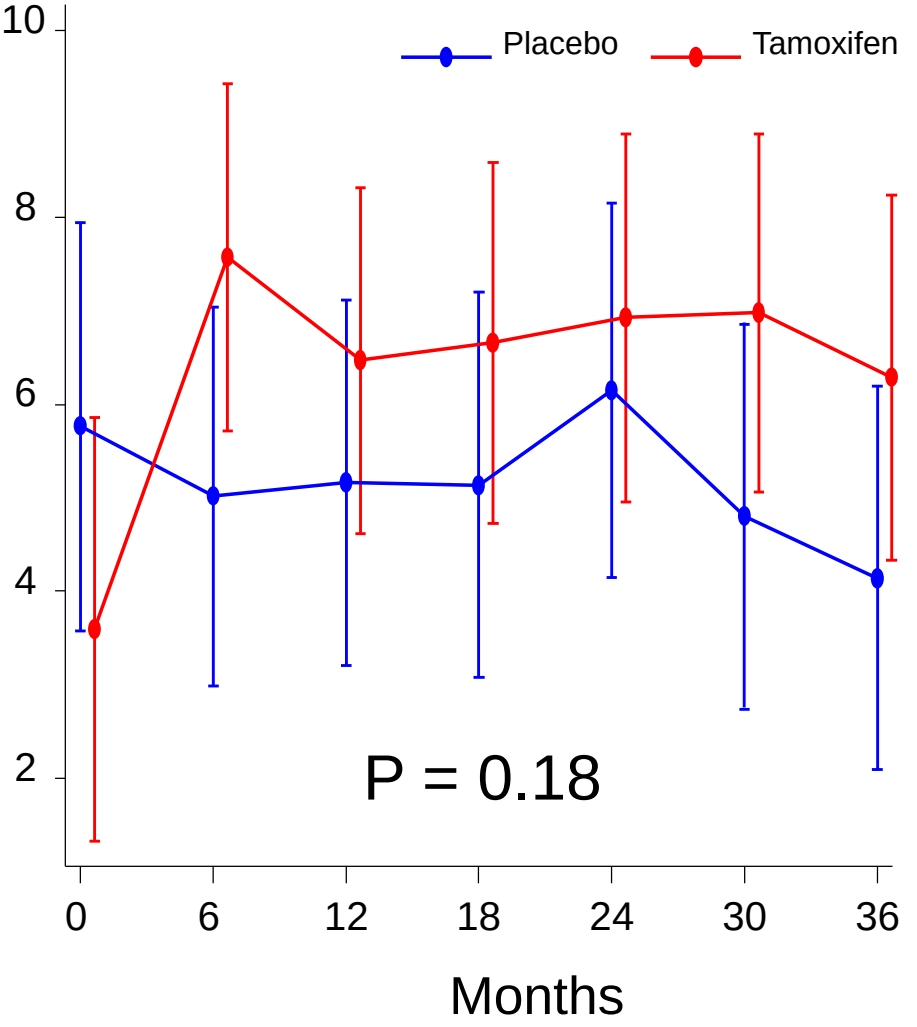
[1]NSABP-P1 trial (Fisher et al. *JNCI* 90:1371-88, 1998).

Daily hot flashes frequency



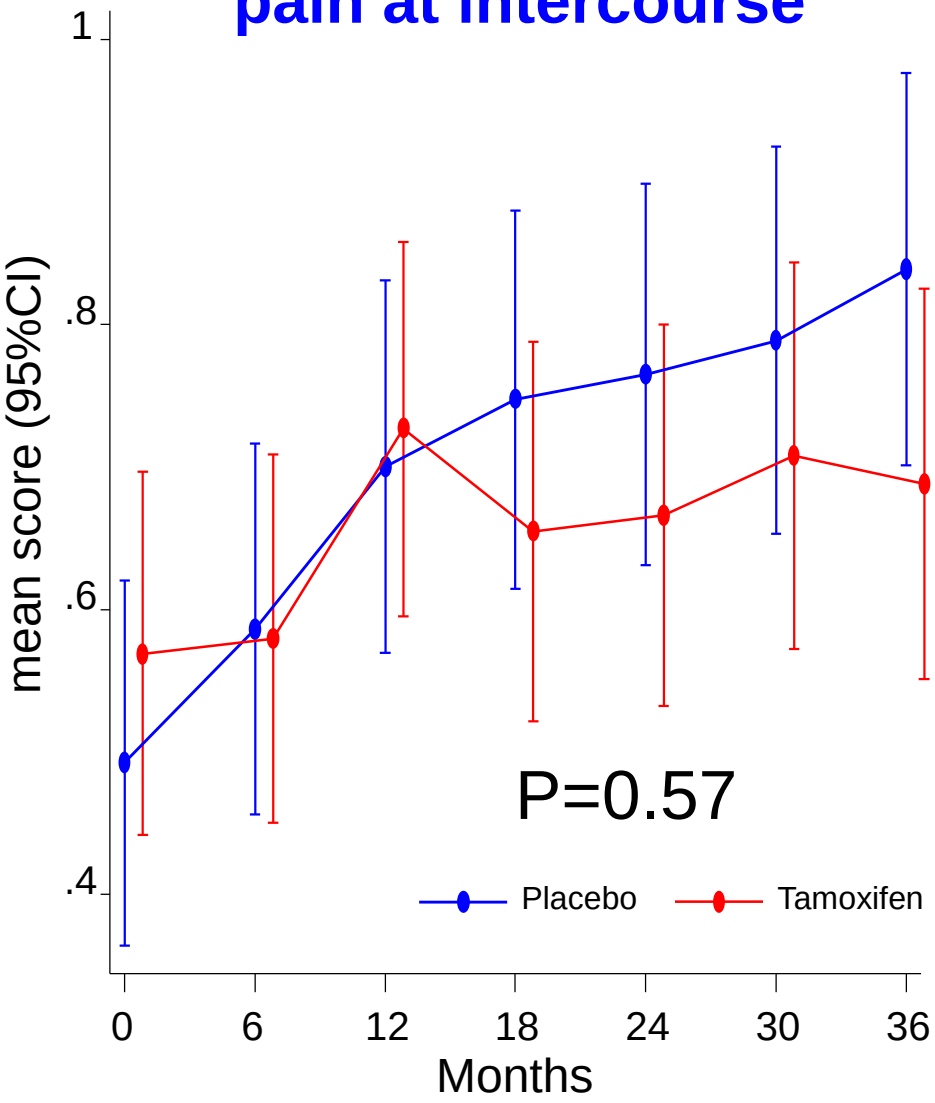
Daily hot flashes score

Frequency by Intensity

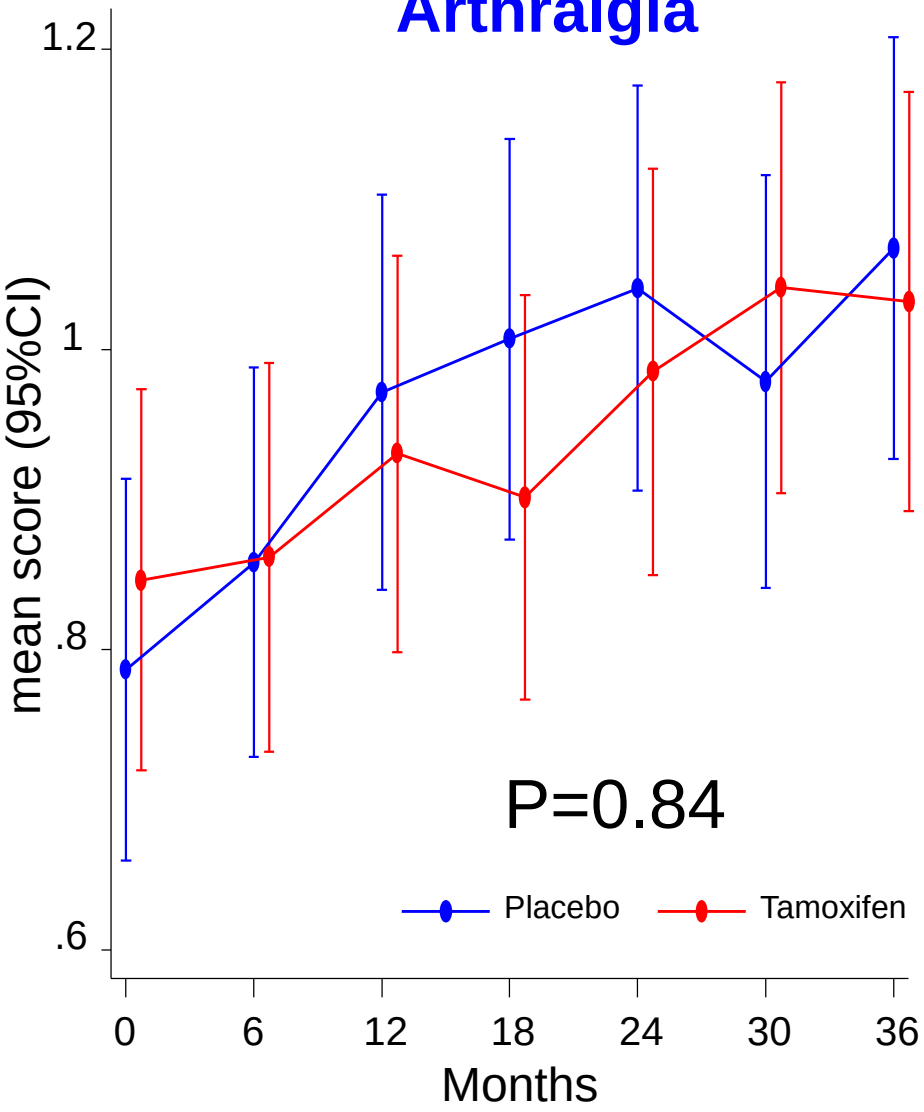


Sloan, Loprinzi et al. *JCO* 19:4280, 2001

Vaginal dryness or pain at intercourse

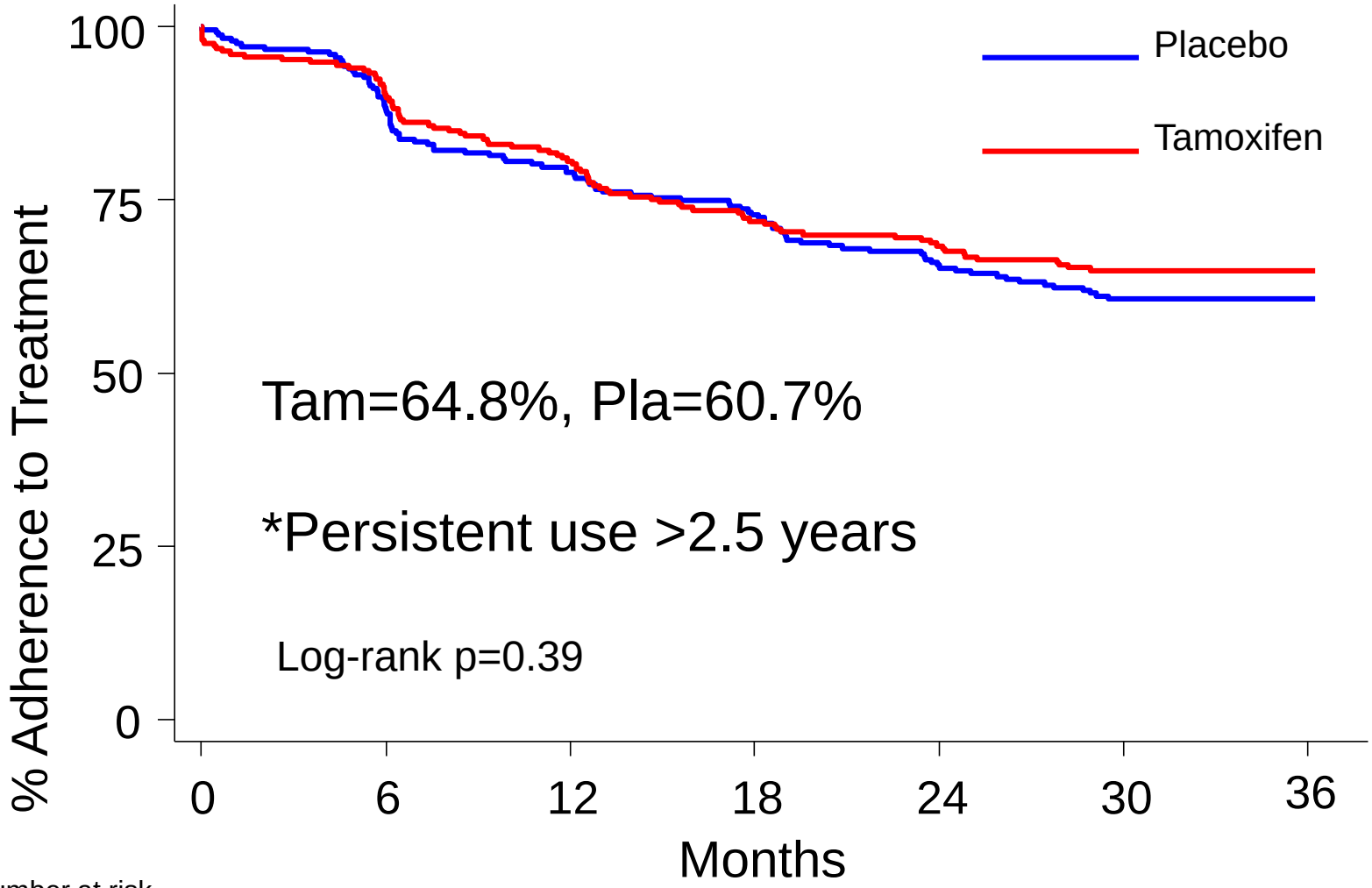


Musculoskeletal pain/ Arthralgia



BCPSC, Stanton et al. *JNCI* 97:448-456, 2005

Treatment adherence*



Number at risk													
Placebo	247	(29)	218	(23)	195	(15)	180	(18)	162	(12)	149	(0)	109
Tamoxifen	253	(25)	228	(24)	204	(22)	182	(9)	173	(9)	163	(0)	114

Conclusions

- Tamoxifen 5 mg/day for 3 years **halves the recurrence** of breast intraepithelial neoplasia in line with 20 mg/day (HR=0.58, 95% CI, 0.42-0.81)[1]

- Low dose Tamoxifen decreased contralateral breast cancer by 75%, suggesting a **strong preventive** potential

- Rate of endometrial cancer and DVT/PE on 5 mg (0.85/1000 py) **not different from placebo** and **2.5 times lower** than 20 mg[2]

- **Menopausal symptoms not worsened** except for a borderline effect on hot flashes

- Our results have external validity and are **generalizable**

- Tamoxifen **10 mg every other day** is **applicable in clinical practice from tomorrow!**

[1]Allred et al. NSABP B-24 trial. *JCO* 30:1268-73, 2012

[2]Fisher et al. NSABP-P1 trial. *JNCI* 90:1371-88, 1998

SAN ANTONIO BREAST CANCER SYMPOSIUM®

SABCS, December 4 -8, 2018

Extended Aromatase Inhibitor treatment following 5 or more years of endocrine therapy: a meta-analysis of 22,192 women in 11 randomised trials

Early Breast Cancer Trialists' Collaborative Group

SAN ANTONIO BREAST CANCER SYMPOSIUM®

Extended AI treatment after 5+ years of prior endocrine therapy: methods

Meta-analysis of individual patient data on postmenopausal women with ER-positive (99%) or ER-unknown (1%) tumours in trials of:

Any third-generation AI (exemestane, anastrozole, letrozole) vs no further adjuvant therapy **following**:

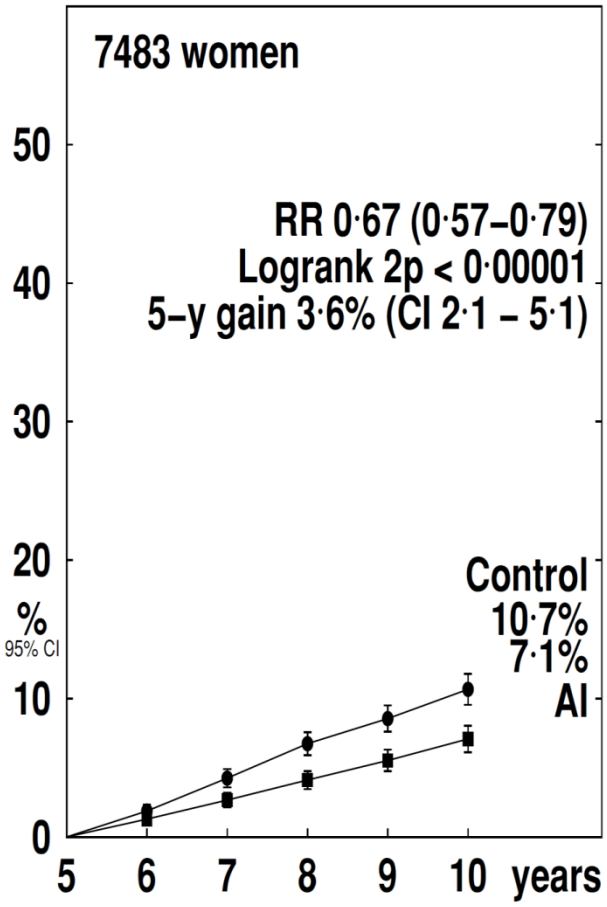
a) ≈ 5 years of tamoxifen alone (n=7,500)

b) ≈ 5-10 years of tamoxifen then AI (n=12,600)

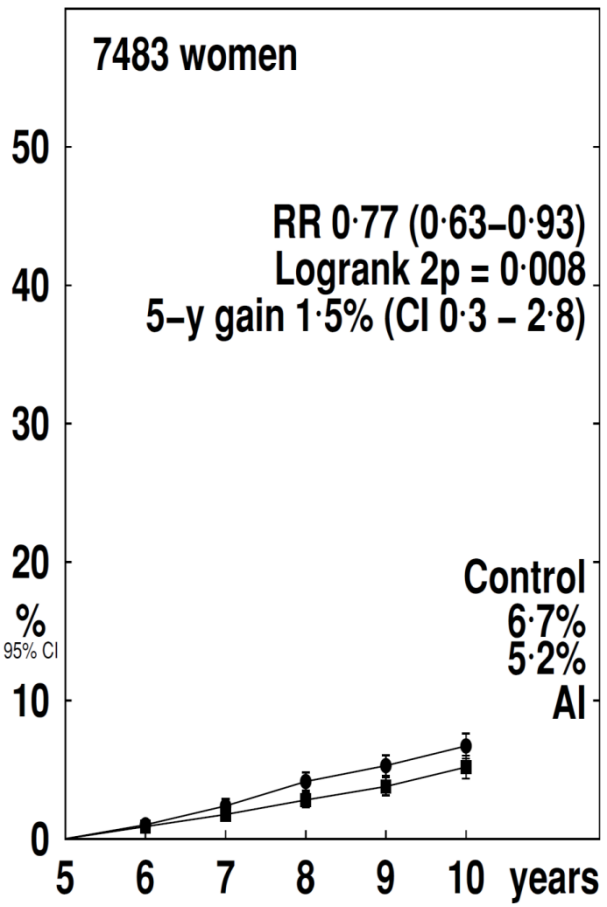
c) ≈ 5 years of AI alone (n=4,800)

(a) Trials of AI after ≈5 years of Tamoxifen alone

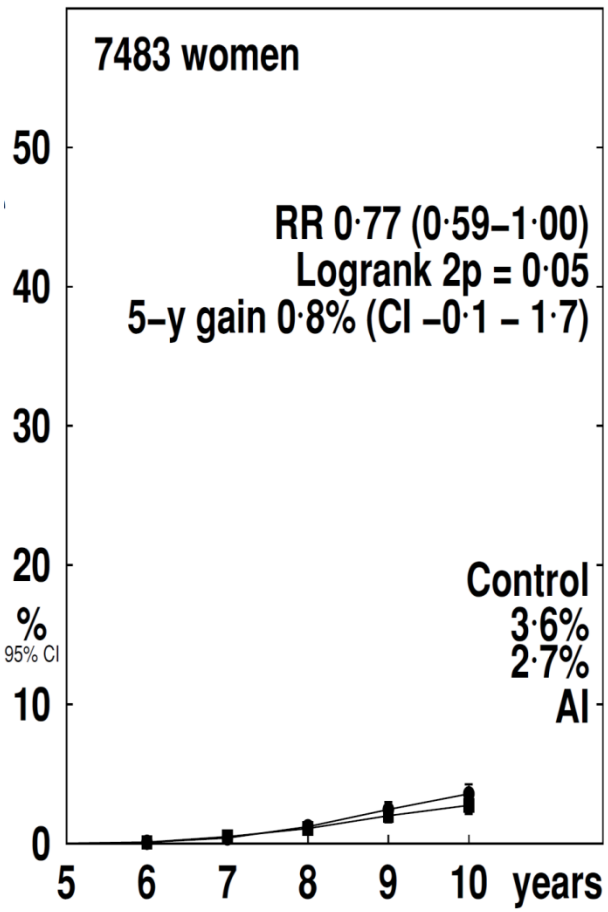
Any recurrence (distant, local or new primary)



Distant Recurrence

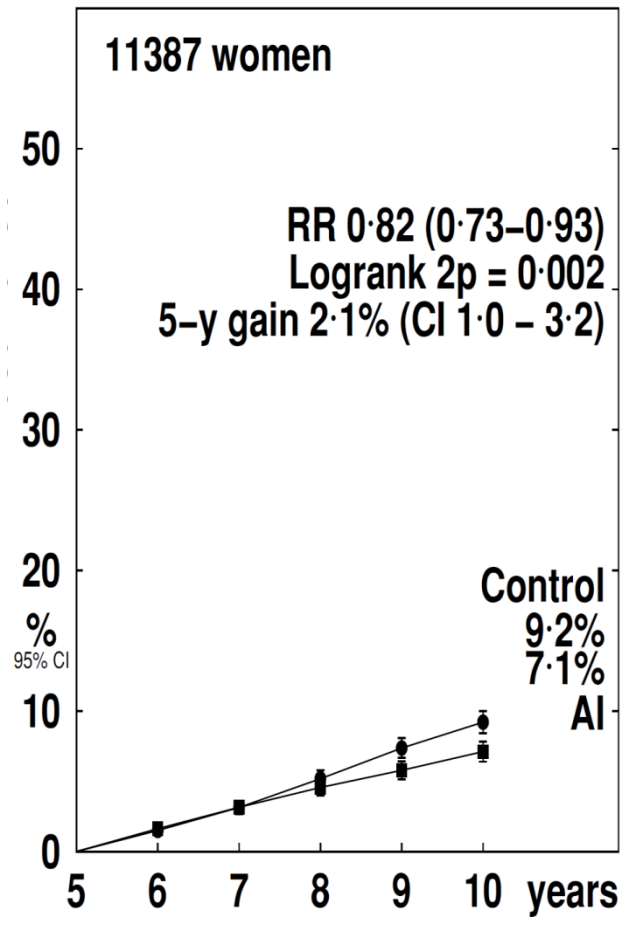


Breast cancer mortality

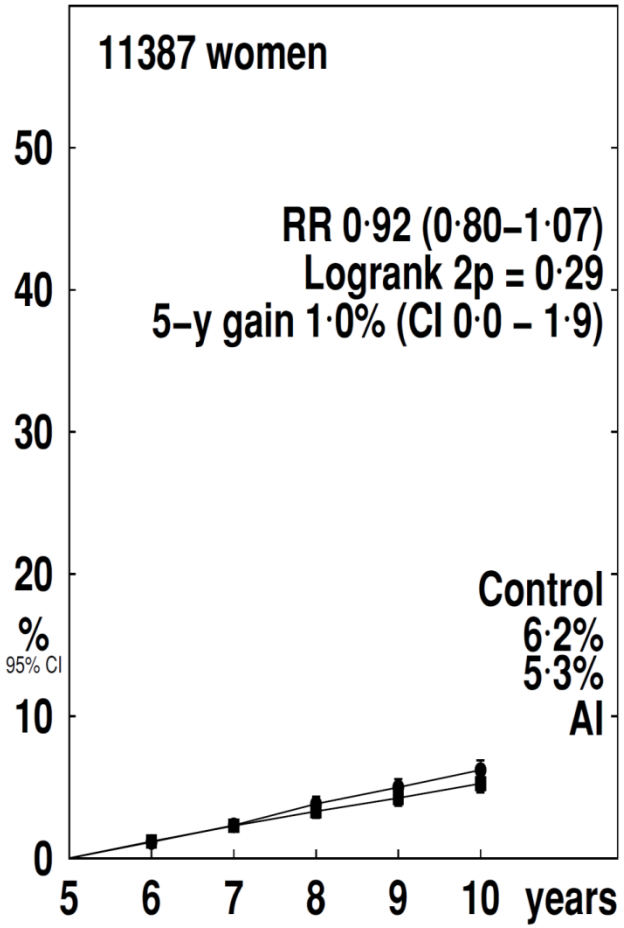


(b) Trials of Extended AI following 5-10 years of Tamoxifen then AI

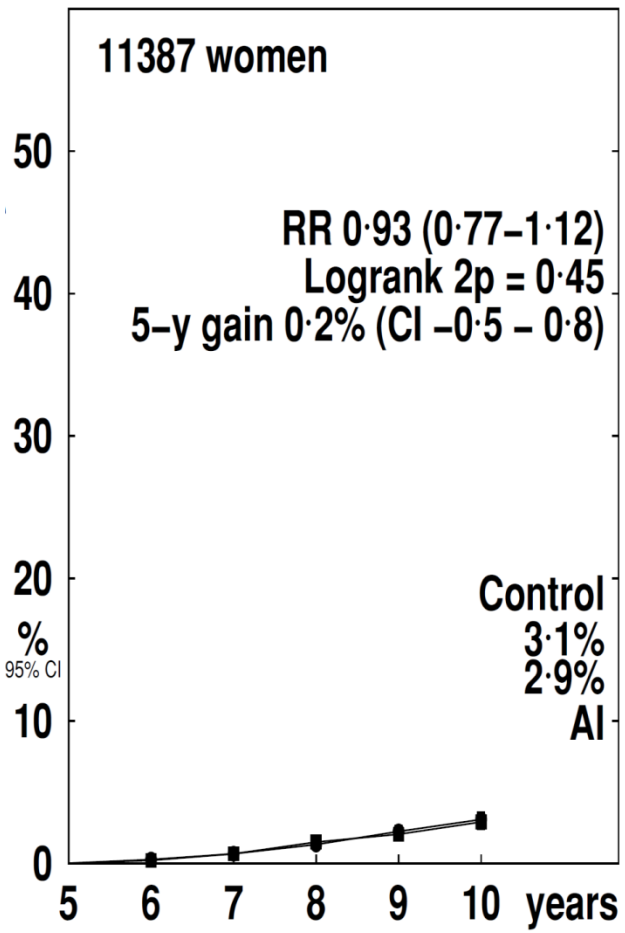
Any recurrence



Distant Recurrence

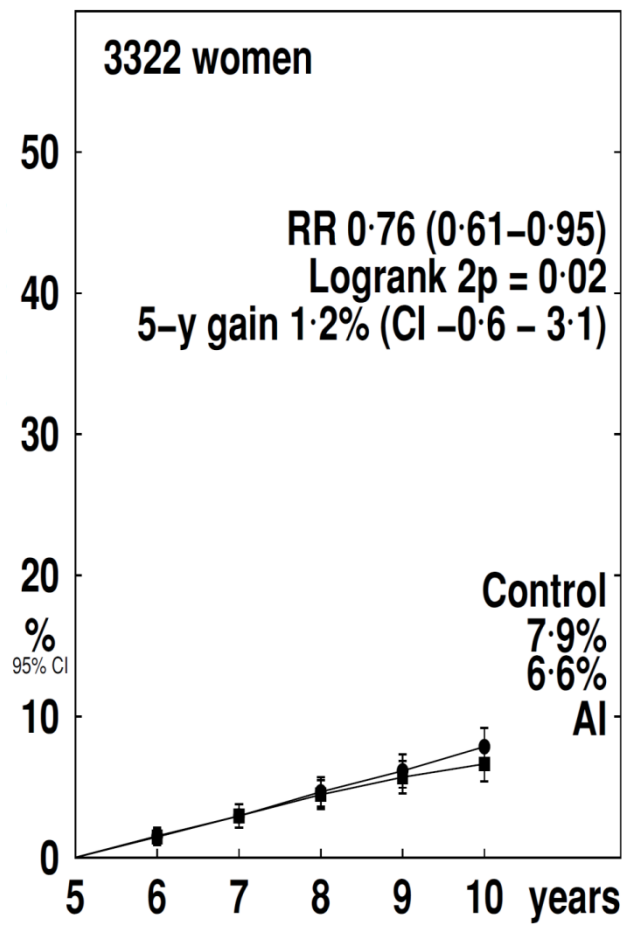


Breast cancer mortality

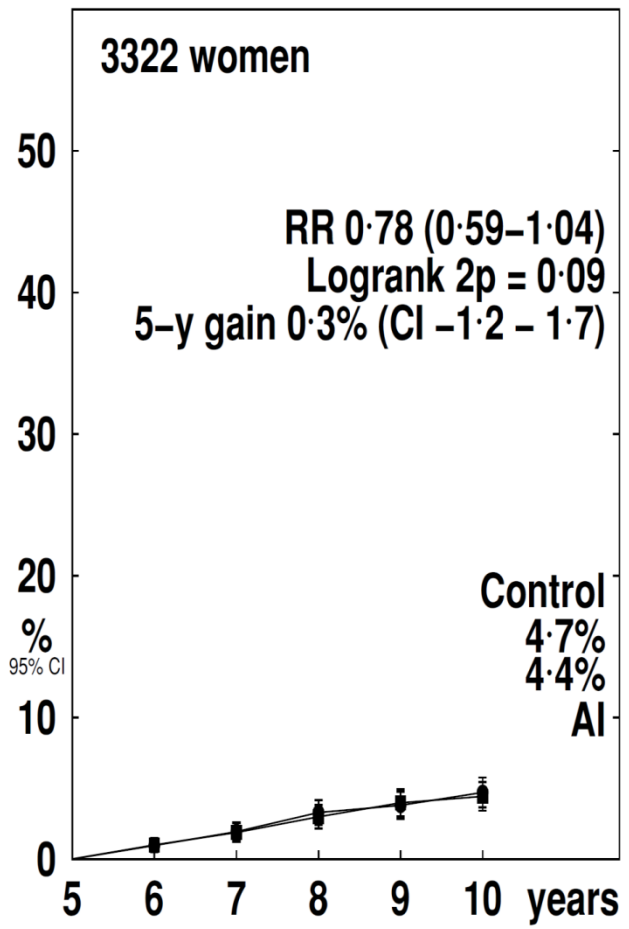


(c) Trials of Extended AI following 5 years of AI alone

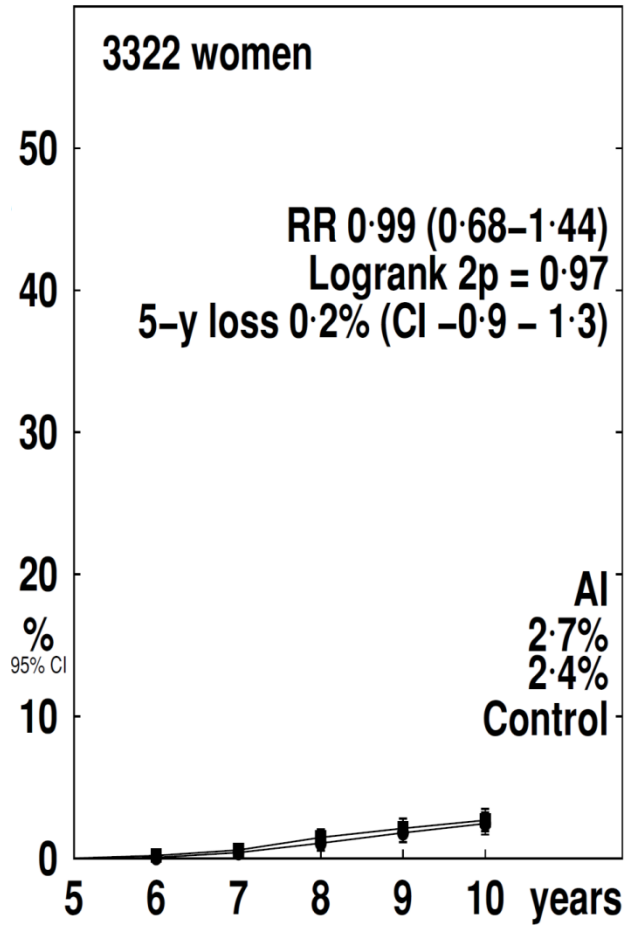
Any recurrence



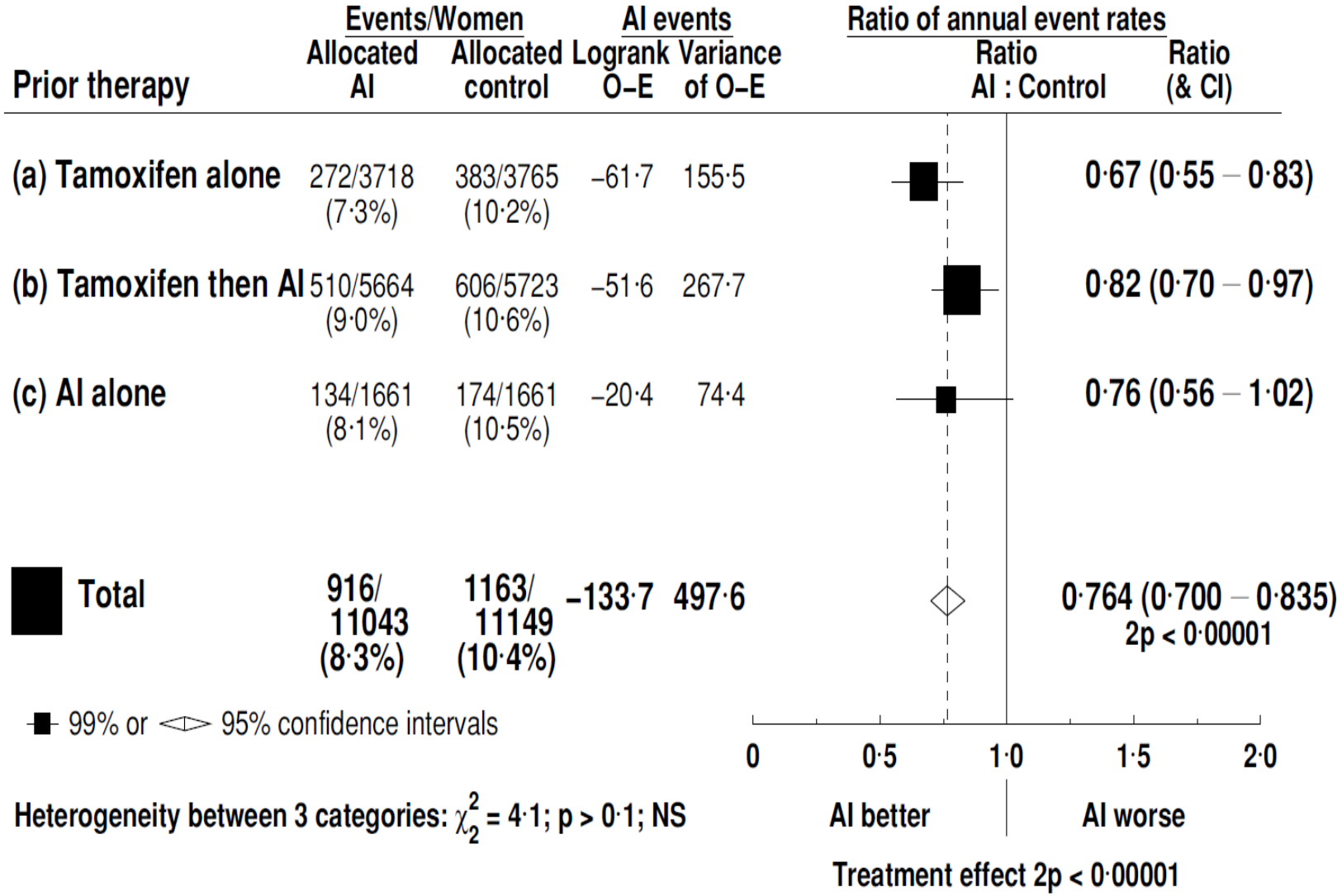
Distant Recurrence



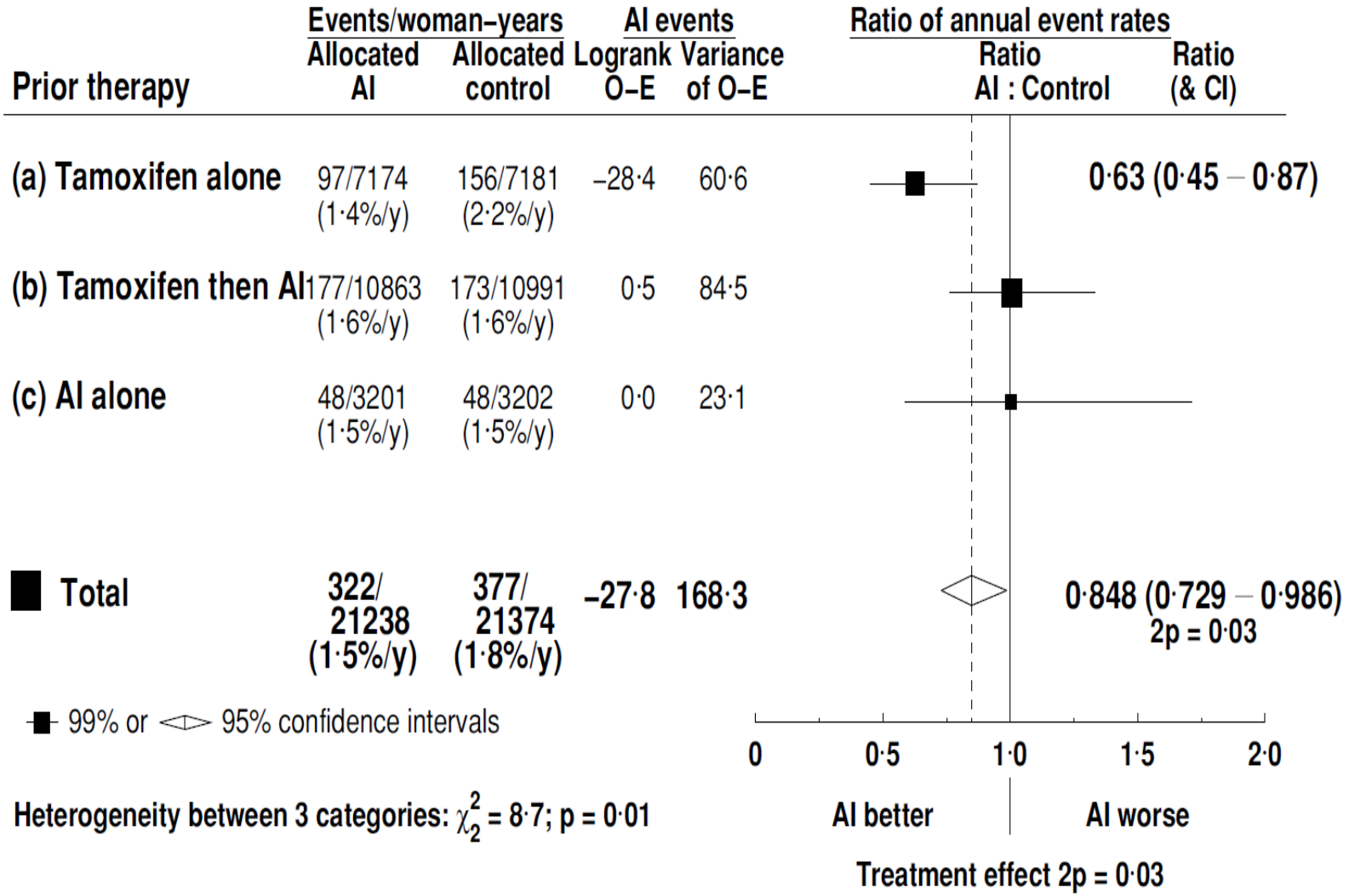
Breast cancer mortality



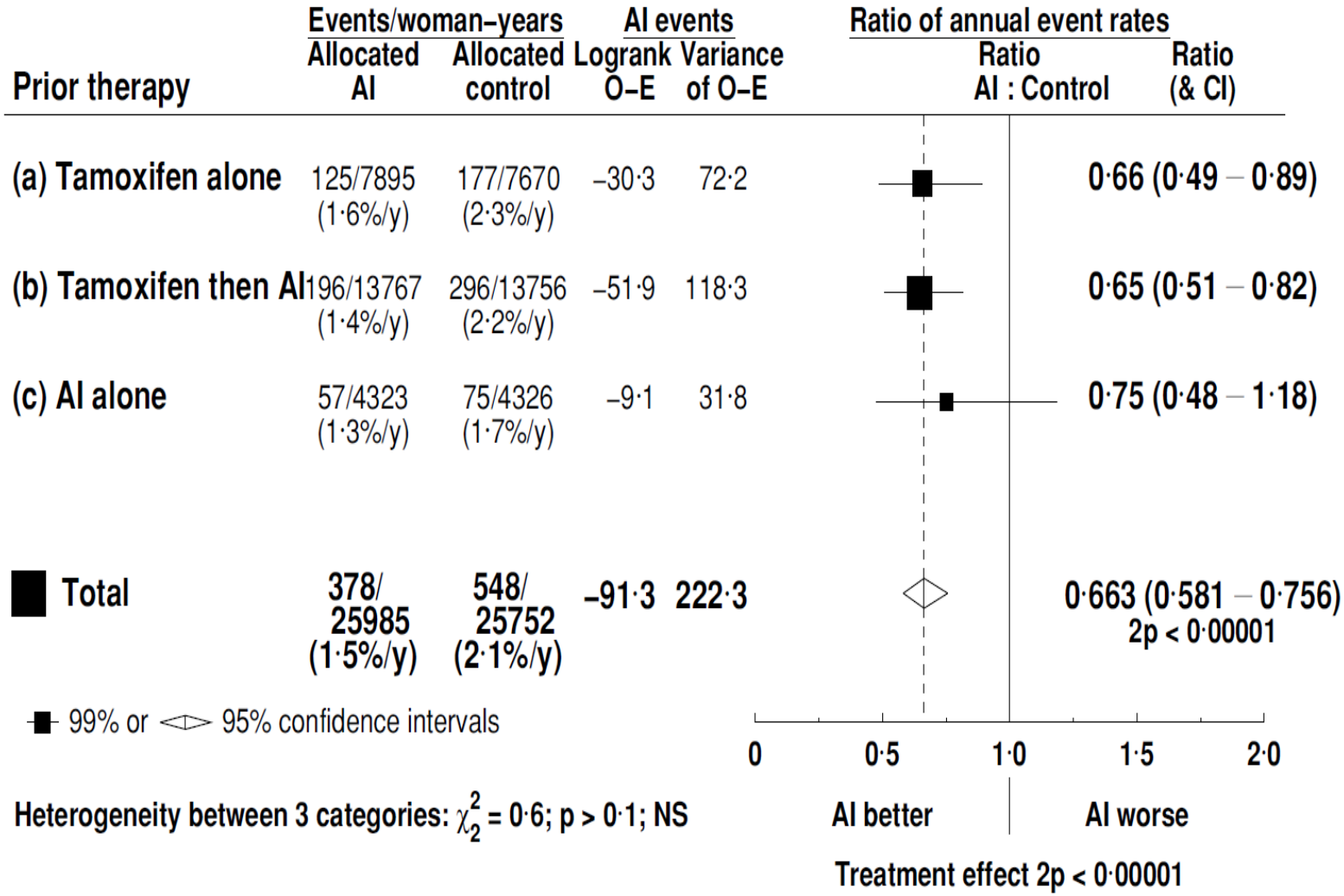
Effect on recurrence by prior endocrine therapy



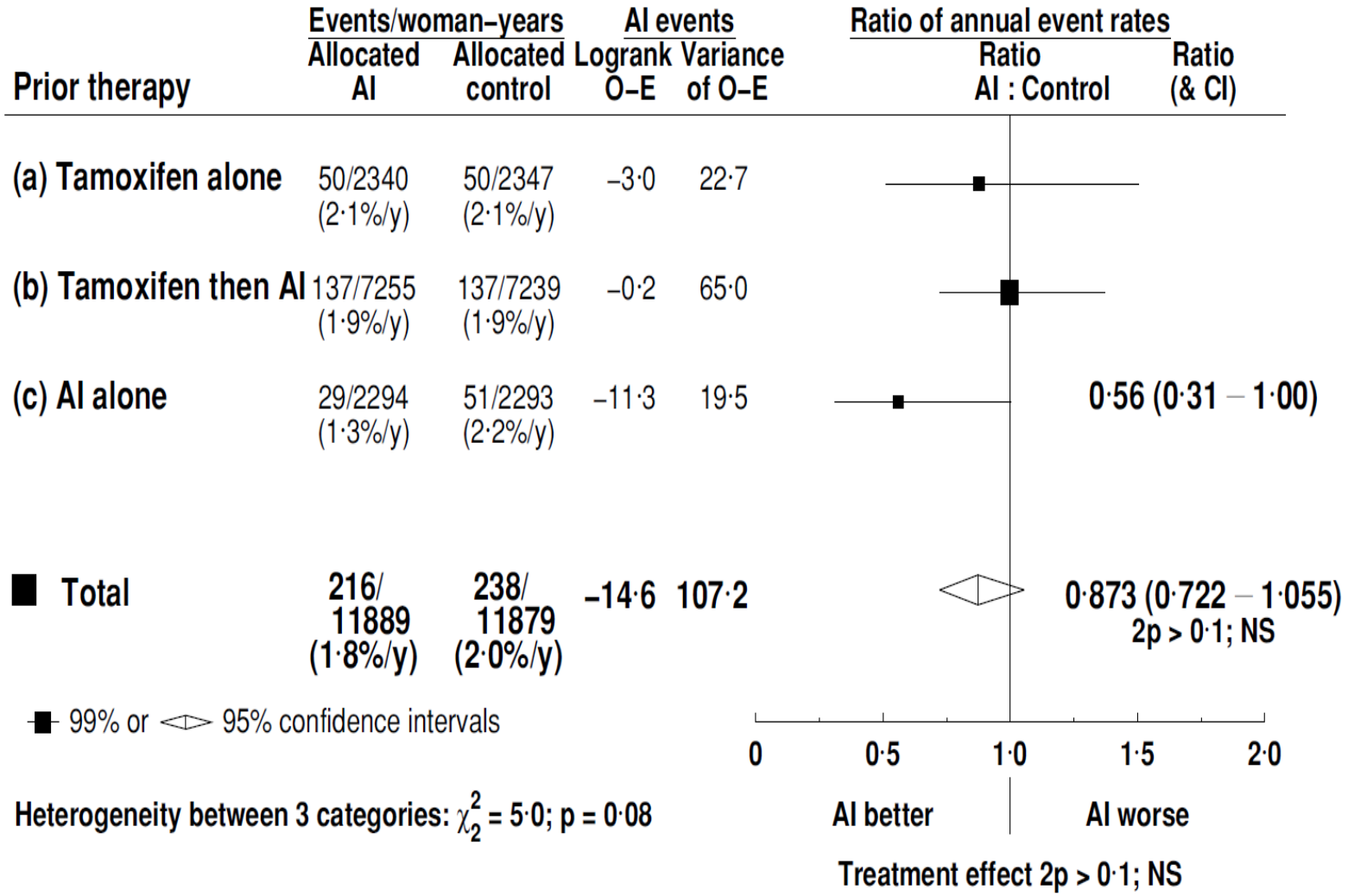
Effect on recurrence in years 0-1 after treatment divergence by prior endocrine therapy



Effect on recurrence in in years 2-4 after treatment divergence by prior endocrine therapy

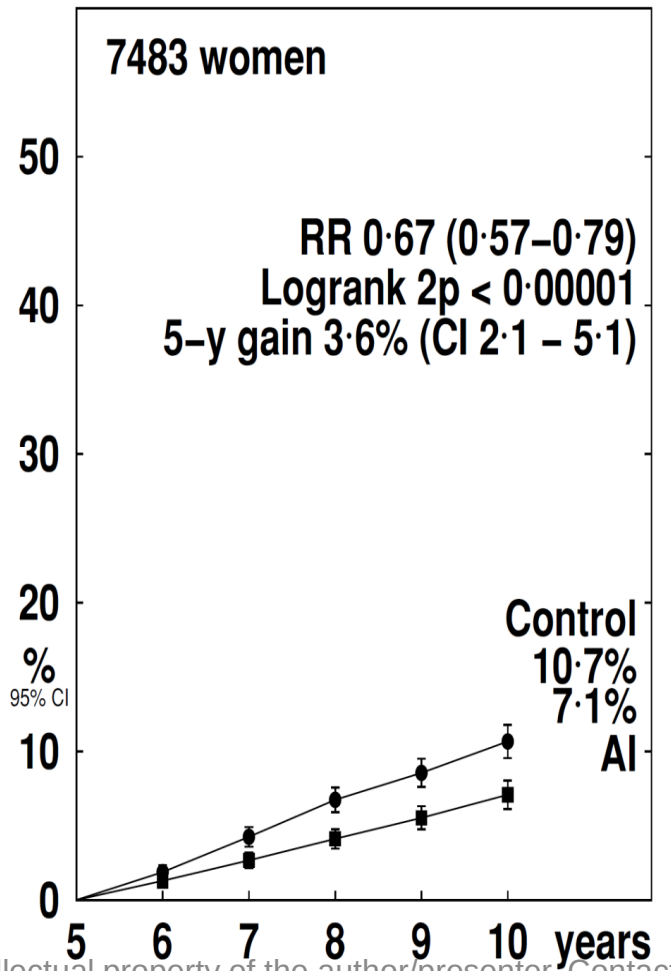


Effect on recurrence in years 5+ after treatment divergence by prior endocrine therapy

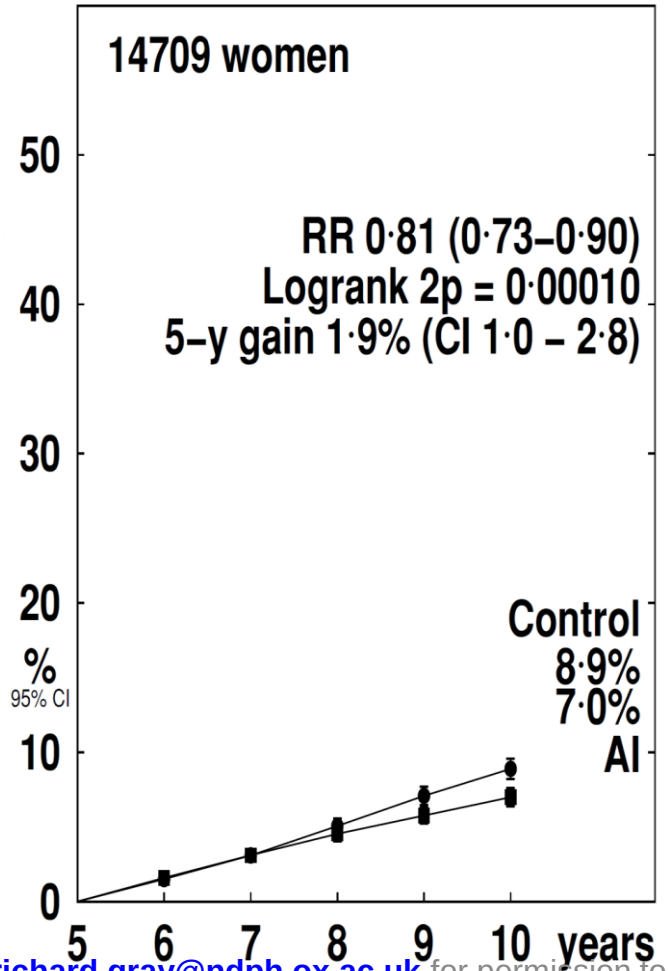


Summary: effect of extended AI therapy after 5-10 yrs on recurrence differs by type of prior endocrine therapy

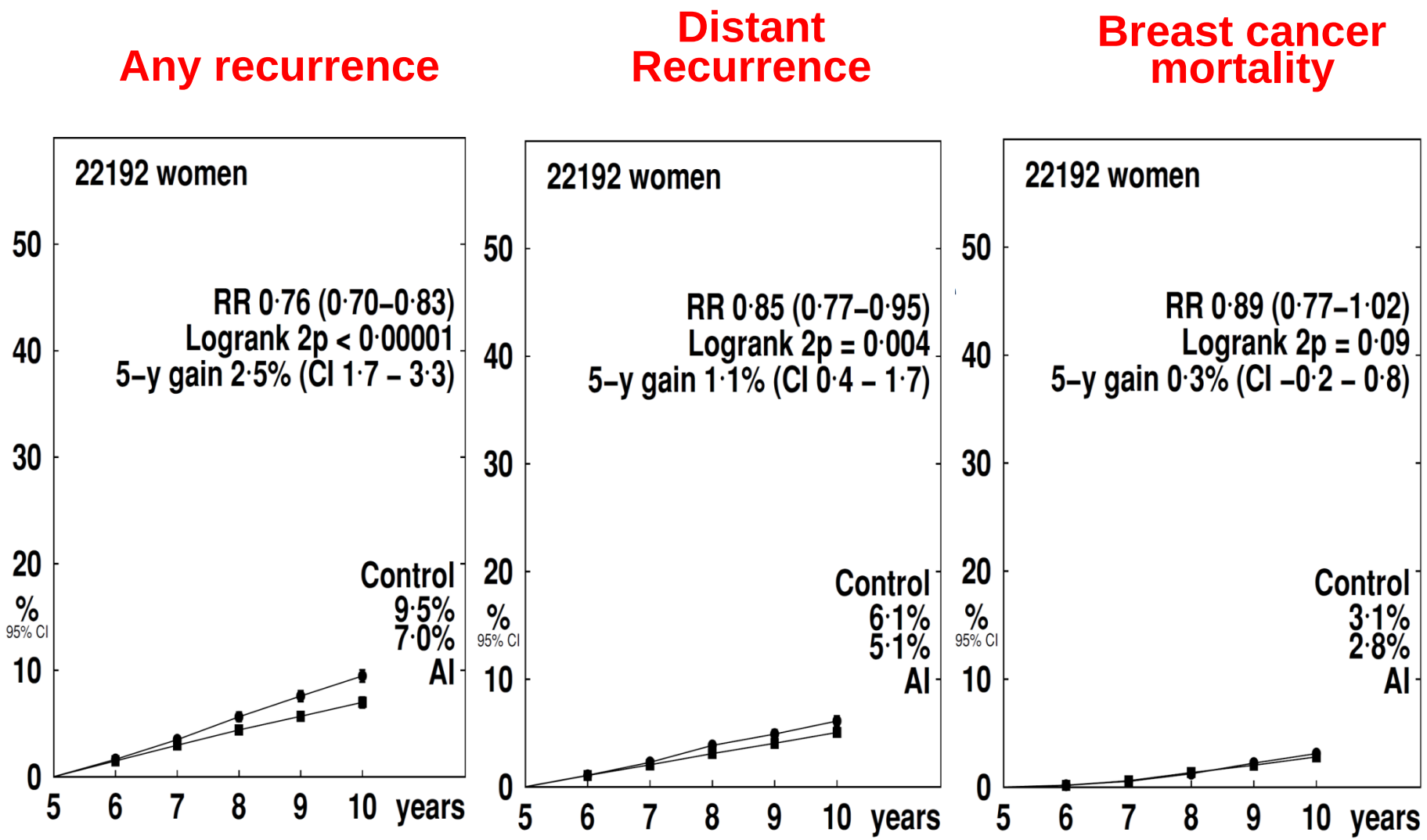
Prior tamoxifen (a)



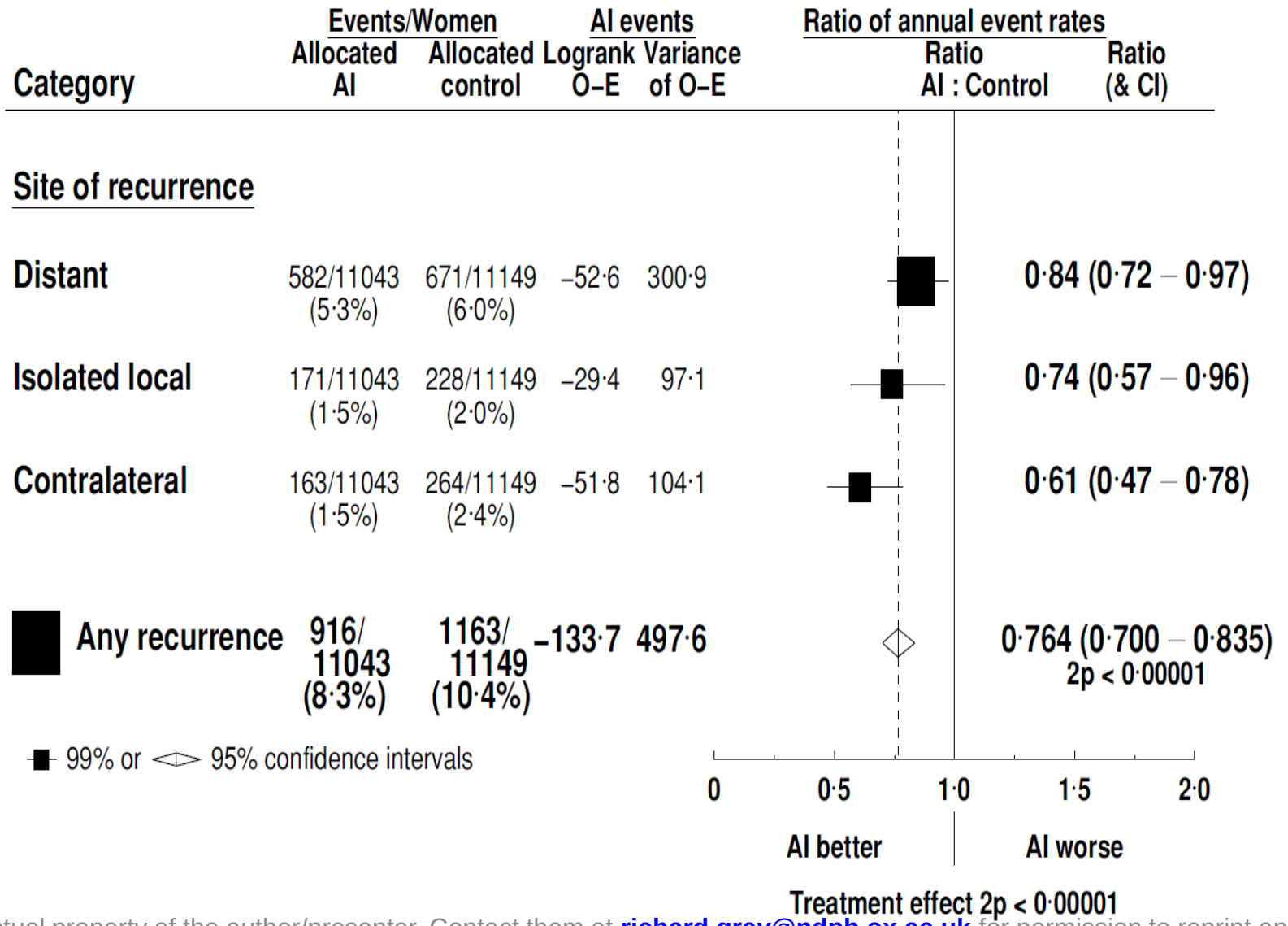
Prior AI (b + c)



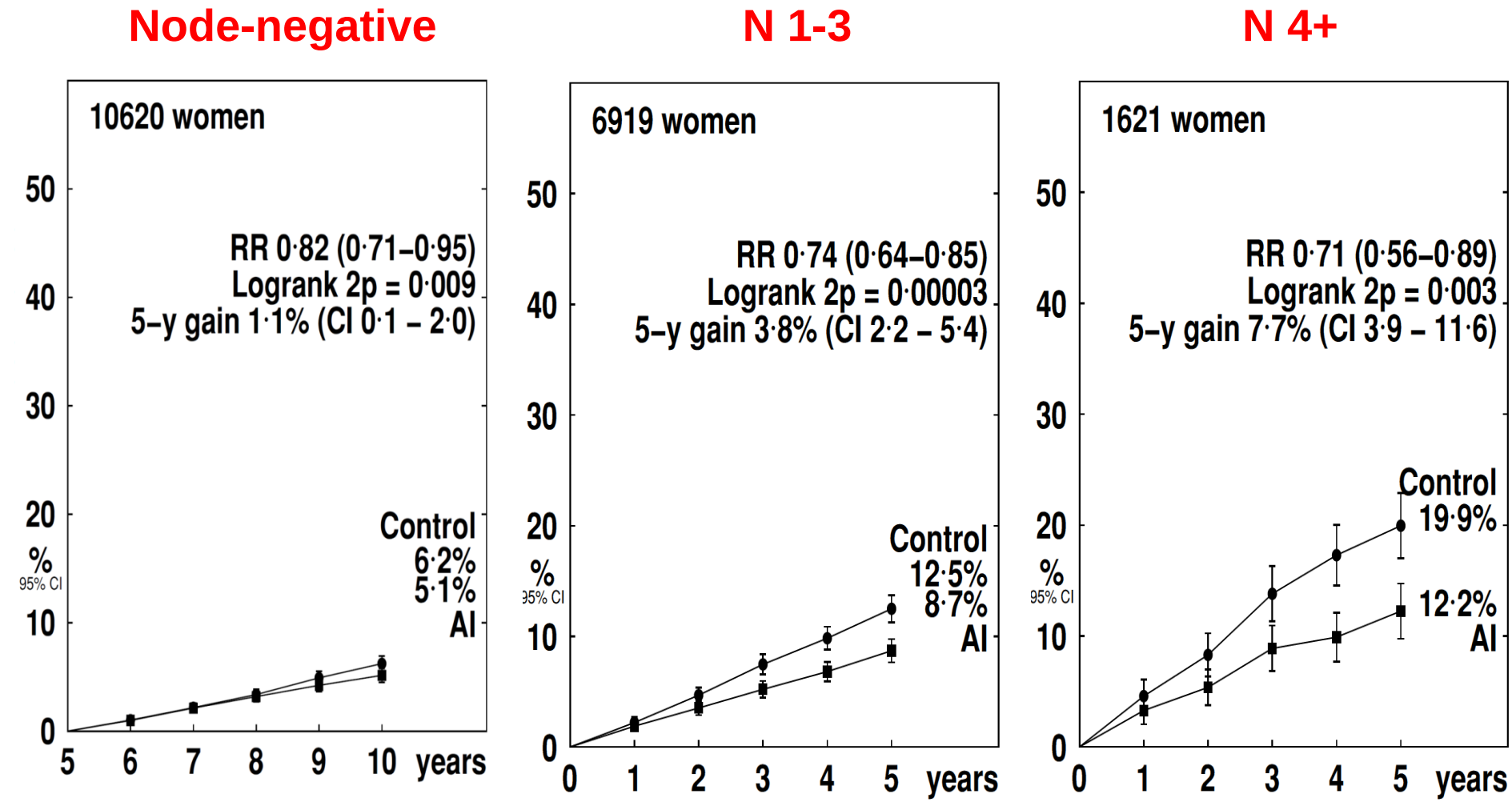
Combined results from all trials of Extended AI following 5-10 years of any prior endocrine therapy



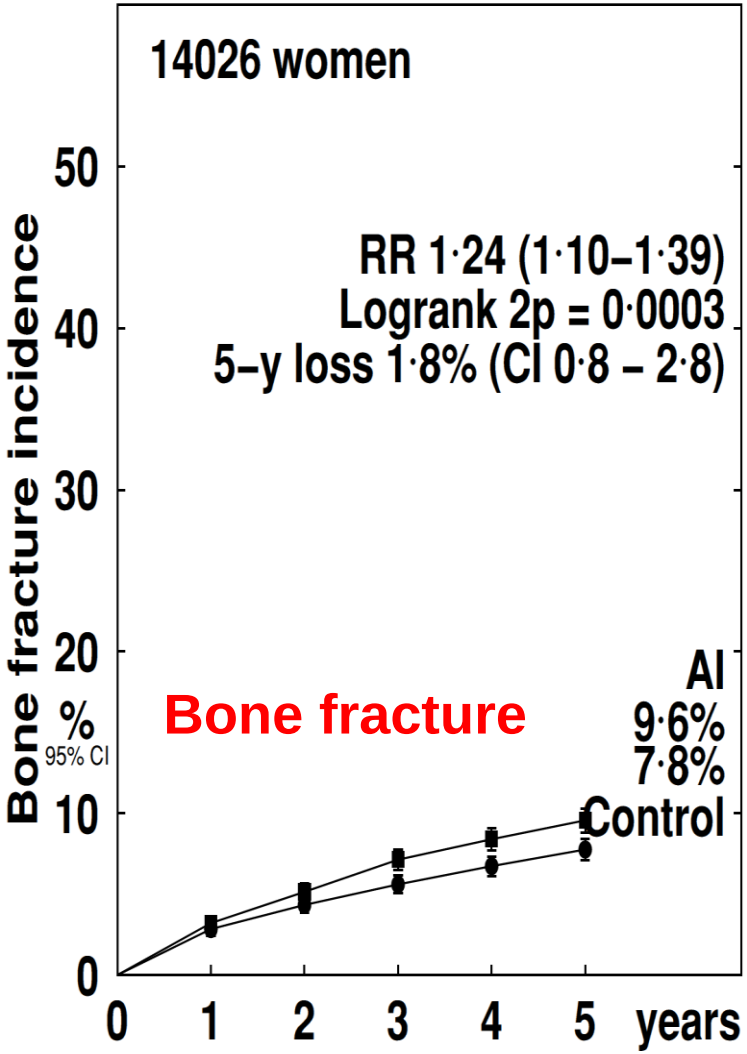
Recurrence by site – combined results from all trials

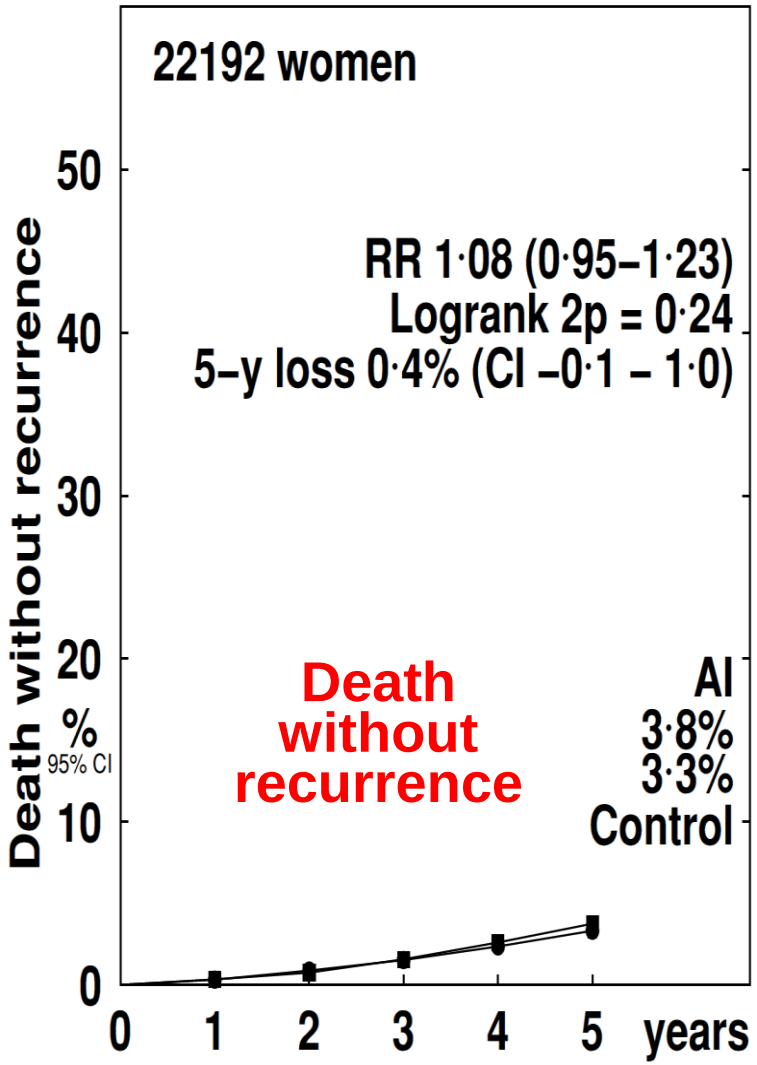


Recurrence by nodal status – all trials



Bone fracture and death without recurrence





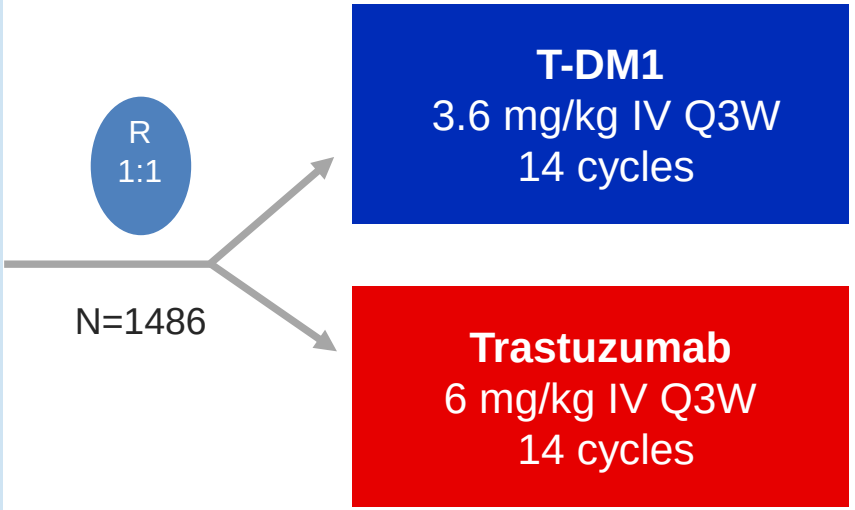
SAN ANTONIO BREAST CANCER SYMPOSIUM®

Conclusions: Benefits and risks of AI after 5+ years of prior endocrine therapy

- ≈35% proportional reduction in recurrence for women who have received ≈5 years of tamoxifen
- ≈ 20% proportional reduction in risk of recurrence for women receiving AI (with or without prior tamoxifen)
- Recurrence reductions apparent in first two years following prior tamoxifen, but not until the third year following prior AI
- Absolute benefits increase the more nodes were involved
- Risk of bone fracture increased by ≈25%

KATHERINE Study Design

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery



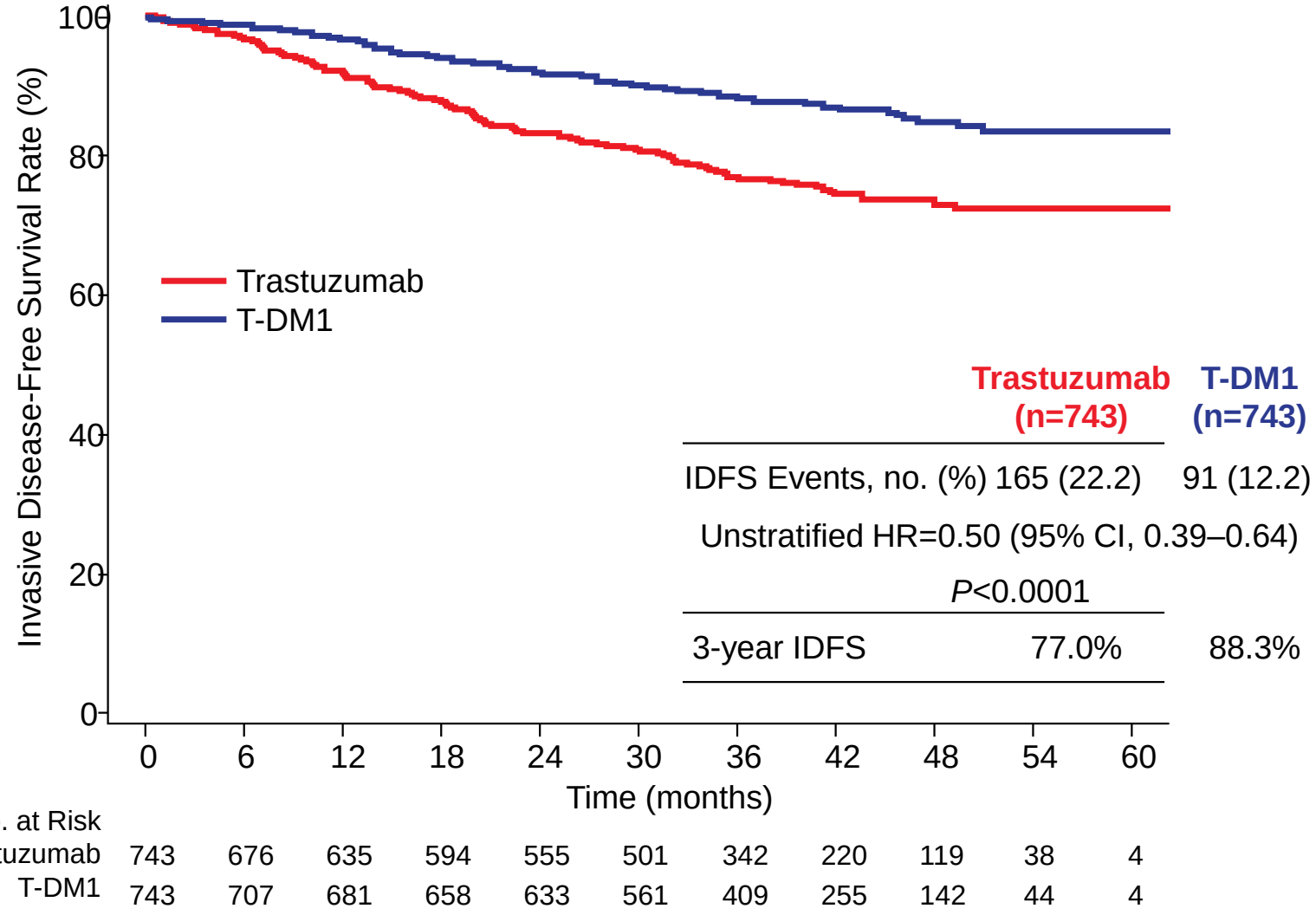
Radiation and endocrine therapy per protocol and local guidelines

Stratification factors:

- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

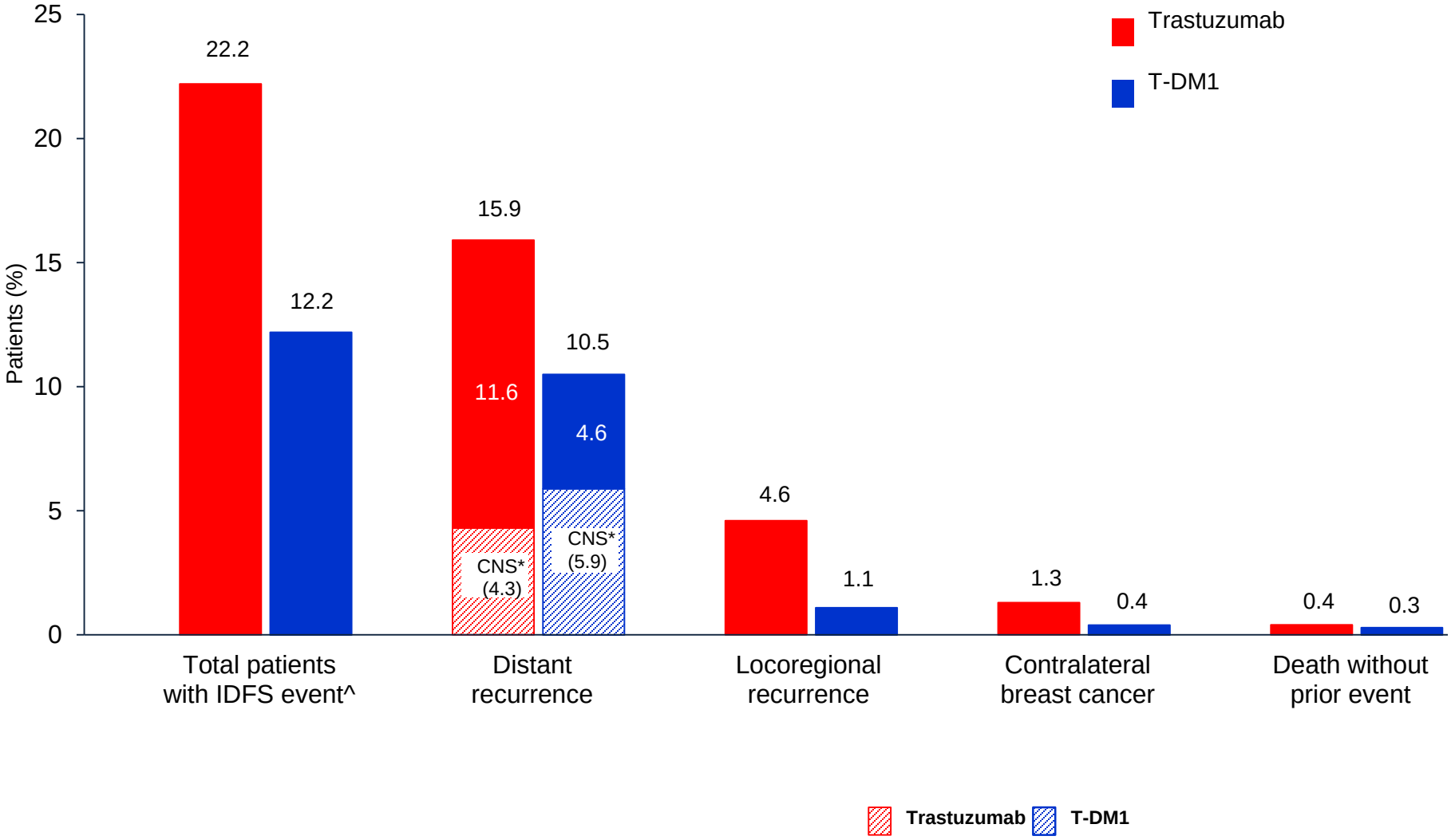
Geyer CE, et al. SABCS 2018

Invasive Disease-Free Survival



Geyer CE, et al. SABCS 2018

First IDFS Events

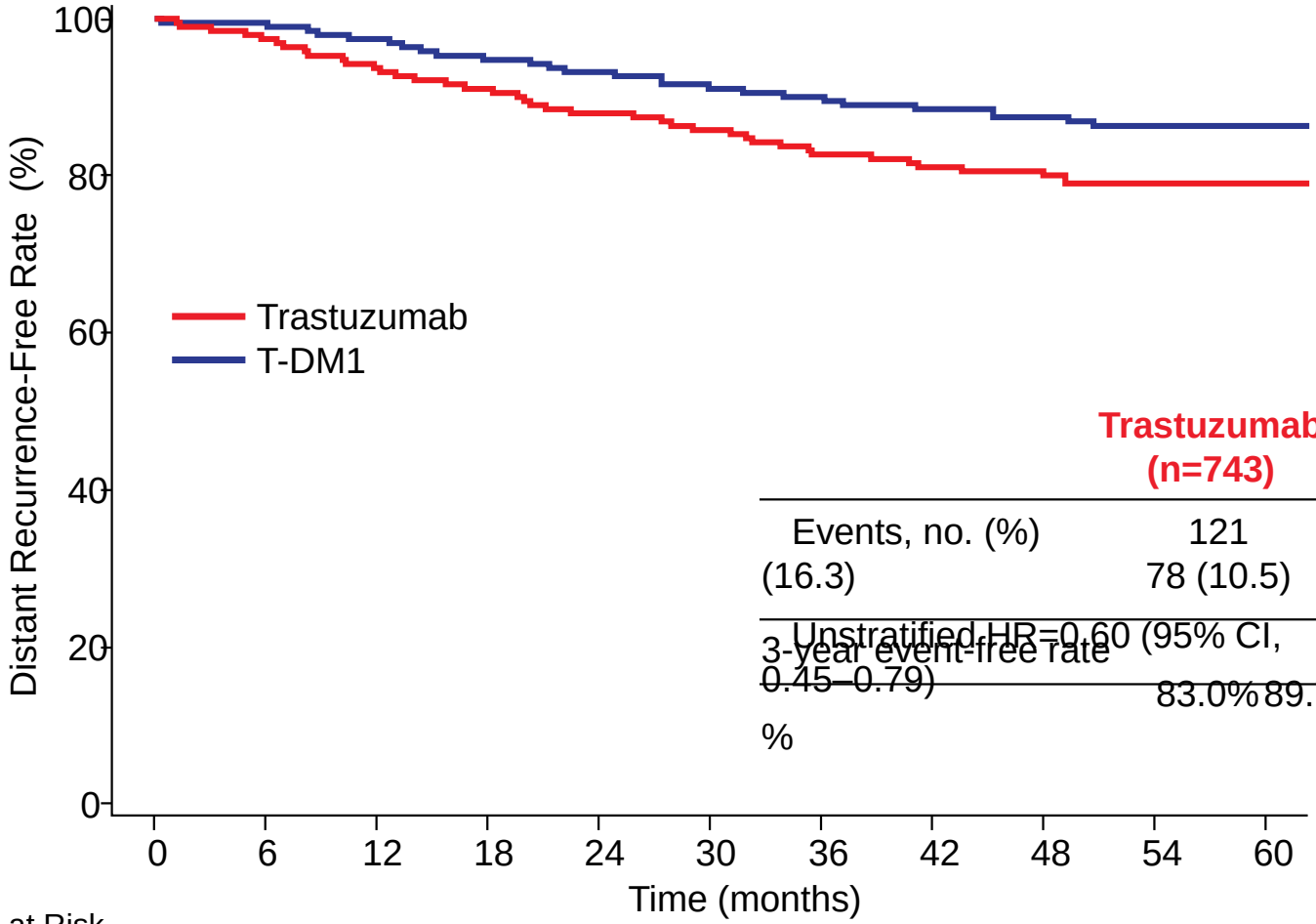


^Patients who experience additional IDFS event(s) within 61 days of their first IDFS event are reported in the category according to the following hierarchy: [1] Distant recurrence; [2] Locoregional recurrence; [3] Contralateral breast cancer; [4] Death without prior event.

***CNS metastases as component of distant recurrence (isolated or with other sites).**

Geyer CE, et al. SABCS 2018

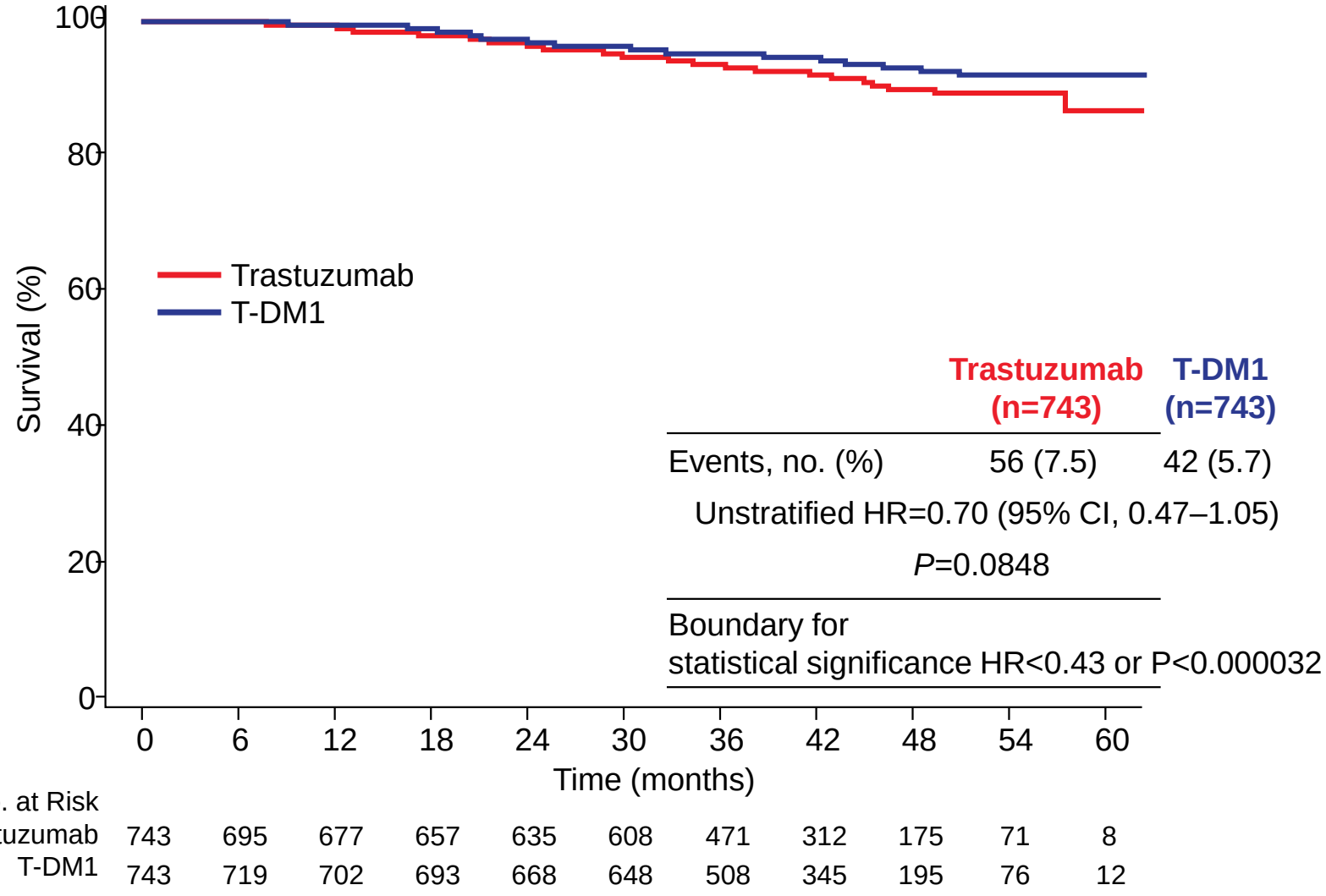
Distant Recurrence



	Trastuzumab (n=743)	T-DM1 (n=743)
Events, no. (%)	121 (16.3)	78 (10.5)
Unstratified HR=0.60 (95% CI, 0.45–0.79)		
3-year event-free rate	83.0%	89.7%

Geyer CE, et al. SABCS 2018

Overall Survival



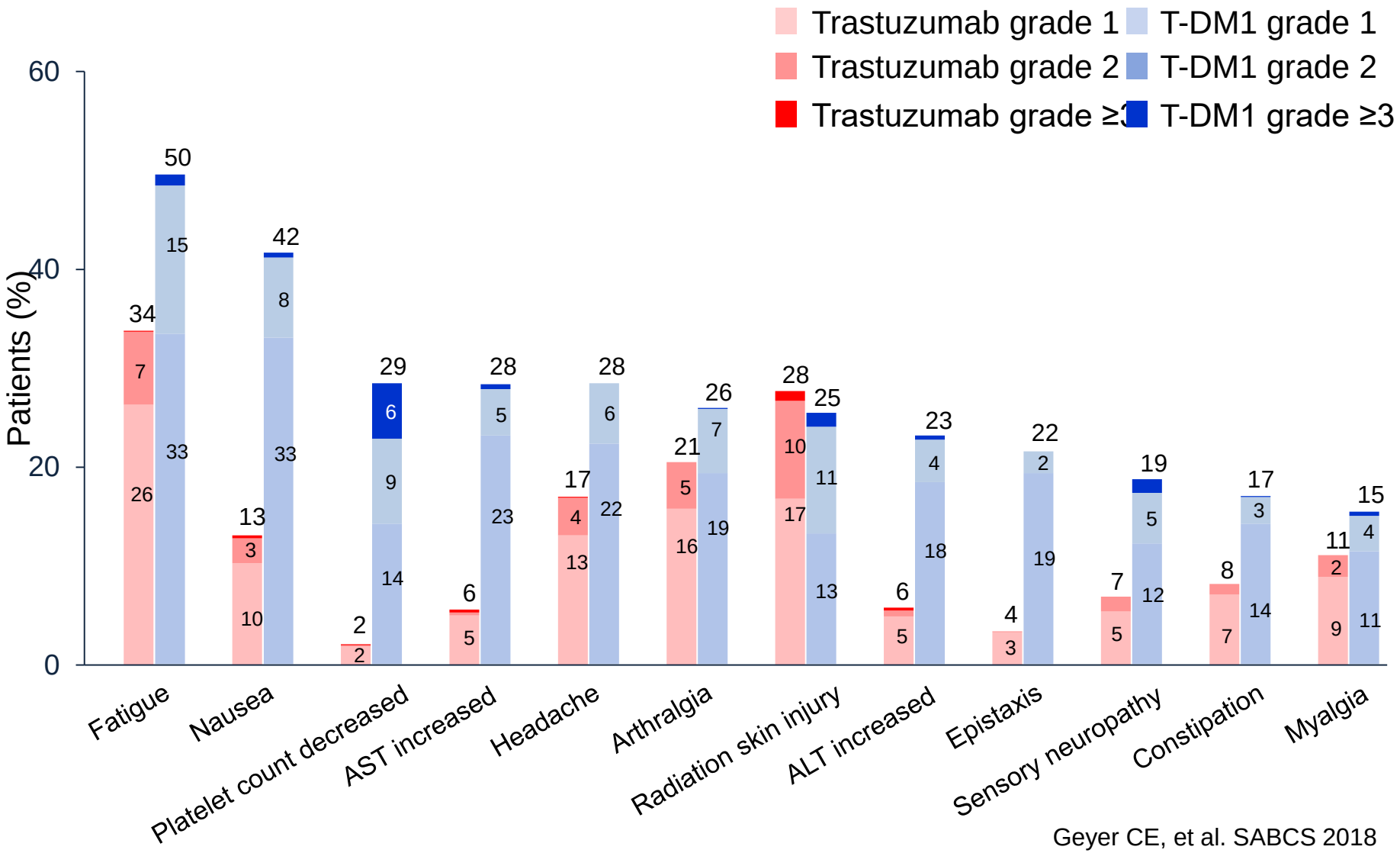
Geyer CE, et al. SABCS 2018

AEs Leading to Treatment Discontinuation (≥1% Incidence Either Arm)

	Trastuzumab n=720	T-DM1 n=740
Patients discontinuing due to adverse events	15 (2.1%)	133 (18.0%)
Platelet count decreased	0	31 (4.2%)
Blood bilirubin increased	0	19 (2.6%)
Aspartate aminotransferase (AST) increased	0	12 (1.6%)
Alanine aminotransferase (ALT) increased	0	11 (1.5%)
Peripheral sensory neuropathy	0	11 (1.5%)
Ejection fraction decreased	10 (1.4%)	9 (1.2%)

Geyer CE, et al. SABCS 2018

All Grade AEs ≥15% Incidence in Either Arm



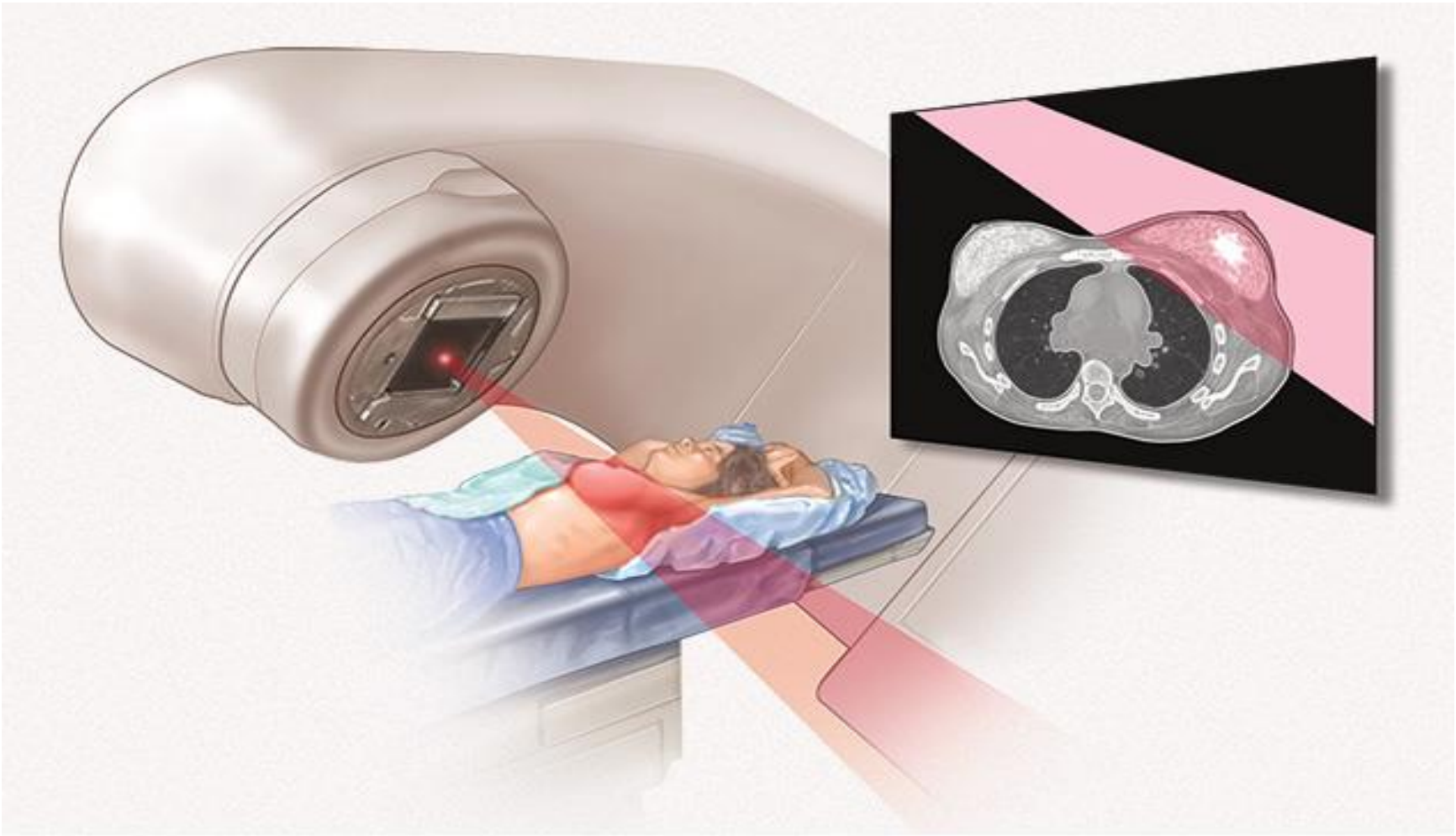
Geyer CE, et al. SABCS 2018

KATHERINE Summary and Conclusions

- Adjuvant T-DM1 demonstrated both a statistically significant and clinically meaningful improvement in IDFS compared with trastuzumab
  - Unstratified HR=0.50; 95% CI 0.39–0.64; *P*<0.0001
  - 3-year IDFS rate improved from 77.0% to 88.3% (difference=11.3%)
- Benefit of T-DM1 was consistent across all key subgroups including HR status, extent of residual invasive disease, and single or dual HER2-targeted neoadjuvant therapy
- The safety data were consistent with the known manageable toxicities of T-DM1, with expected increases in AEs associated with T-DM1 compared to trastuzumab
- Additional follow-up will be necessary to evaluate the effect of T-DM1 on OS
- The KATHERINE data will likely form the foundation of a new standard of care in this population and increase the use of neoadjuvant therapy in HER2-positive EBC

Geyer CE, et al. SABCS 2018

Traditional whole breast radiation

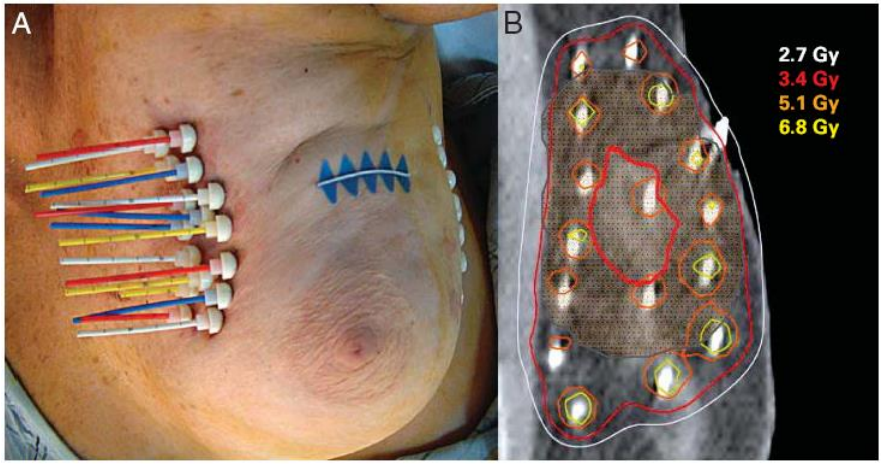


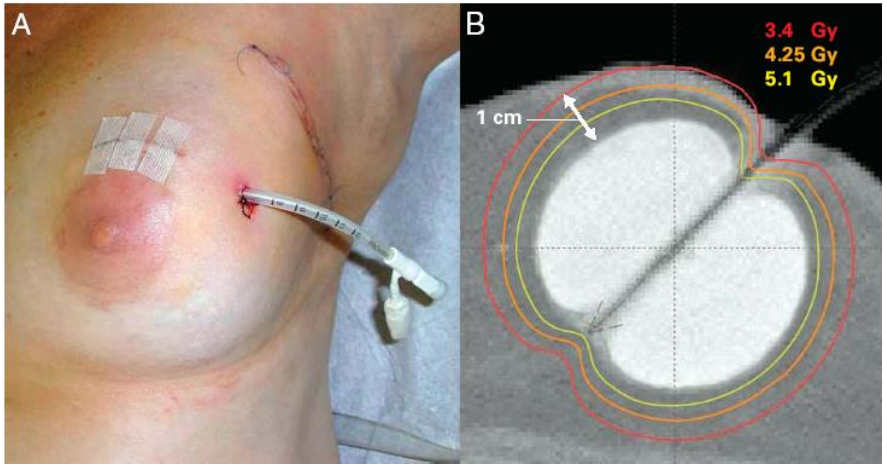
Breast Conserving Therapy

- BCT = Lumpectomy + whole breast RT
  - Standard of care for early stage Breast Cancer/DCIS
  - RT typically 3- 6 weeks

- Mastectomy or Lumpectomy w/o RT remains common
  - Access to care-COMPLIANCE ISSUES!!
  - Length of treatment
  - Distance to treatment – as distance increases, BCT decreases
    - 82% <10miles
    - 69% 50-75 miles
    - 42% if >100 miles

Partial Breast Irradiation (PBI)

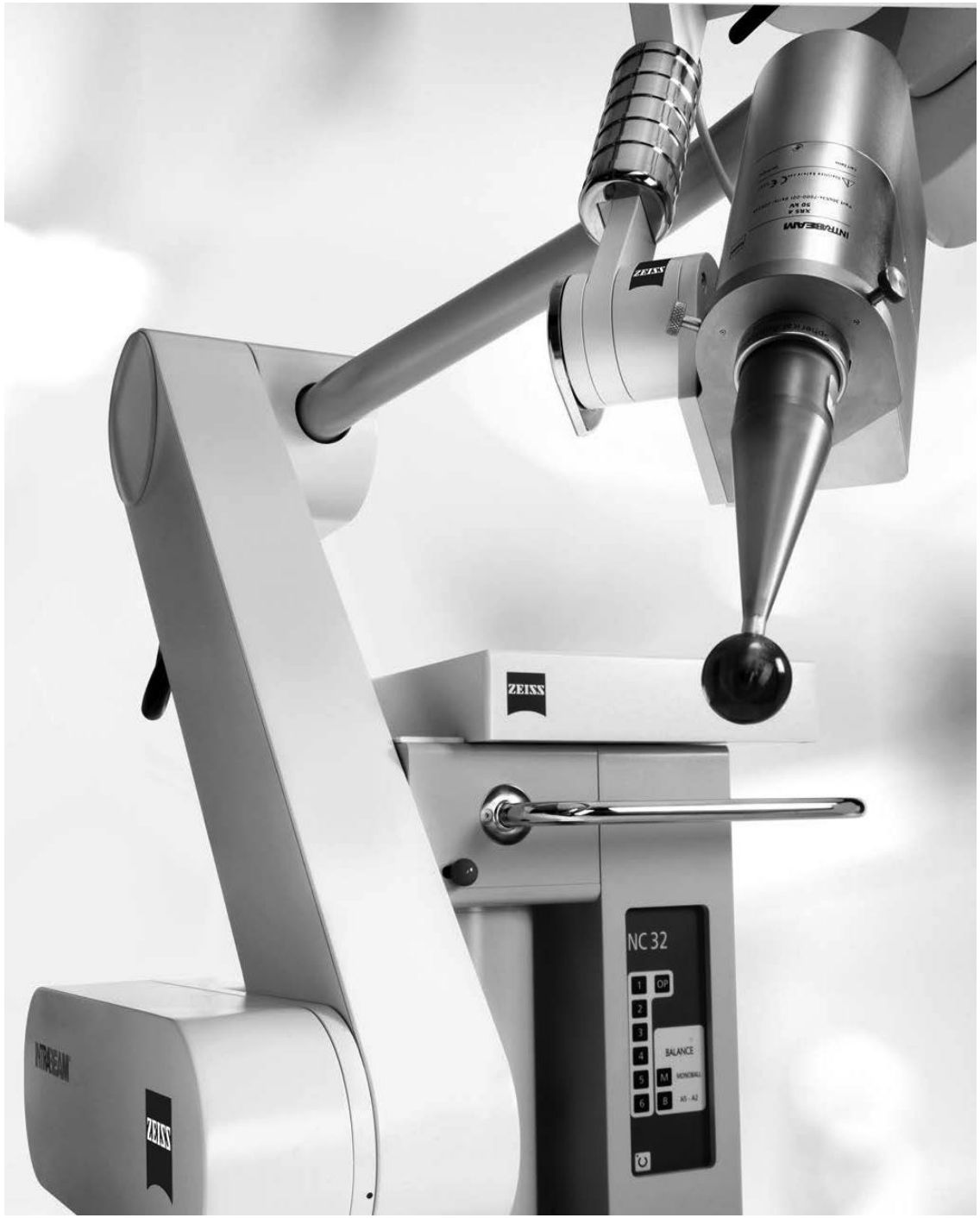




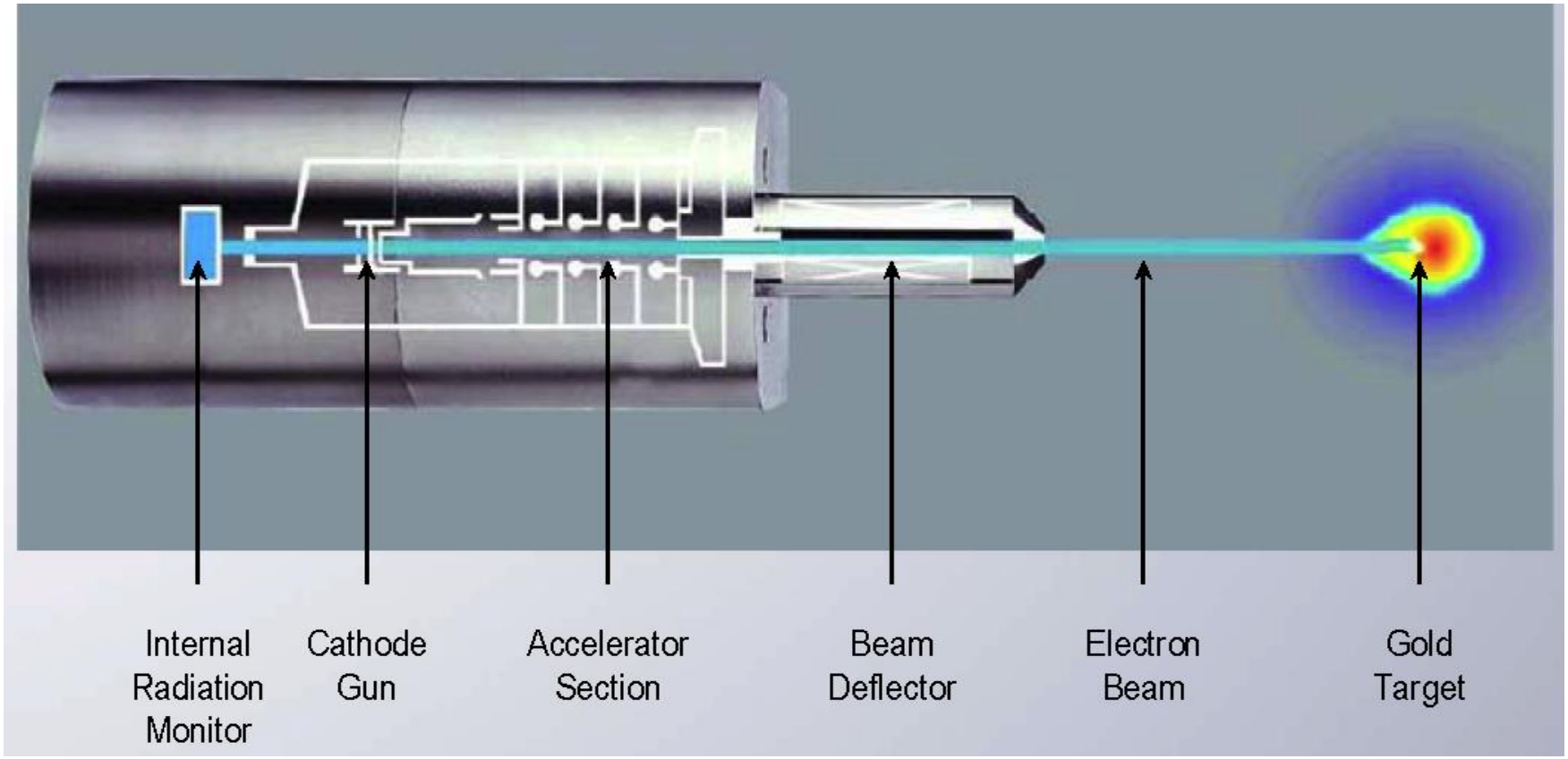
- **Larger radiation dose/fraction**
- **Brachytherapy or external beam**
- **Complete RT in 0-5 days instead of 6-7 weeks**

What is Intraoperative Radiation Therapy? (IORT)

- Technique developed since 1998
- IORT delivers dose of radiation directly to the tumor bed in the operating room
- Single dose is higher than that delivered during conventional radiation therapy, but cumulative amount of radiation is similar to conventional treatment
- Been shown to give results equivalent to weeks of whole breast radiation therapy at 6 years

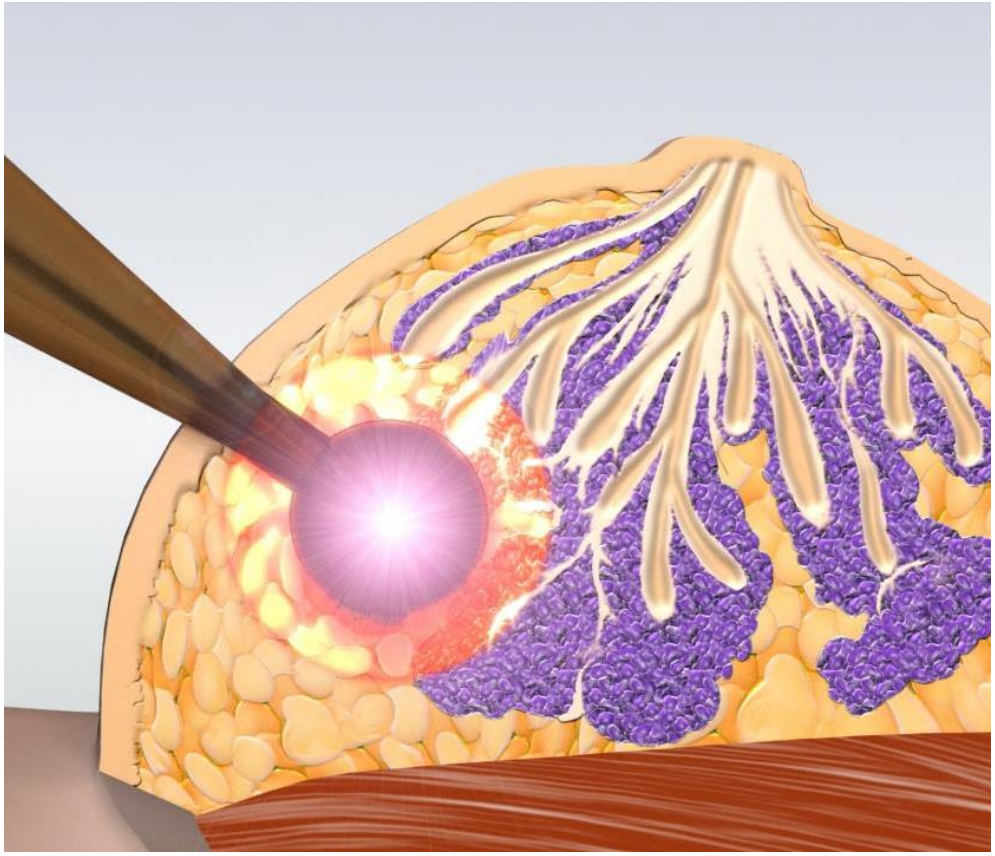


- Generates and delivers a high dose of low energy (50KeV) x-rays in a precise, spherical distribution pattern around a point source


Internal Radiation Monitor
Cathode Gun
Accelerator Section
Beam Deflector
Electron Beam
Gold Target

IORT Procedure in the OR

Intraoperative radiation (IORT)

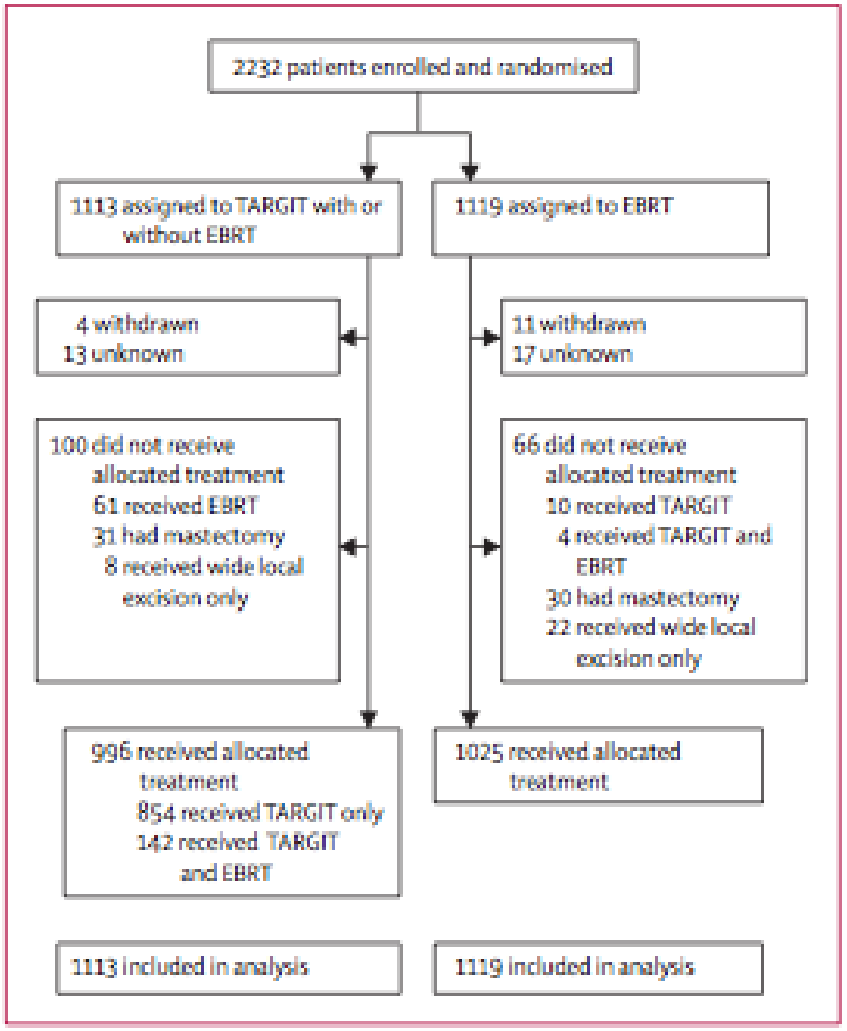


- IORT delivers a single dose of radiation directly to the tumor bed, given at the time of surgery, greatly shortening treatment compared to the conventional 6 weeks of daily radiation
- IORT improves patient convenience and quality of life, and same low recurrence at 5 years compared to traditional radiation

IORT with Intrabeam

- Single procedure(lumpectomy, repair breast defect and sentinel nodebx,IORT (ONE AND DONE)
- RT compliance-logistics-travel issues resolved
- Patient centered- high satisfaction
- Robust research platform
- Can allow second chance at breast conservation

IORT



- Targit-A Trial
- Age >45yo
  - Low risk IDC or DCIS
  - Randomized pre-operatively
  - Non-inferiority trial
  - 6 year follow-up
    - LR
      - 1.2% IORT(HIGHER POST PATHOLOGY!!!!)
      - 0.95% WBI
    - Equivalent toxicity
      - Grade 3-4: 3.3% vs 3.9%

NSABP B-39/RTOG 0413 Schema

Patients with Stage 0, I, or II Breast Cancer Resected by Lumpectomy
Tumor Size ≤ 3.0 cm
No More Than 3 Histologically Positive Nodes

STRATIFICATION

- **Disease Stage (DCIS; Invasive N0; Invasive N1)**
- **Menopausal Status (pre- and post-)**
- **Hormone Receptor Status (ER and/or PR+; ER and PR-)**
- **Intention to Receive Chemotherapy**

RANDOMIZED **(n = 4,216)**

Whole Breast Irradiation after Adjuvant Chemotherapy

50 Gy (2.0 Gy/fraction) or
50.4 Gy (1.8 Gy/fraction) to whole breast,
followed by optional boost to ≥ 60 Gy

Partial Breast Irradiation prior to Adjuvant Chemotherapy

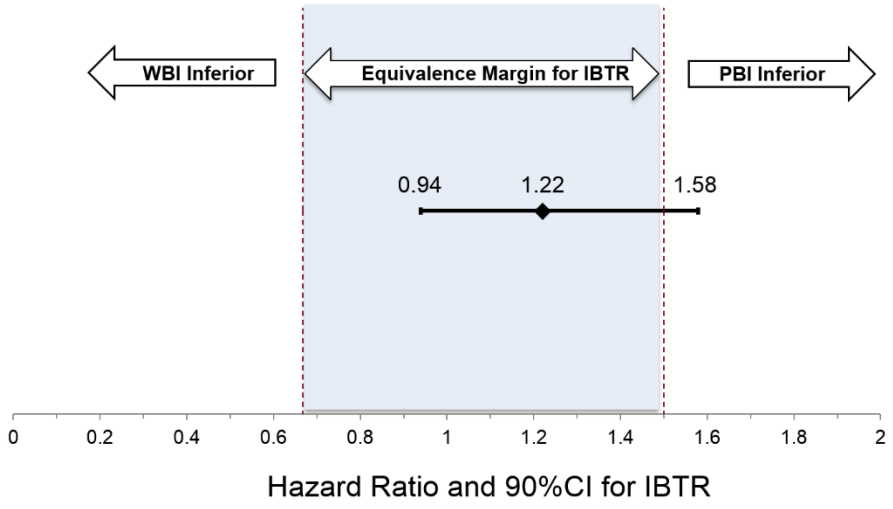
For a total of 10 treatments given on 5 days over 5 to 10 days:

34 Gy in 3.4 Gy fractions Interstitial Brachytherapy
or Mammosite Balloon Catheter
or 38.5 Gy in 3.85 Gy fractions
3D Conformal External Beam

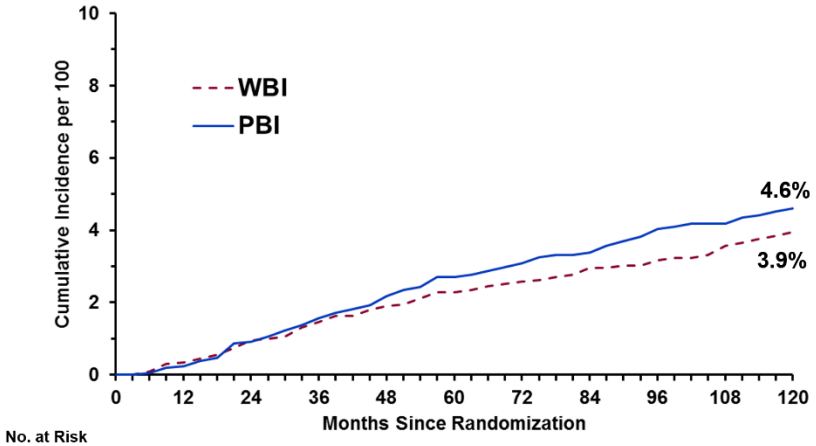
NRG ONCOLOGY™

NSABP B-39/RTOG 0413

Ipsilateral Breast Tumor Recurrence (IBTR)



Cumulative Incidence of IBTR



Absolute difference in 10-yr rate of IBTR between PBI and WBI was *0.7%*

IBTR by PBI Method and Location in the Breast

Treatment Group	# of Pts	# of Events	Hazard Ratio (HR)	HR 95% Confidential Interval	10-yr Cum Incidence
WBI	2,011	67	REF		3.8%
PBI					
Multi-catheter brachytherapy	130	9	2.21	1.10 – 4.46	7.7%
Single-entry brachytherapy device	358	24	2.15	1.34 – 3.44	7.8%
3DCRT (external beam)	1,535	55	1.04	0.73 – 1.49	3.7%

This analysis used a per-protocol population, which excluded those who did not receive their randomly assigned treatment

	# of Pts		# of Events		Hazard Ratio (HR)	HR 95% Confidential Interval	10-yr Cum Incidence	
Location of IBTR	WBI	PBI	WBI	PBI			WBI	PBI
At site of primary tumor	2109	2107	46	39	0.81	0.53 - 1.24	2.4%	1.9%
Elsewhere in the breast	2109	2107	25	51	1.99	1.23 - 3.23	1.5%	2.7%

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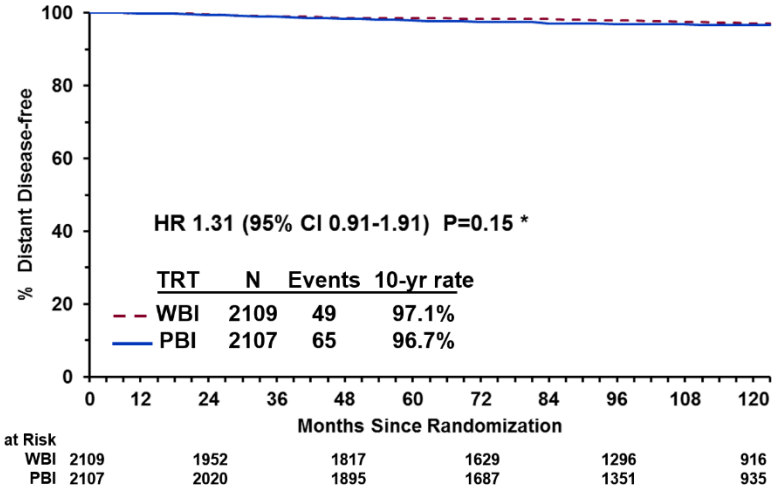
NSABP B-39/RTOG 0413

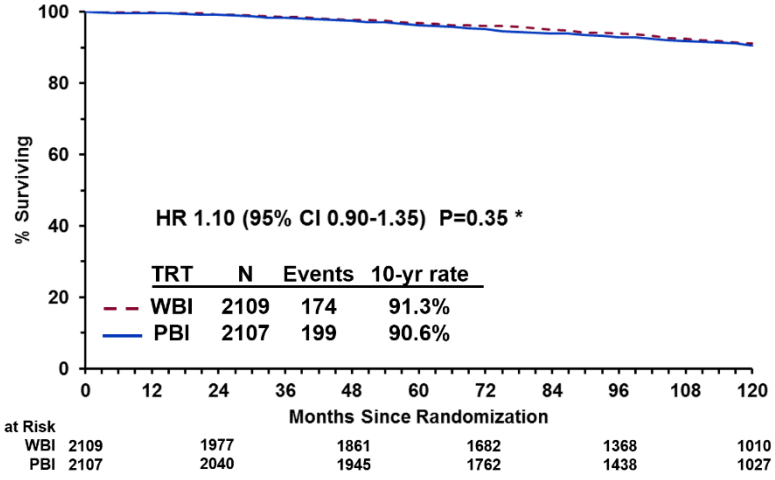
Distant Disease-free Interval



No. at Risk						
WBI	2109	1952	1817	1629	1296	916
PBI	2107	2020	1895	1687	1351	935

*Based on Cox proportional hazards models stratified on disease stage, menopausal status, hormone receptor status, and intention to receive chemotherapy.

Overall Survival



No. at Risk						
WBI	2109	1977	1861	1682	1368	1010
PBI	2107	2040	1945	1762	1438	1027

*Based on Cox proportional hazards models stratified on disease stage, menopausal status, hormone receptor status, and intention to receive chemotherapy.

NSABP B-39/RTOG 0413

Adverse Events

Toxicity:

- **Grade 3 toxicity was 9.6% PBI *v* 7.1% WBI**
- **Grade 4-5 toxicity was 0.5% PBI *v* 0.3% WBI**

Second Cancers:

First Site of Second Primary Cancer	WBI	PBI	Total
Contralateral breast	72	63	135
All other sites	128	129	257
Total	200	192	392

No statistically significant differences

Conclusions

- **Intent-to-treat and as-treated analyses could not refute the hypothesis that PBI is inferior and cannot declare that WBI and PBI are equivalent in controlling local in-breast tumor recurrence. However, the absolute difference in the 10-yr cumulative incidence of IBTR was only 0.7%.**
- **Risk of an RFI event was statistically significantly higher for PBI *v* WBI, but again, the absolute difference in 10-yr RFI cumulative incidence was also small (1.6%)**
- **Breast cancer event rates at a median follow-up of 10.2 yrs in this population were overall low: IBTR rate: ~4.5%, DM rate: ~3%, and breast cancer death rate: ~2%**
- **Because the differences relative to both IBTR (0.7%) and RFI (1.6%) were small, PBI may be an acceptable alternative to WBI for a proportion of women who undergo breast-conserving surgery**
- **Grade 3-5 toxicities were low. Additional analyses are underway to evaluate secondary endpoints of QOL and cosmesis**

NRG ONCOLOGY™

San Antonio Breast Cancer Symposium, December 4-8, 2018

Regional node irradiation:

Meta-analysis of 13,500 women in 14 trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

Writing Committee: David Dodwell (presenter), Carolyn Taylor, Paul McGale, Charlotte Coles, Fran Duane, Richard Gray, Thorsten Kühn, Christophe Hennequin, Robert Hills, Sileida Oliveros, Yaochen Wang, Jonas Bergh, Kathy Pritchard, Sandra Swain, Jens Overgaard, Philip Poortmans, Tim Whelan

EBCTCG: REGIONAL LYMPH NODE RADIATION

Regional node RT versus not

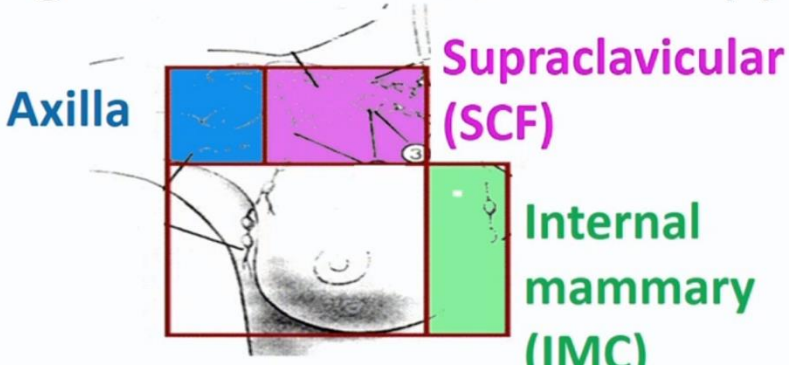
14 trials, ~13,500 women

Comparison: Node RT versus not	No. trials	No. women
Axilla SCF	2	652
IMC	3	4683
IMC SCF axilla	9	8069
All trials	**14**	**13,404**

4

San Antonio Breast Cancer Symposium, December 4-8, 2018

Regional node radiation therapy (RT)



Same treatment to breast

EBCTCG: REGIONAL LYMPH NODE RADIATION

Data analysis plan: regional node RT

1. **All trials together**
2. **Separate older & newer trials**

Target coverage better in newer trials

Heart dose: Older trials >8 Gy

Newer trials <8 Gy

San Antonio Breast Cancer Symposium, December 4-8, 2018

Older trials (began 1961-1978)

Total with data available ≈2,500

Year began	Name	Women	RT sites randomised
1961	NSABP B-03	1103	IMC, SCF, axilla
1968	Oslo	542	IMC, SCF, axilla
1969	Heidelberg	142	IMC, SCF, axilla
1972	WSSA	217	SCF, axilla
1973	Milan 1	56	IMC, SCF
1974	Piedmont	160	IMC, SCF
1974	Mayo	241	IMC, SCF
1978	Toronto	74	'regional'

Median FU (IQR): 9.2 (3.4 – 17.5) years

Newer trials (began 1989 onwards)

Total with data available ≈11,000

Year began	Name	Women	RT sites randomised
1989	Tampere	270	IMC
1991	French IM*	1407	IMC
1995	Italian Senology	435	axilla
1996	EORTC 22922	4004	IMC, SCF
2000	MA.20	1832	IMC, SCF, axilla
2003	DBCG-IMN**	3089	IMC

*Data available only on overall mortality **RT allocated by tumour laterality

Median FU (IQR): 9.1 (7.0 – 11.0) years

EBCTCG: REGIONAL LYMPH NODE RADIATION

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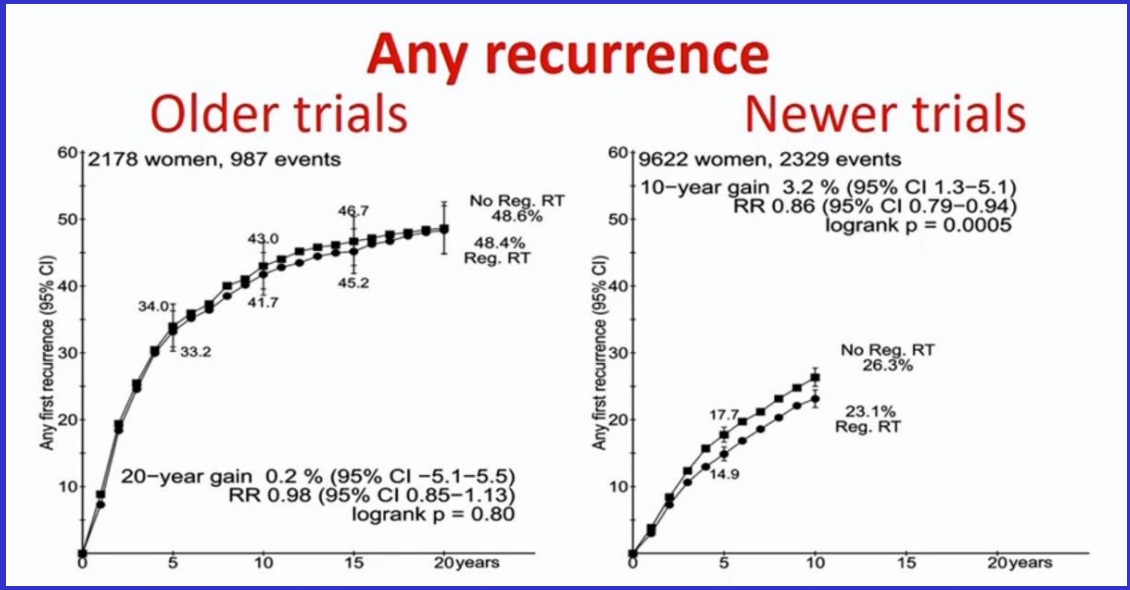
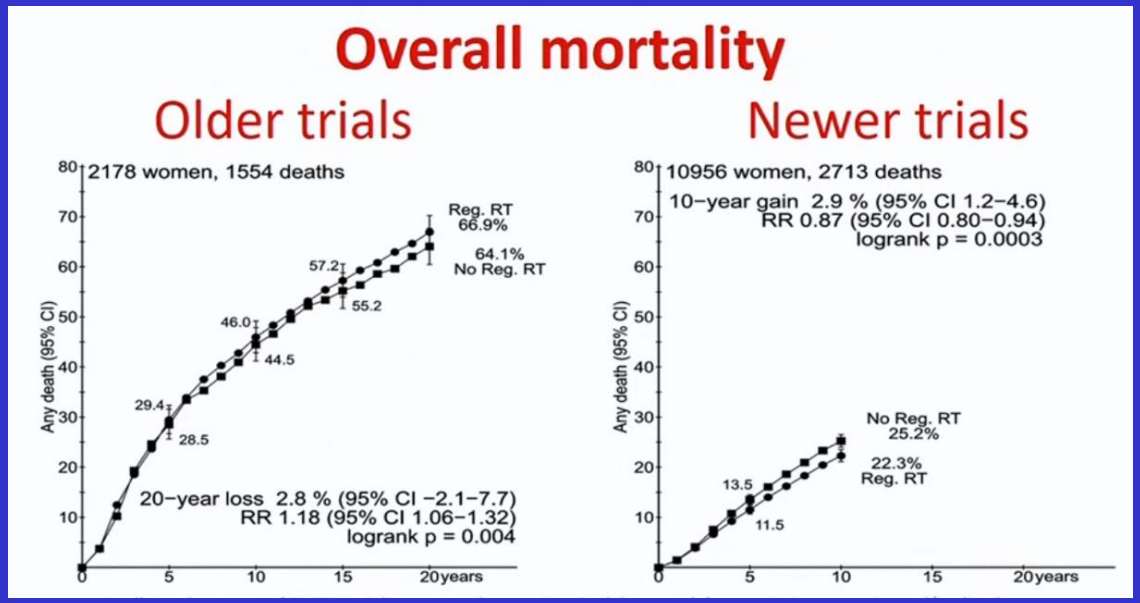
**RT allocated by tumour laterality

Median FU (IQR): 9.1 (7.0 – 11.0) years

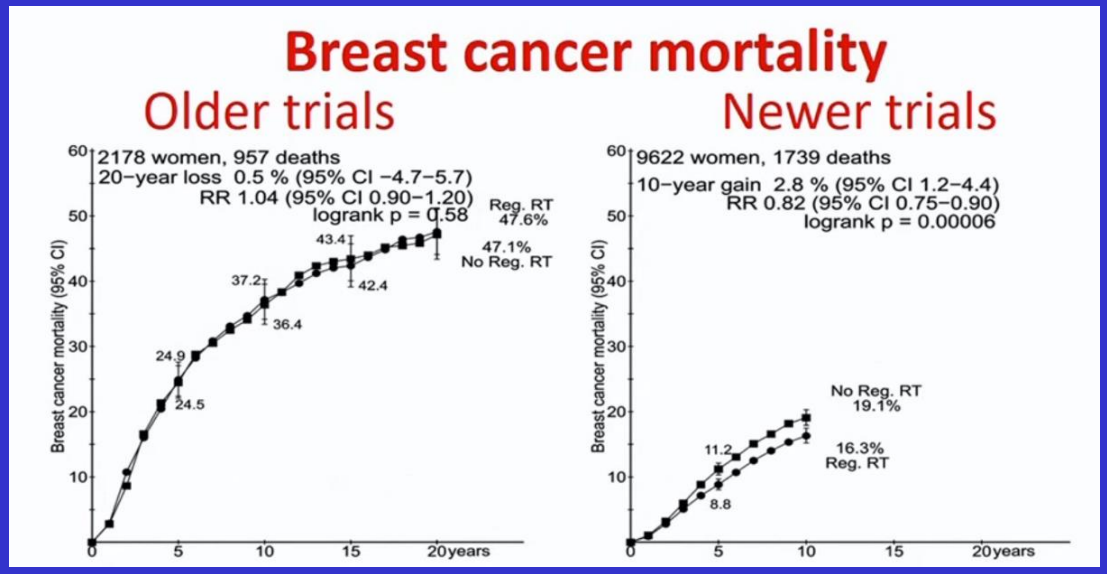
IPD Meta-analysis

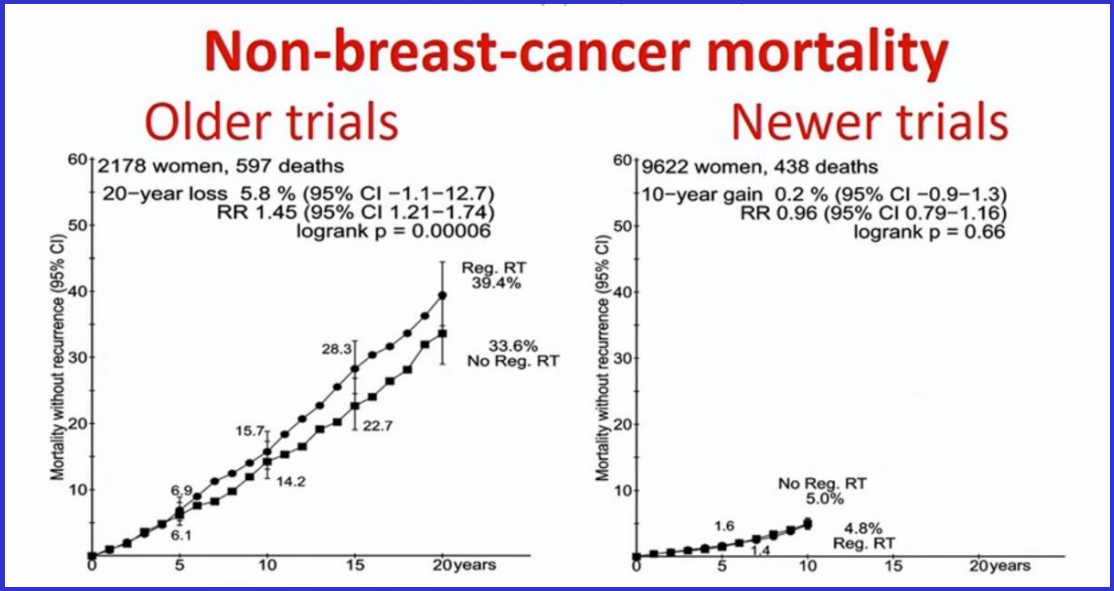
EBCTCG: REGIONAL LYMPH NODE RADIATION



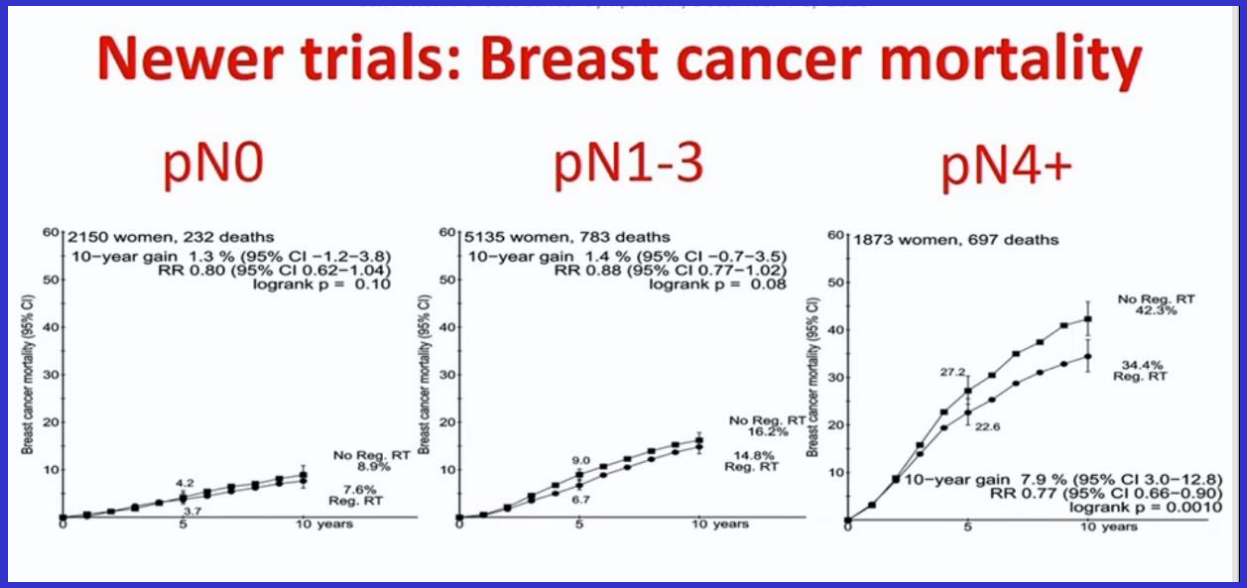


EBCTCG: REGIONAL LYMPH NODE RADIATION





EBCTCG: REGIONAL LYMPH NODE RADIATION



Breast cancer mortality did not vary according to:

- **Regional LNs irradiated**
- **Breast quadrant**
- **Use of chemotherapy**
- **Use of endocrine therapy**

All p > .10

EBCTCG: REGIONAL LYMPH NODE RADIATION

Conclusions: regional node irradiation

- **Older trials (began 1961-1978)**
  - Breast cancer mortality – little effect
  - Overall mortality – significantly increased

- **Newer trials (began 1989+)**
  - Breast cancer mortality – significantly reduced
  - Overall mortality – significantly reduced
  - Absolute mortality reduction greatest in N4+

GAINS WITH NODAL RADIATION TREATMENT

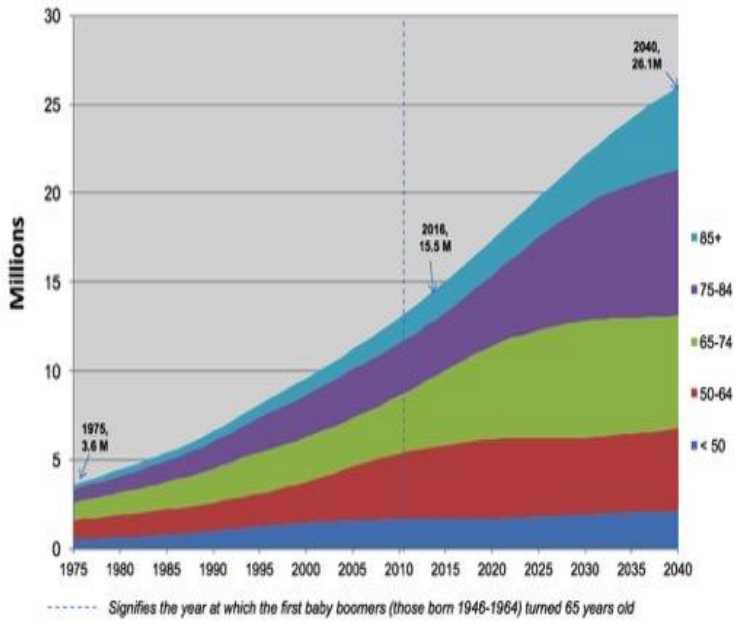
	EORTC 22922/10925 15-year gain with nodal RT	P value	NCIC MA20 10-year gain with nodal RT	P value	EBCTCG (SABCS) 10-year gain with nodal RT	P value
Breast cancer mortality	3.8%	.0055	--	--	2.8%*	.00006
Distant metastases	3.4%	--	3.6%	--	--	--
Distant disease-free survival	1.8%	.18	1.9%	.03	--	--
Overall survival	2.2%	.18	1.0%	.38	2.9%*	.0003
Local-regional recurrence	(-0.4%)	--	3.0%	.009	--	--

*Newer trials

“SILVER TSUNAMI”

Changing Demographics

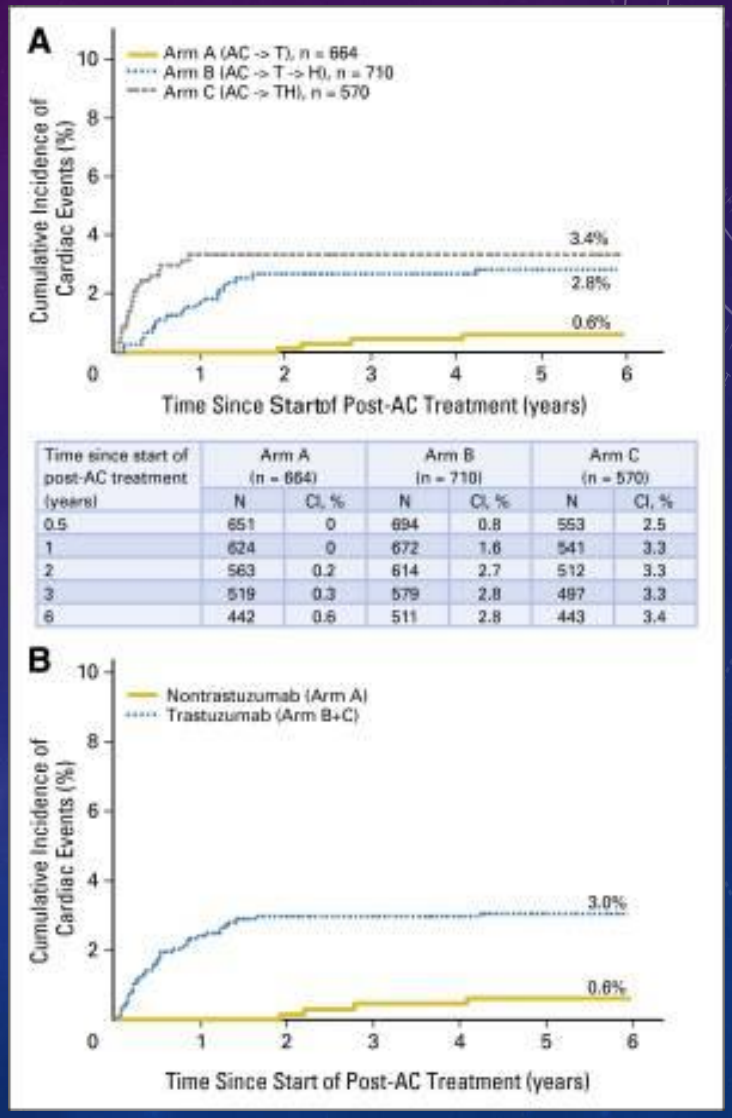
Figure 1: Estimated cancer prevalence by age in the US population from 1975 (216 M) to 2040 (380 M)



Shapiro CL NEJM 2018:379; 2438-50

CARDIOTOXICITY: HER2-BASED ADJUVANT REGIMENS

- No standard definition of cardiac toxicity
- Trastuzumab-induced cardiac toxicity:
  - Not dose related
  - No myocardial cell death
  - 2.3% developed CHF; 0.1% cardiac death
  - In over 50% trastuzumab retreatment
  - No late trastuzumab toxicity



Time since start of post-AC treatment (years)	Arm A (n = 664)		Arm B (n = 710)		Arm C (n = 570)	
	N	CI, %	N	CI, %	N	CI, %
0.5	651	0	694	0.8	553	2.5
1	624	0	672	1.6	541	3.3
2	563	0.2	614	2.7	512	3.3
3	519	0.3	579	2.8	497	3.3
6	442	0.6	511	2.8	443	3.4

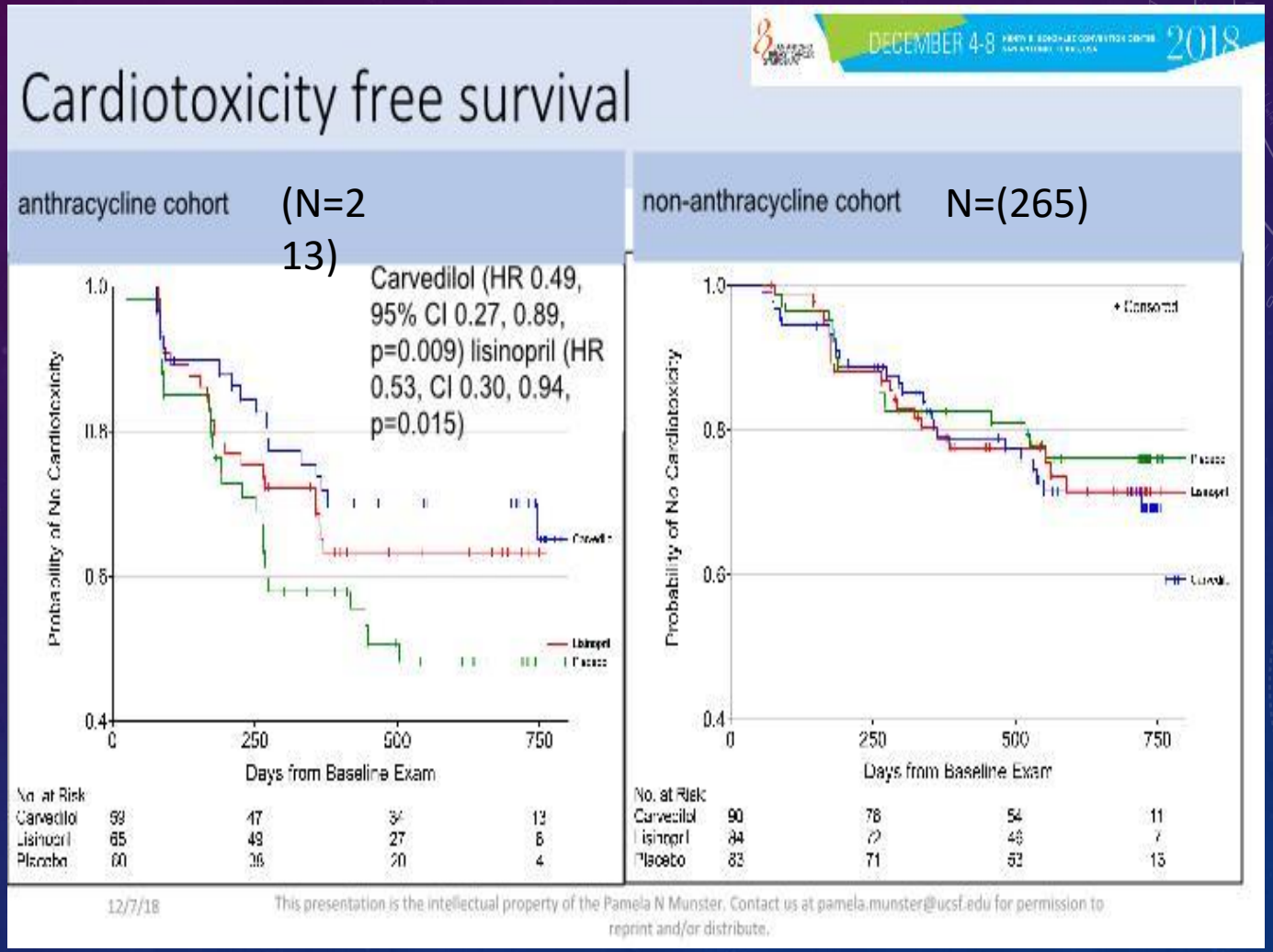
Advani *et al*. J Clin Oncol 2016;34:581-7

ABSTRACT GS5-1

N=468
Anthracyclines
Non-Anthracyclines

- Cardiac Toxicity:
  - Decrease in LVEF by ≥ 10%, ≥ 5% ↓ 50%
- Primary Objective:
  - Cardiac events during and the year after trastuzumab
- Secondary objectives:
  - Toxicity, QoL, cardiac biomarkers
- Statistics:
  - None presented

RESULTS


DECEMBER 4-8 2018
Cardiotoxicity free survival
anthracycline cohort (N=213)
Carvedilol (HR 0.49, 95% CI 0.27, 0.89, p=0.009) lisinopril (HR 0.53, CI 0.30, 0.94, p=0.015)
Probability of No Cardiotoxicity
1.0
0.8
0.6
0.4
0
250
500
750
Days from Baseline Exam
No. at Risk
Carvedilol 99 47 34 12
Lisinopril 85 49 27 6
Placebo 80 36 20 4
non-anthracycline cohort N=(265)
+ Censored
Probability of No Cardiotoxicity
1.0
0.8
0.6
0.4
0
250
500
750
Days from Baseline Exam
No. at Risk
Carvedilol 90 76 54 11
Lisinopril 84 62 46 7
Placebo 83 71 52 13
12/7/18
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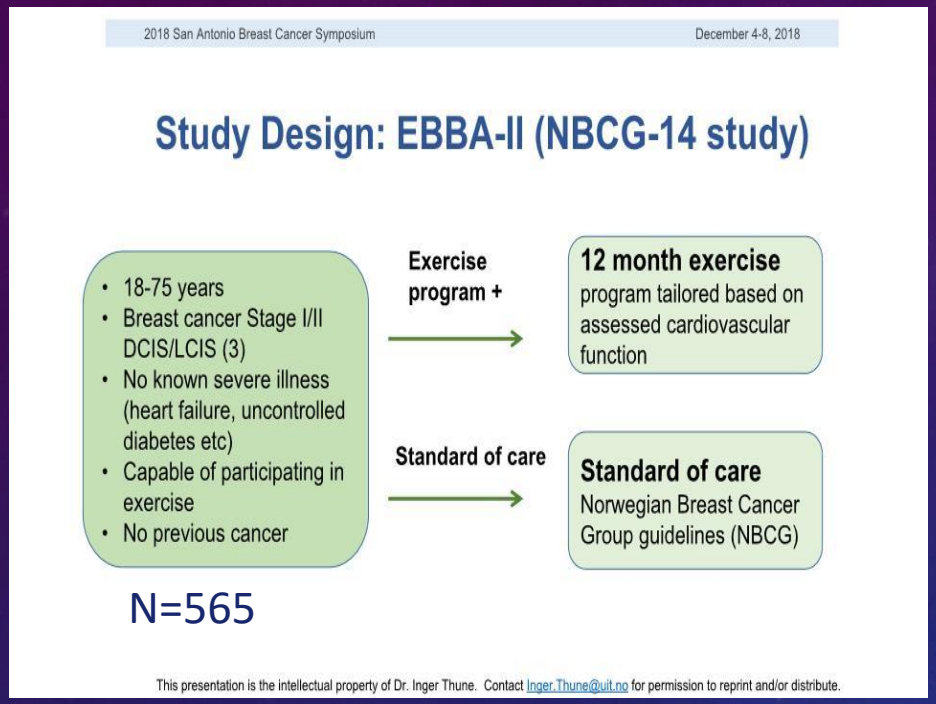
CAVEATS, CONCLUSIONS

- No info on type of cardiac event, reversibility, or long term outcome
- Decreasing anthracycline use
- *Until long follow-up and additional studies, lisinopril and carvedilol should NOT be used outside a clinical trial in women receiving anthracyclines*

ABSTRACT GS5-2

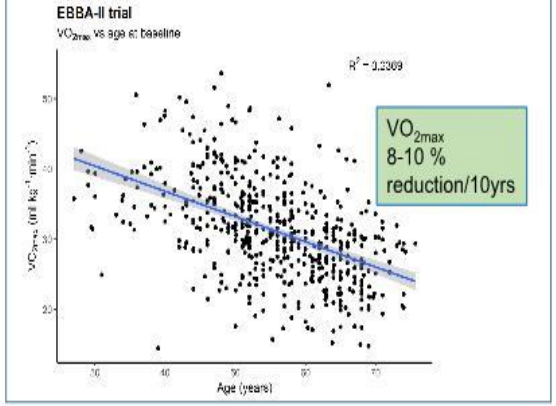


- Resource and time intensive intervention
  - 120 min/week supervised, +120 min
- Heathy population
  - Mean age 55; BMI 25; VO2 baseline 31
- Primary endpoint:
  - VO2 baseline – 12 mo

Adherence and Adverse Events (AE)
Cardiovascular capacity (VO_{2max})

Adherence to the intervention

Overall cardiovascular function

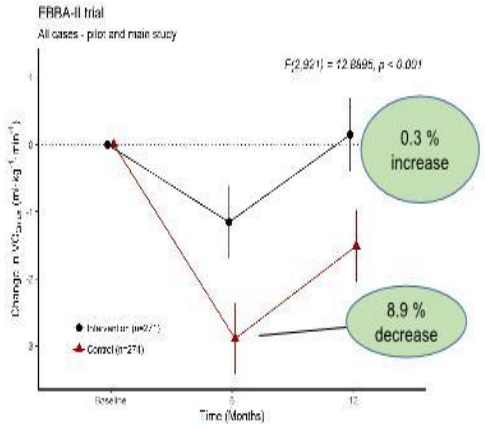


AE's: Fatigue during CPET/exercise, one injured shoulder

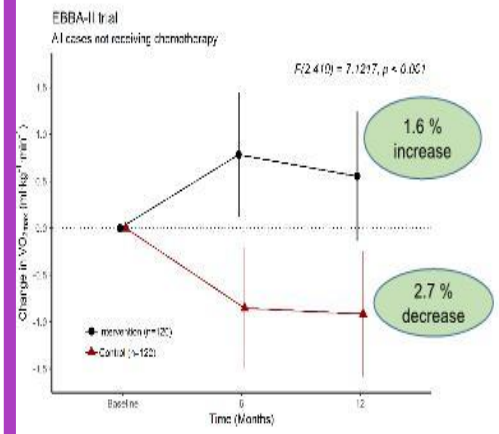
EBBA-II STUDIEN

Final results - The EBBA-II (NBCG-14)

All participants (n= 545)

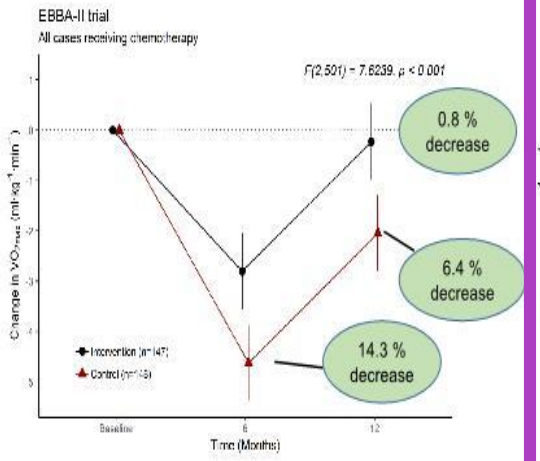


No chemotherapy (n=242)

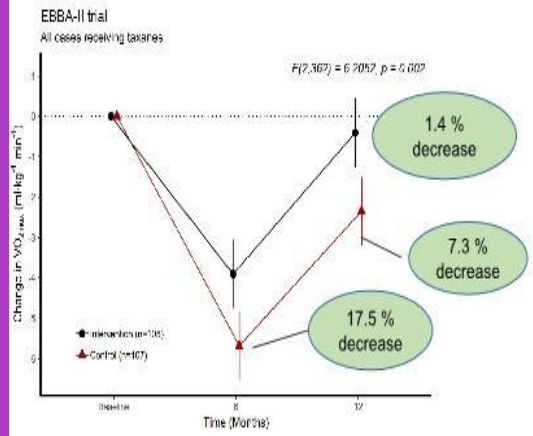


Patients receiving chemotherapy

Receiving chemotherapy (n= 295)



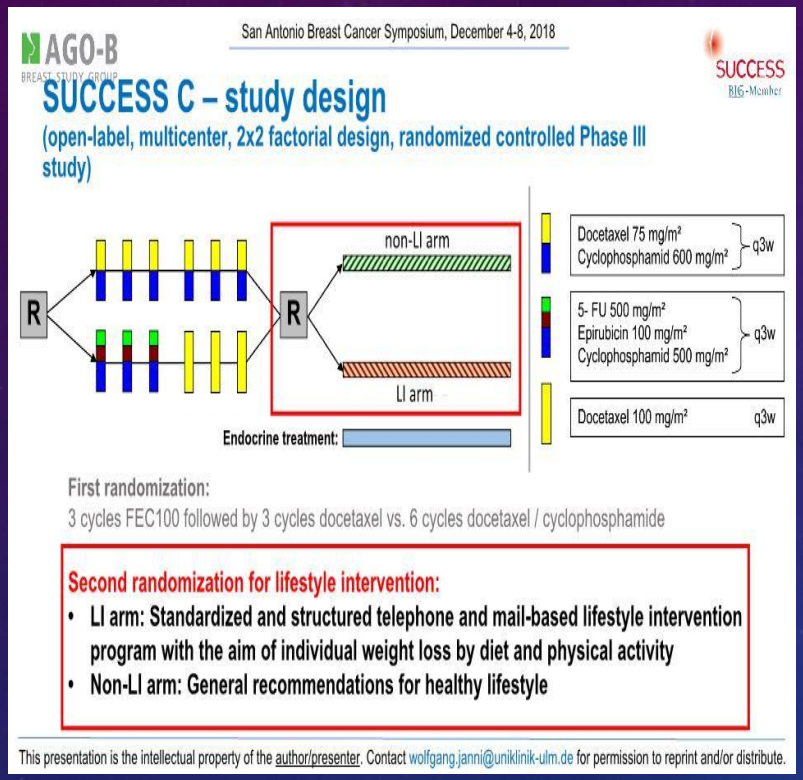
Receiving taxanes (n= 212)



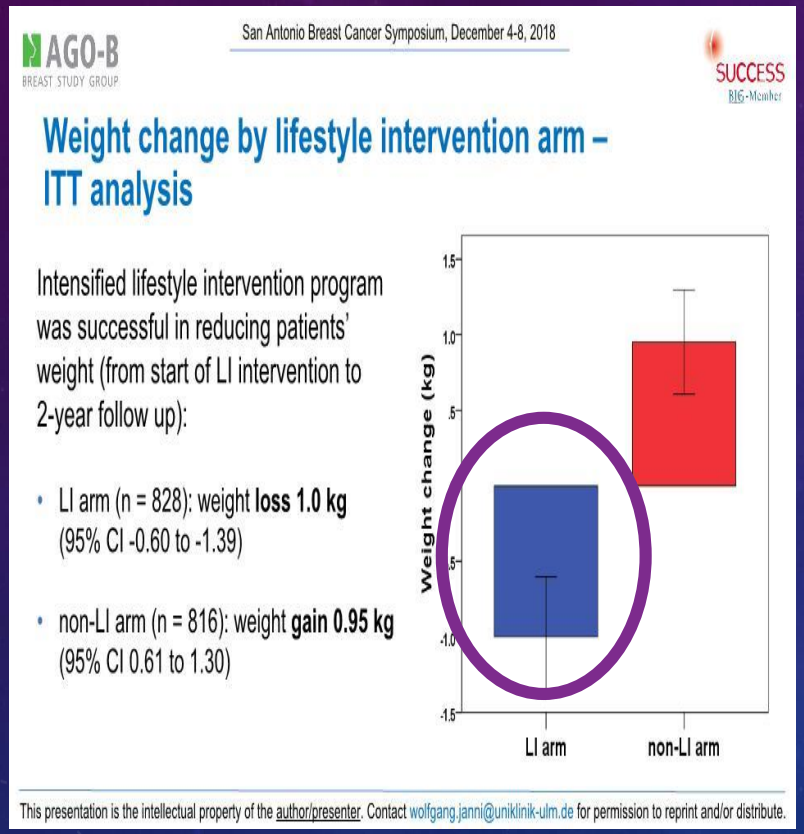
CAVEATS AND CONCLUSIONS

- Relatively young healthy population able to undergo an intensive intervention. ***Are the results generalizable?***
- Intensive intervention results in preservation of VO2 during chemo
- ***What about a less intensive intervention in a more representative population?***
- ***Do the control and intervention arms come together over time?***

ABSTRACT GS5-03

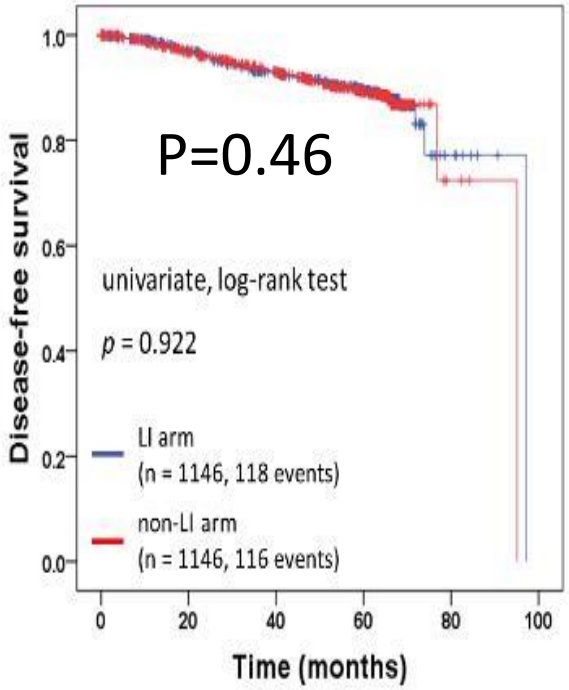


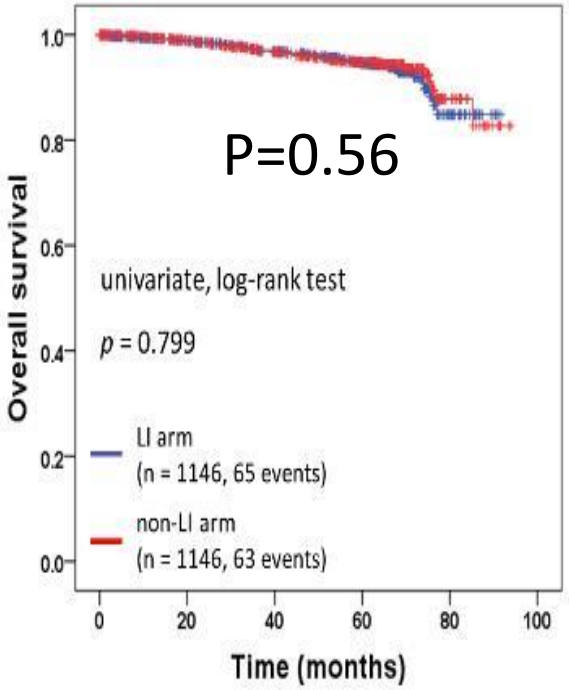
- 2 year intervention- telephone based
  - 19 calls and mailings; physical activity ↑ weight ↓
  - Formal V02 testing
- 2292 randomized
  - Age 58; N+ 60%; postmenopausal 68%; ER+ 77%
- Primary Endpoint
  - DFS and OS



- Compliance: Only 48% completed intervention
- Completers vs. non-completers were different
  - Younger age, lower grade, higher ER+

Disease-free survival (DFS) and overall survival (OS) by lifestyle intervention arm – ITT analysis





CAVEATS AND CONCLUSIONS

- Intervention was not feasible as 50% did not complete the 2 yrs.
- ***Ongoing trials are addressing weight loss and physical activity (BWEL trial)***

HOT FLASHES

HOT FLASHES: MAYO CLINIC

Randomized, Placebo Control

Drug	Benefit
Placebo	20%
Clonidine/ MPA	Pos (side effects)
Fluoxetine	Pos, (interferes tam)
Gabapentin	Pos, (fatigue)
Venlafaxine	Pos (no interference with tam)
Soy, Flaxseed	Neg

Mechanism

Oxybutynin

- **Anticholinergic** (oral or transdermal).
- FDA approved for overactive bladder (5-20 mg daily).
- **"Decreased sweating" common** → effective for hyperhidrosis.
- **Data in refractory hot flashes:**
  - **Retrospective study:** Sexton et al, Menopause, 2007.
  - **Prospective study:** Simon et al, Menopause, 2016. Oxybutynin XR 15 mg/d improved HF but with toxicity. Investigators recommended studying lower doses.

Abstract GS6-02

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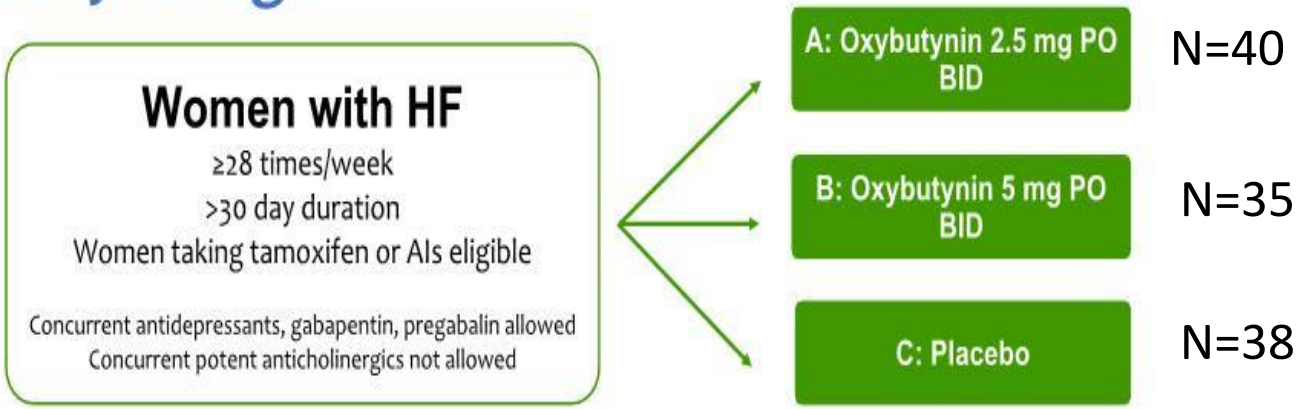
Study design



Treatment duration = 6 weeks, after a baseline week without medication (questionnaires)

Weekly questionnaires:
Hot Flash Diary
HFRDIS
Symptom experience questionnaire

Endpoints:
Primary: Intra-patient change in weekly HF score[1] and frequency
Secondary: change in HFRDIS, change in self-reported symptoms

[1]Sloan et al, JCO 2001

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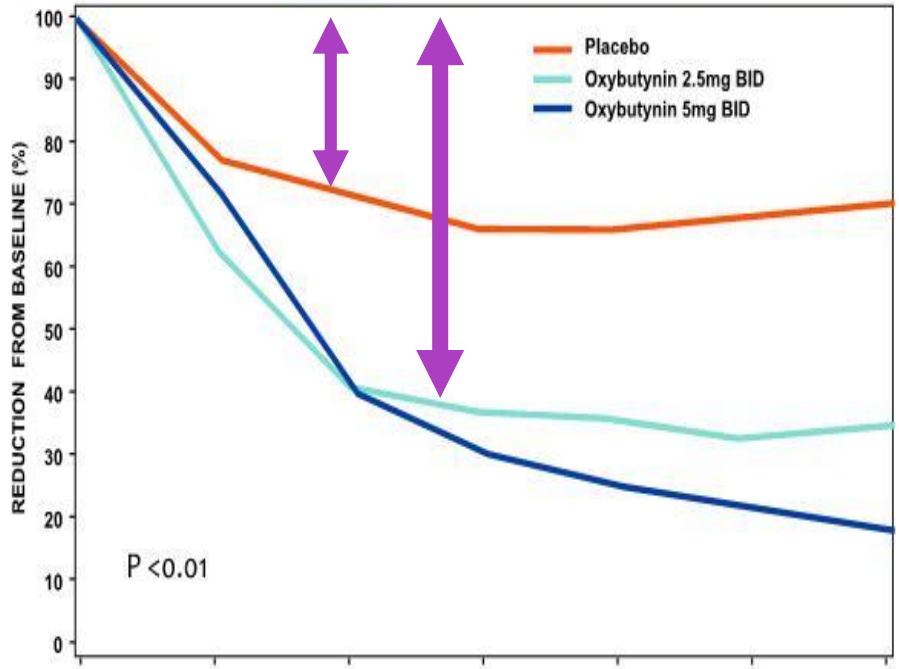
Results: Mean Hot Flash Score % Reduction from Baseline

HF Score = HF frequency x average severity

G1 = mild, G2= moderate, G3 = severe, G4 = very severe



WEEKS	Baseline	1	2	3	4	5	6
Placebo	38	38	38	37	35	35	35
Oxybutynin 2.5 mg BID	40	40	38	36	35	35	34
Oxybutynin 5mg BID	35	35	34	32	32	31	31

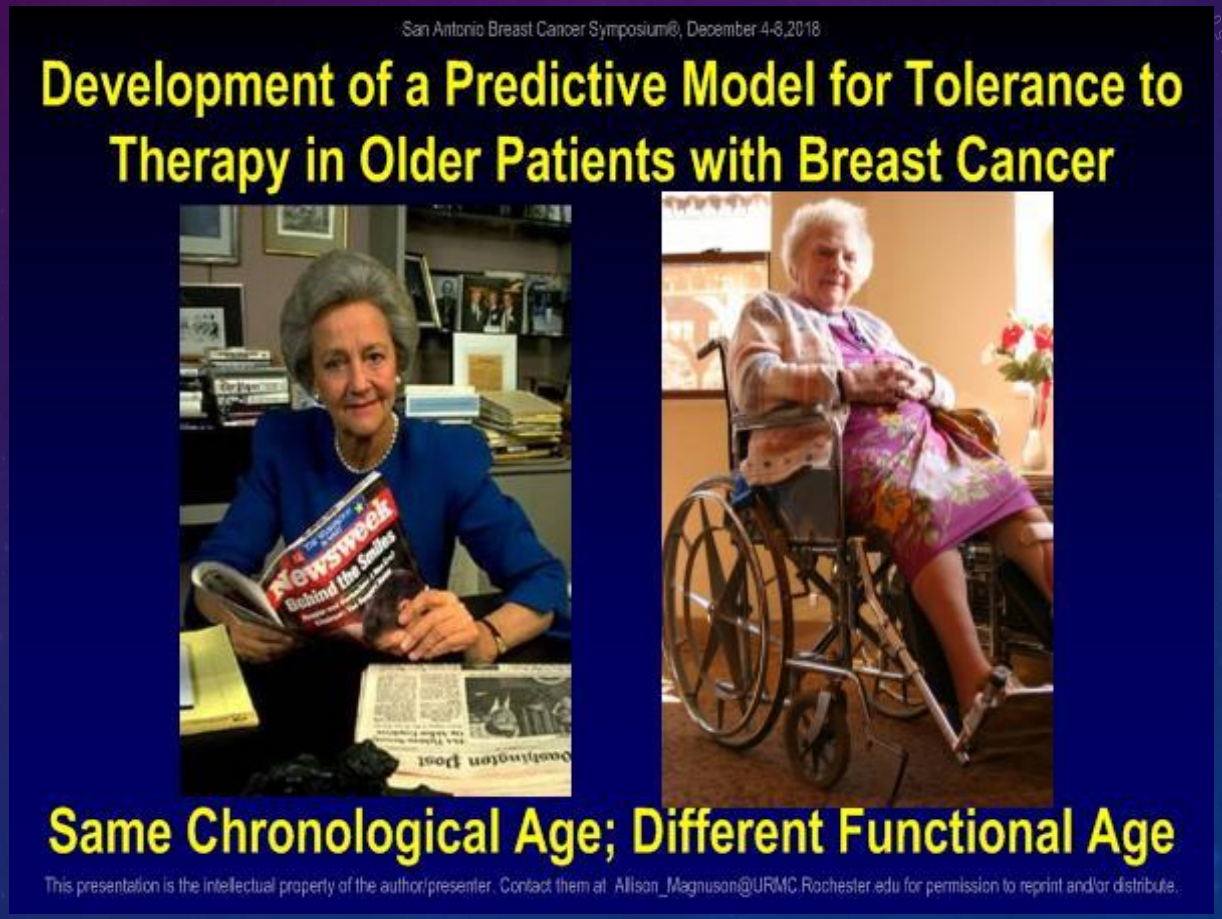
MAYO CLINIC

CONCLUSIONS

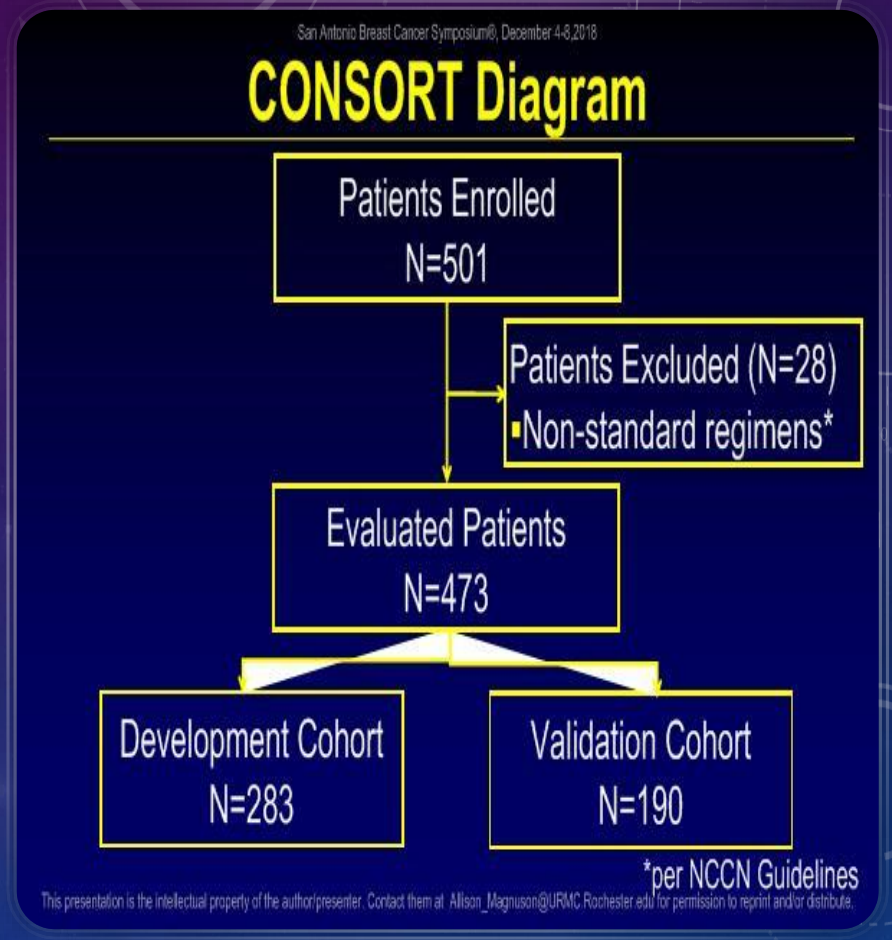
- Oxybutynin improved severity and frequency of hot flashes, with 5 mg > 2 mg
  - *No formal comparison between doses*
- HRQOL was improved except for sexuality and concentration
  - *2.5 mg BID did not improve mood and life enjoyment*
- Side effects: Dry mouth, abdominal pain, difficult urination
  - *5 mg BID-dry eyes, confusion, diarrhea, headaches*
- What's the correct dosage?

ABSTRACT GS6-04

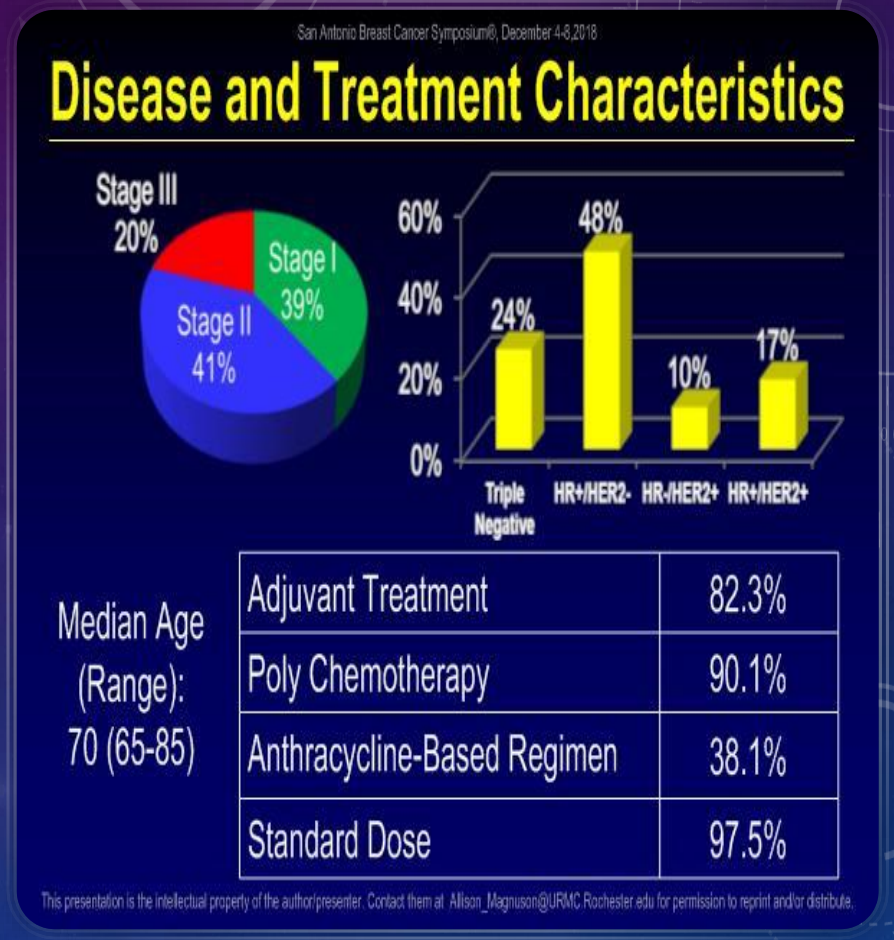
Cancer and Aging Research Group (CARG) Scor



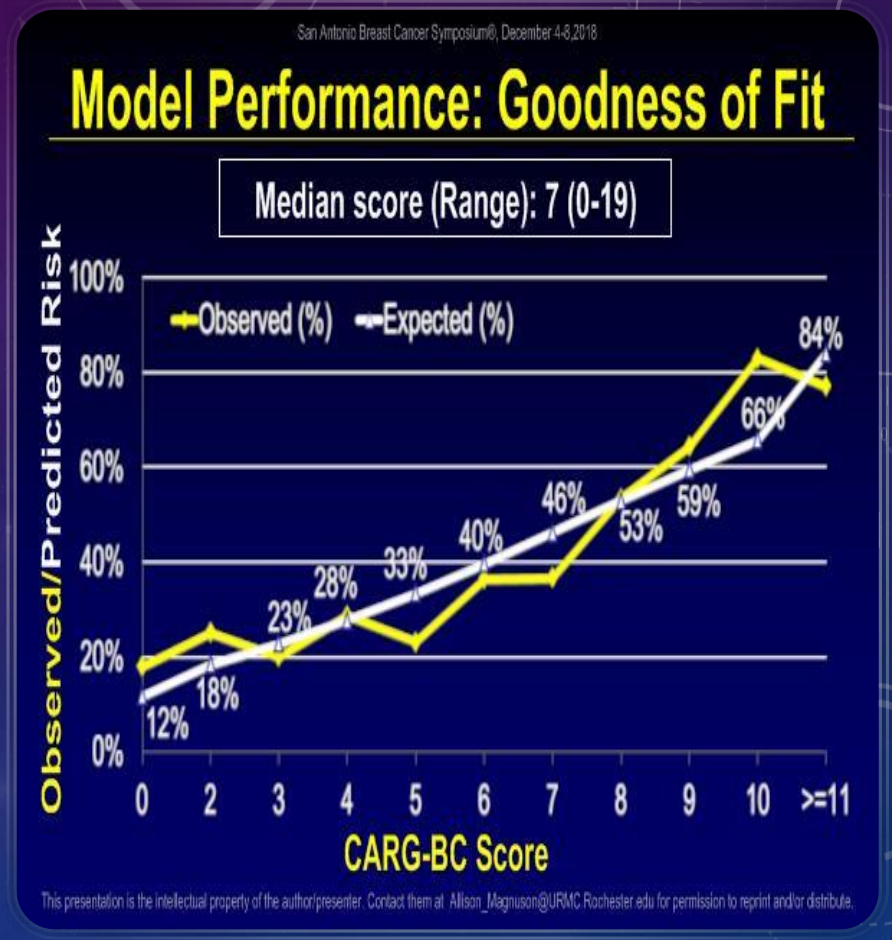
PROSPECTIVE COHORT STUDY DESIGN



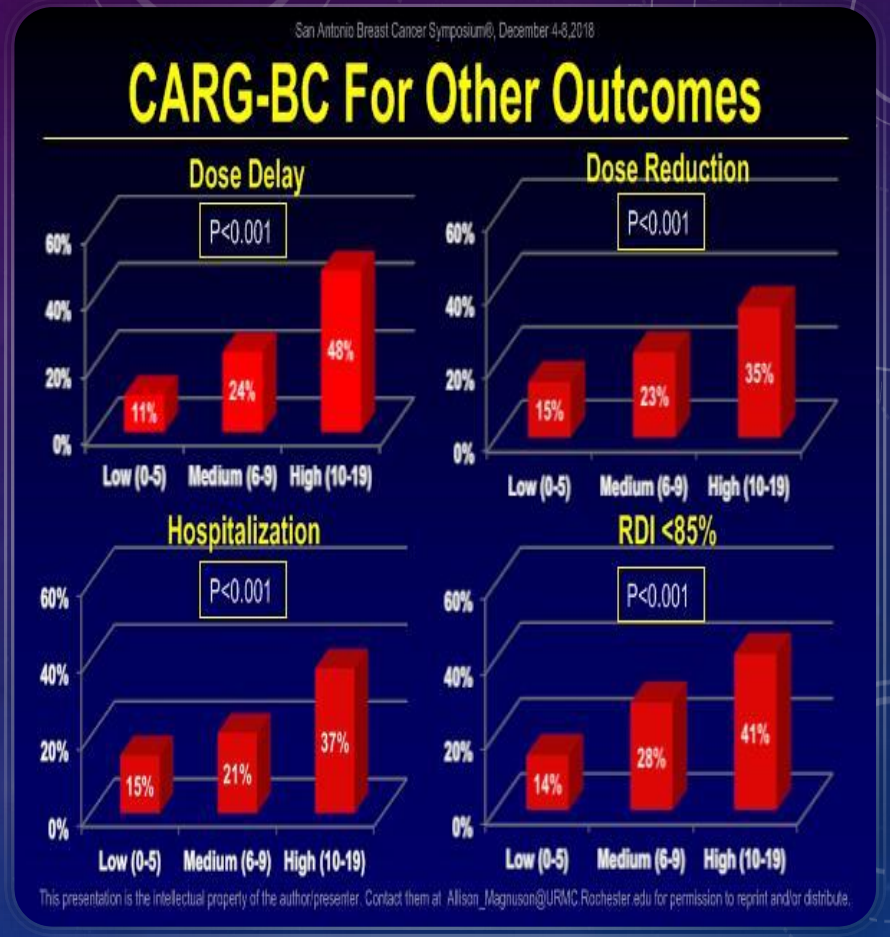
DISEASE CHARACTERISTICS



GOODNESS OF FIT



OUTCOMES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CARG-BC For Other Outcomes
Dose Delay
P<0.001
60%
40%
20%
0%
11%
24%
48%
Low (0-5)
Medium (6-9)
High (10-19)
Dose Reduction
P<0.001
15%
23%
35%
Hospitalization
P<0.001
15%
21%
37%
RDI <85%
P<0.001
14%
28%
41%
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CONCLUSION

- CARG Score is a validated tool to predict chemotherapy side effects in elder women with breast ca
- Predicts dose reductions, delays, and hospitalizations

Thank
You
Merci
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Dankscheen
Biyan
Grazie
Juspa
Shukuria
Tashakkur
bolzïn
Mehrbani
suksama
Shukria
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Denkauja
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Komapsumnida
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Paldies
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Spassibo
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