The Latest Research: Hormonal Therapies

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Disclosures

- No Pertinent Financial Disclosures

Objectives

- Discuss types of anti-estrogen therapies available after diagnosis of early stage breast cancer to reduce the risk of recurrence
- Latest research and recommended guidelines on the duration of therapy
- Side effect profiles and how to manage side effects to minimize impact on overall quality of life
- Compliance issues and common reasons (medical, practical and emotional) that effect this

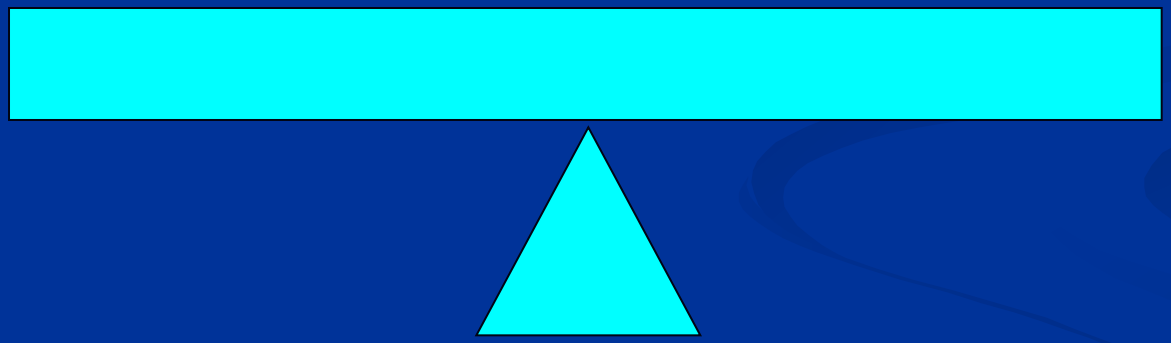
Adjuvant Systemic Therapy

- Goal to eliminate or delay appearance of micrometastatic disease
  - Anti Estrogen therapy (ER positive)
  - Chemotherapy (Some ER positive, ER negative, Her-2/neu amplified)
  - Her-2/neu directed therapy (for Her-2/neu amplified disease)
- Current Strategies: Individualizing treatment to the cancer and the patient

Adjuvant Systemic Therapy for Breast Cancer: Decision Making

Risks: Adverse Events

Benefits: Risk Reduction



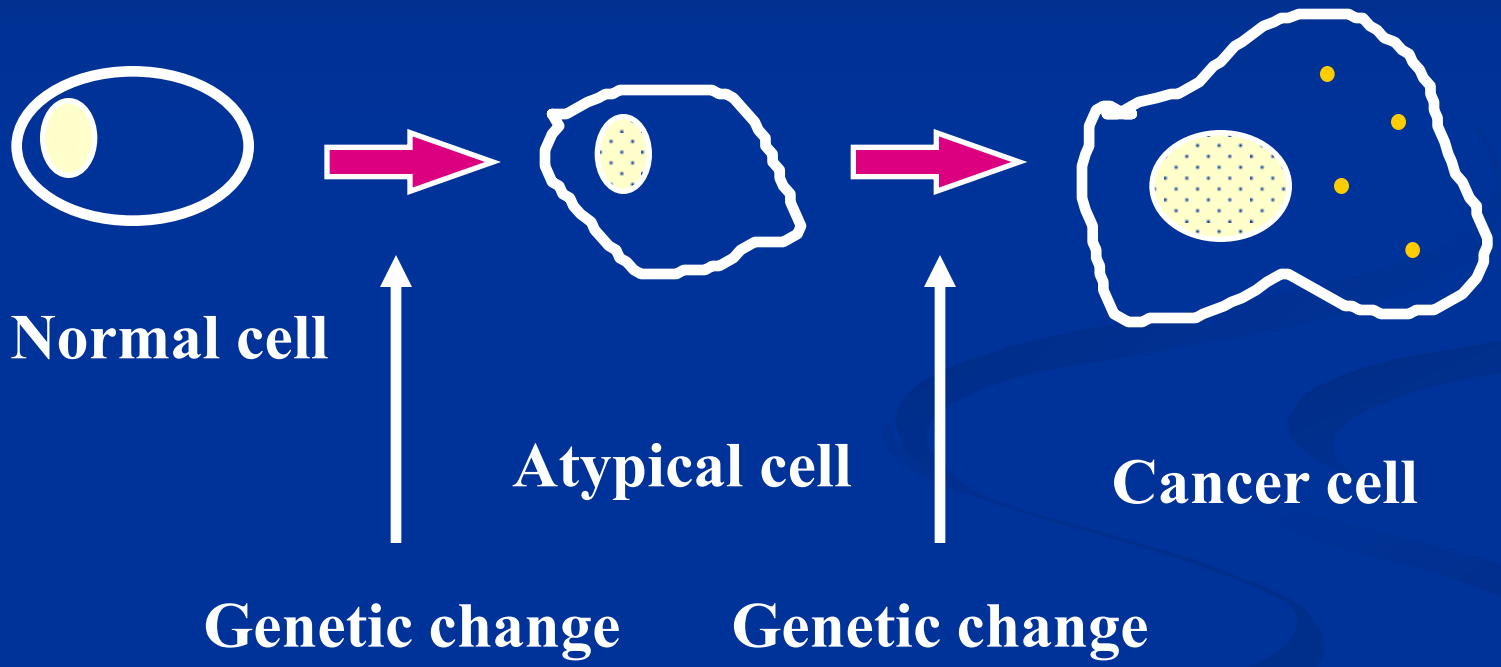
Organ Function, Age, Co-morbidities

Prognostic & Predictive Factors

Adjuvant Systemic Treatment of Early Stage Breast Cancer

- THE PAST (2000 NCI Consensus Development Conference on Adjuvant Breast Cancer)
  - *Chemotherapy should be offered to the majority of women with early stage breast cancer regardless of size, lymph node, menopausal or hormone receptor status*
- THE PRESENT AND FUTURE
  - Individualizing estimates of recurrence risk and chemotherapy benefit using genomic/molecular profiling
  - *Many patients **don't need** chemotherapy*

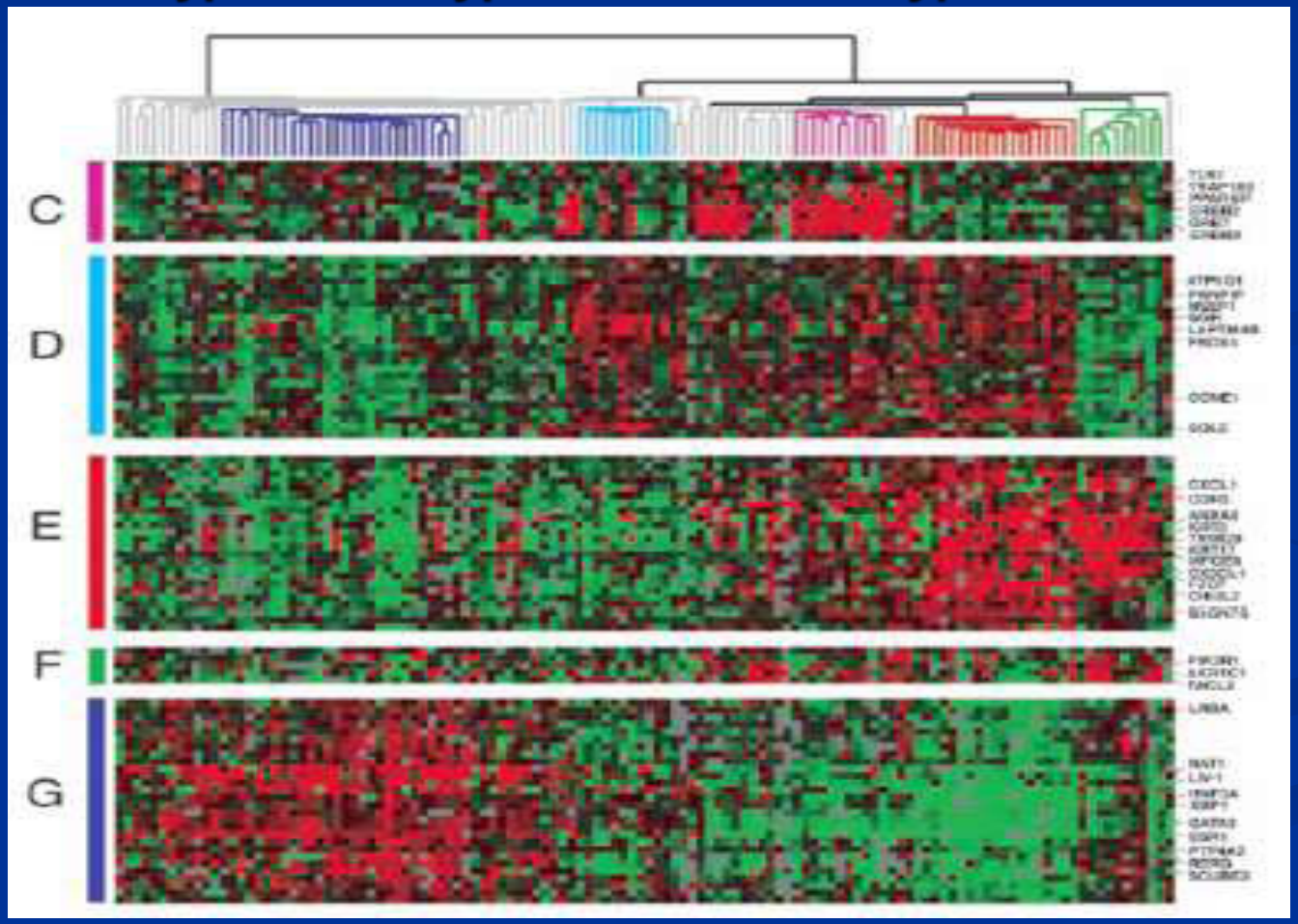
The Genomic Era: Understanding the Genetic Changes in Each Individual Tumor



Testing the acquired genetic makeup of the tumor can lead to more effective treatment strategies

Genomics of Breast Cancer: DNA Microarray and hierarchical clustering

Luminal Subtype A | Luminal Subtype B | HER-2+ | Basal Subtype | Normal Breast–like



Subtypes vary with respect to:

- Likelihood of recurrence
- Sites of metastases
- Response to treatment

Oncotype DX 21-Gene Recurrence Score (RS) Assay

16 Cancer and 5 Reference Genes From 3 Studies

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN
ER
PR
Bcl2
SCUBE2

GSTM1

BAG1

INVASION
Stromelysin 3
Cathepsin L2

CD68

HER2
GRB7
HER2

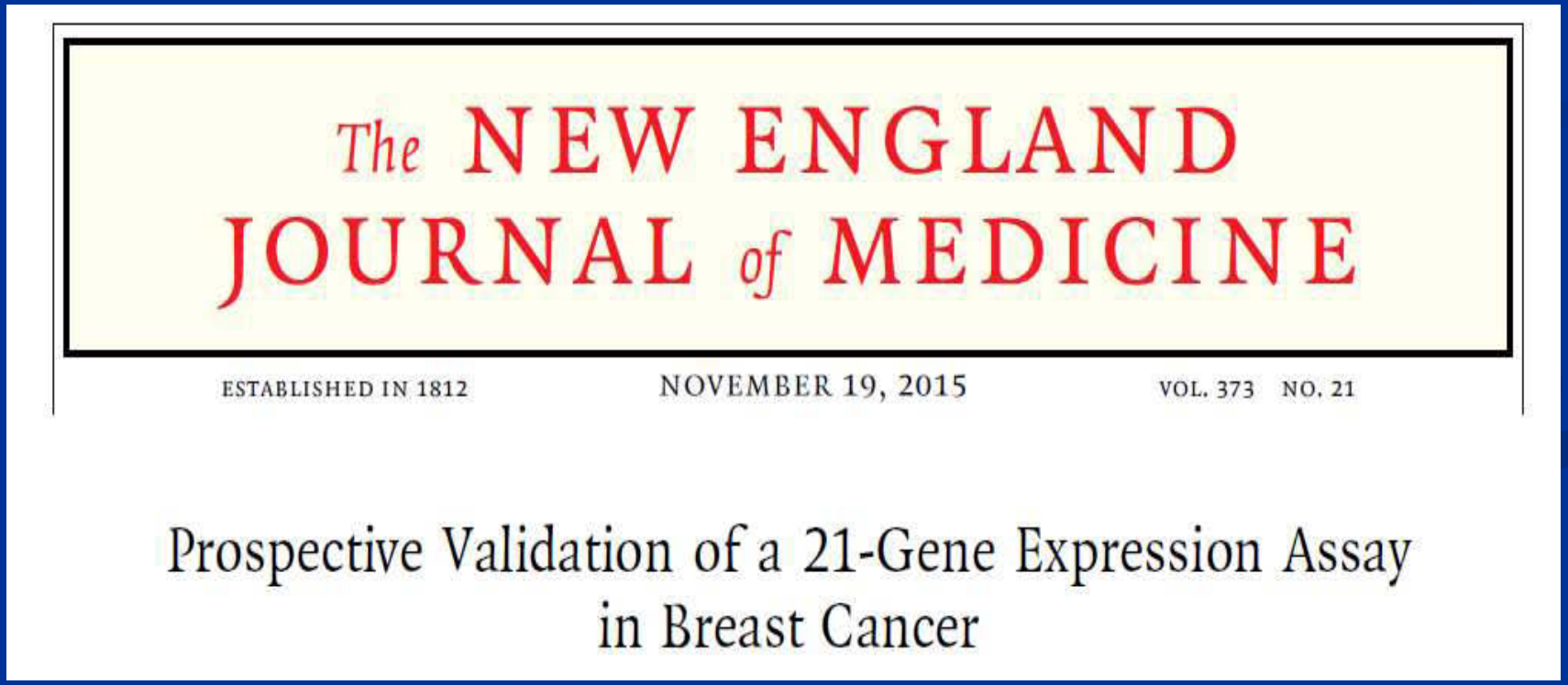
REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

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

Category	RS (0-100)
Low risk	RS <18
Int risk	RS ≥18 and <31
High risk	RS ≥31

Trial Assigning IndividuaLized Options for TReatment (TAILORx):

Phase III trial of chemoendocrine therapy versus endocrine therapy alone in hormone receptor-positive, HER2-negative, node-negative breast cancer and an intermediate prognosis 21-gene recurrence score



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

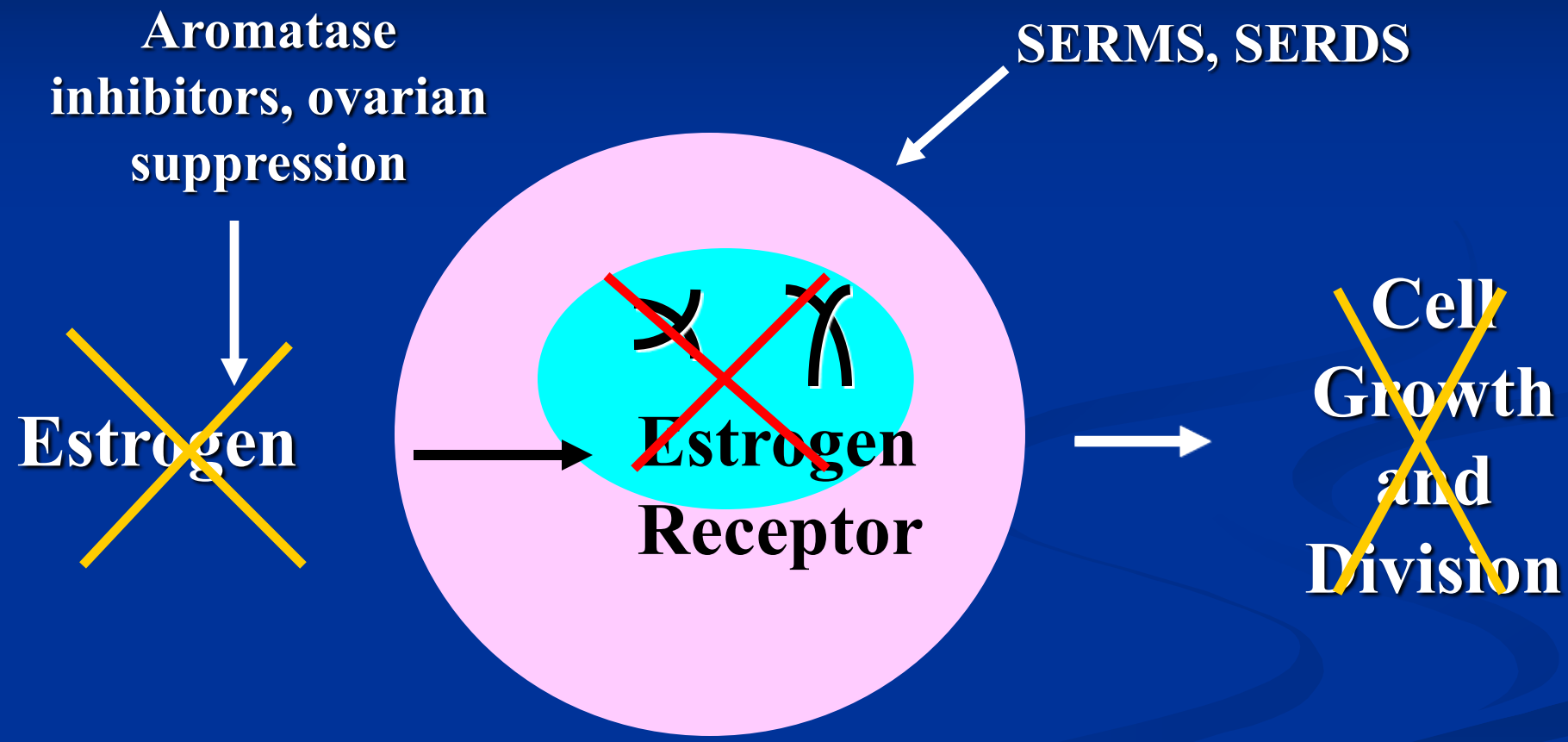
- TAILORx: 10,253 eligible women enrolled
- 1626 women (15.9%) had a recurrence score of 0 to 10
  - Assigned to receive Anti Estrogen therapy alone
- 5 Year Data
  - Freedom from recurrence of breast cancer at a distant or local–regional site: 98.7%
  - Freedom from recurrence of breast cancer at a distant site: 99.3%
  - Overall Survival: 98.0%

N Engl J Med 2015; 373:2005-2014

Adjuvant Endocrine Therapy in Early Breast Cancer

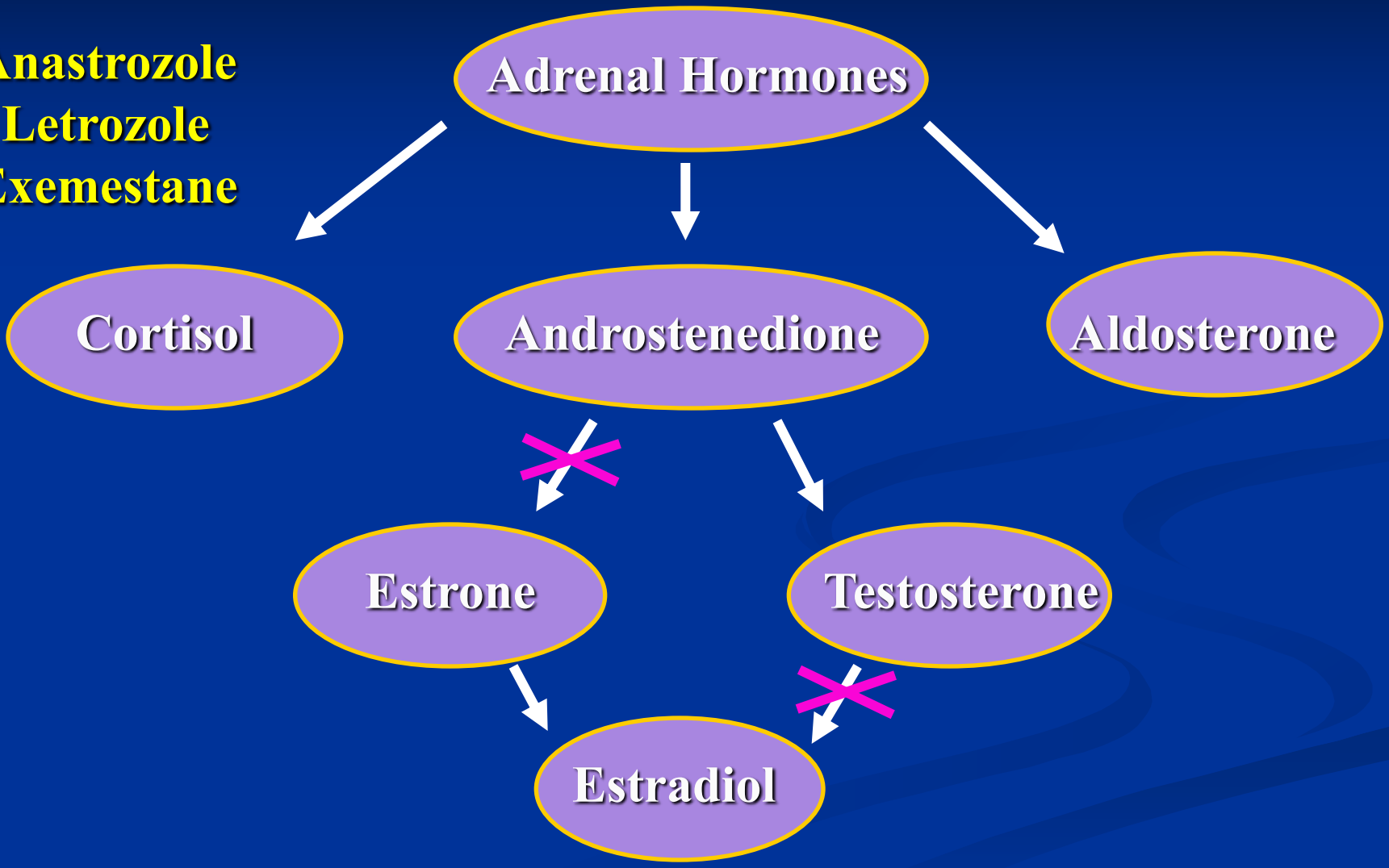
- Selective Estrogen Receptor Modulators
  - Tamoxifen
- Aromatase inhibitors (postmenopausal)
  - Anastrozole (ARIMIDEX)
  - Letrozole (FEMARA)
  - Exemestane (AROMASIN)
- Medical or surgical ovarian suppression in some premenopausal patients

Estrogen and Breast Cancer

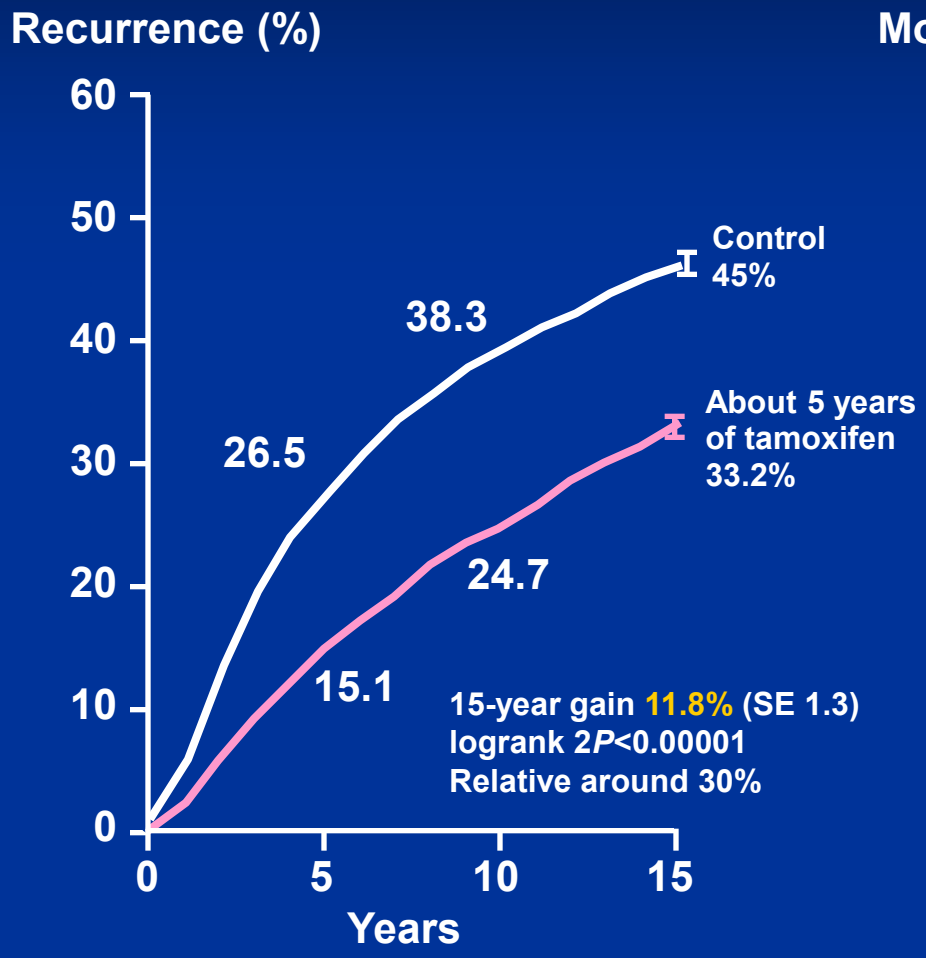


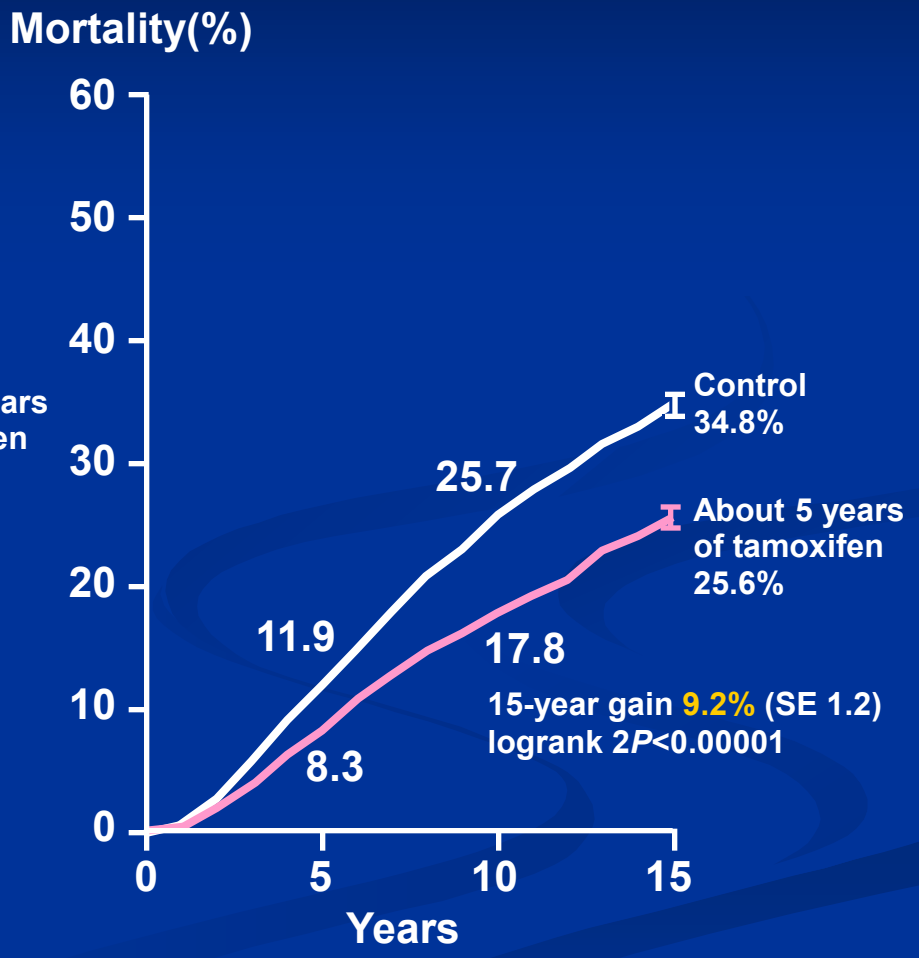
Aromatase Inhibitors

Anastrozole
Letrozole
Exemestane



Tamoxifen: Efficacy Data (15 Year)

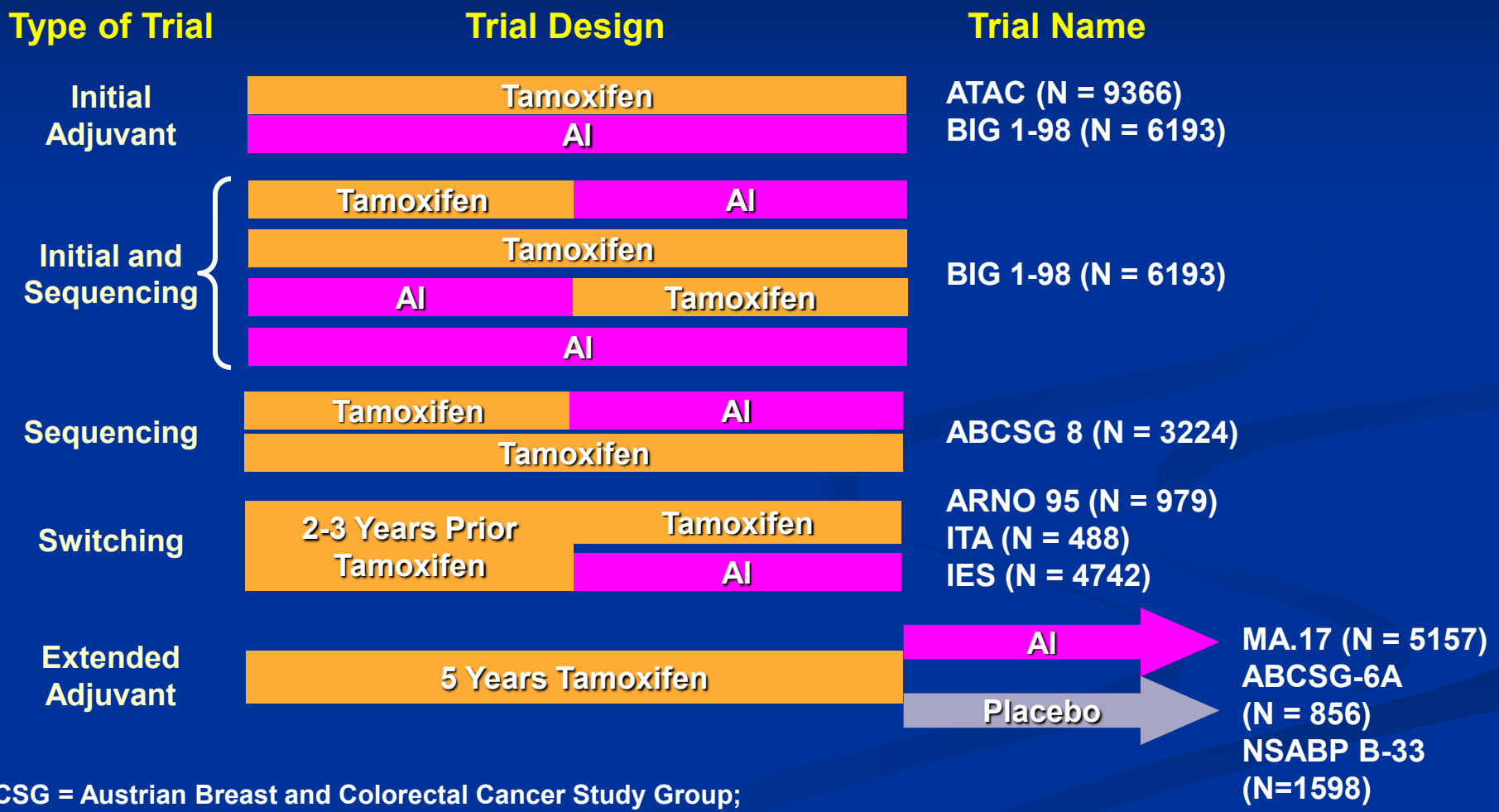




About 5 years of tamoxifen versus not in ER-positive (or ER-unknown) disease: 15-year probabilities of recurrence and of breast cancer mortality. 10,386 women: 20% ER-unknown, 30% node-positive. Error bars are ±1SE

Lancet 2005;365:1687-1717

Adjuvant Endocrine Therapy Trials



ABCSG = Austrian Breast and Colorectal Cancer Study Group; ARNO = Arimidex-Nolvadex; ATAC = Arimidex, Tamoxifen, Alone or in Combination; BIG = Breast International Group; IES = Intergroup Exemestane Study; ITA = Intergruppo Tamoxifen Anastrozole.

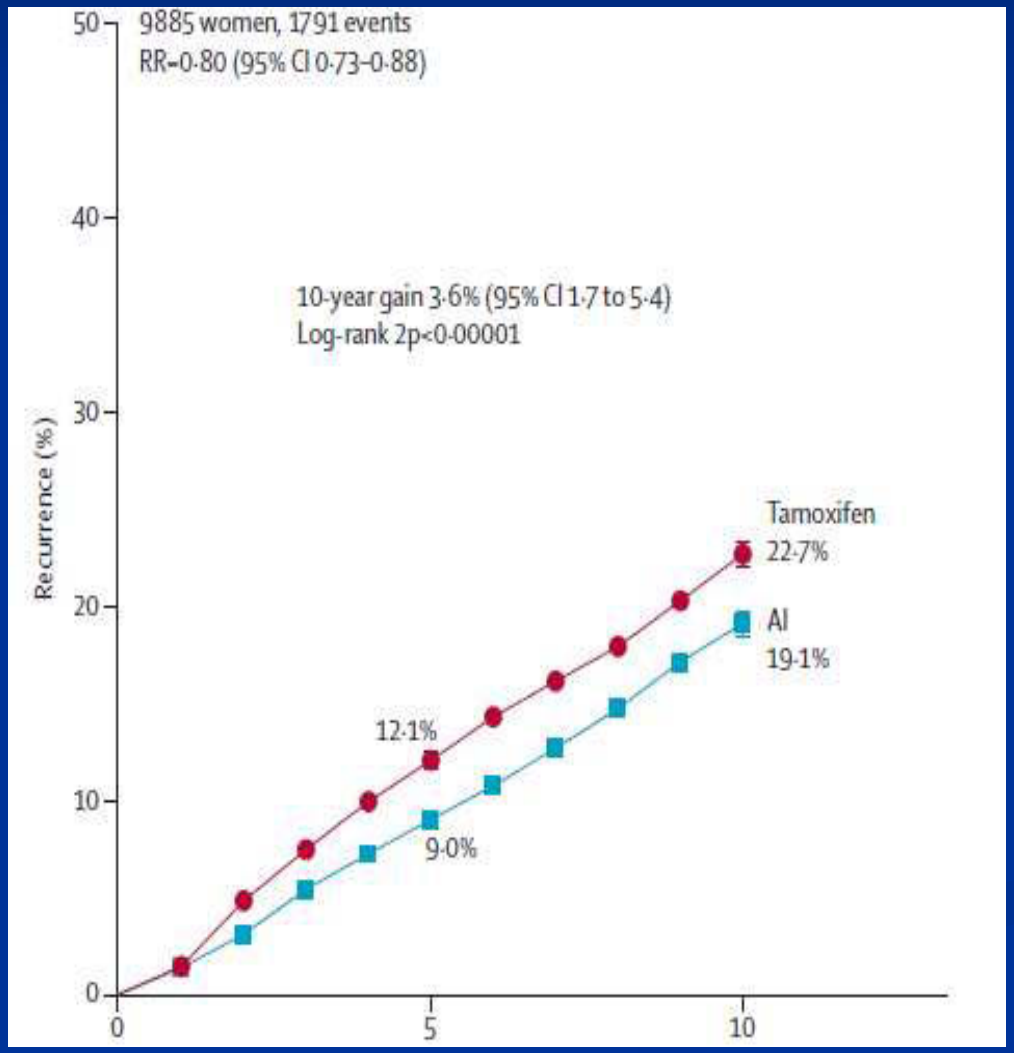
Upfront Use of Aromatase Inhibitors vs. Tamoxifen

ATAC Trial: 68 months follow-up:
17% relative reduction in events for A vs T
(3% absolute difference)
No difference in overall survival

BIG 1-98 Trial: 26 months follow-up:
19% relative reduction in events for L vs. T
(3% absolute difference)
No difference in overall survival

Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)** ***Lancet 2015, >31000 in complete analysis***



- 5 yr of AI's vs 5 yr of Tamoxifen
- Recurrence Risk Ratio favored AI's significantly in years 0-1, 2-4, and non significantly thereafter
- 10 yr Breast Cancer Mortality
  - 15% Proportional Improvement with AI's wrt Tamoxifen (12.1 vs 14.2%);
  - 40% proportional improvement wrt no Endocrine treatment

Absolute Improvements in Freedom from Distant Recurrence with Adjuvant Endocrine Therapies for Premenopausal Women with HR+ HER2-negative Breast Cancer: Results from TEXT and SOFT

Meredith M. Regan, Prudence A. Francis, Olivia Pagani, Gini F. Fleming, Barbara A. Walley, Giuseppe Viale, Marco Colleoni, István Láng, Henry L. Gómez, Carlo Tondini, Graziella Pinotti, Angelo Di Leo, Alan S. Coates, Aron Goldhirsch, Richard D. Gelber, for the SOFT and TEXT Investigators and International Breast Cancer Study Group

2018 ASCO ANNUAL MEETING
#ASCO18

IBCSG
INTERNATIONAL BREAST CANCER STUDY GROUP
Presented By Meredith Regan

SOFT and TEXT Designs

Enrolled: Nov03 - Apr11

- Premenopausal HR+
- ≤12 wks after surgery
- Planned OFS
- No planned chemo (40%)
  OR planned chemo (60%)

RANDOMIZE

TEXT (n=2672)

→ **Tamoxifen+OFS x 5y**

→ **Exemestane+OFS x 5y**

Current Follow-up

Median follow-up 9 years

- Premenopausal HR+
- ≤12 wks after surgery
- No chemo (47%)

OR

- Remain premenopausal ≤ 8 mos after chemo (53%)

RANDOMIZE

SOFT (n=3066)

→ **Tamoxifen x 5y**

→ **Tamoxifen+OFS x 5y**

→ **Exemestane+OFS x 5y**

Median follow-up 8 years

OFS=ovarian function suppression

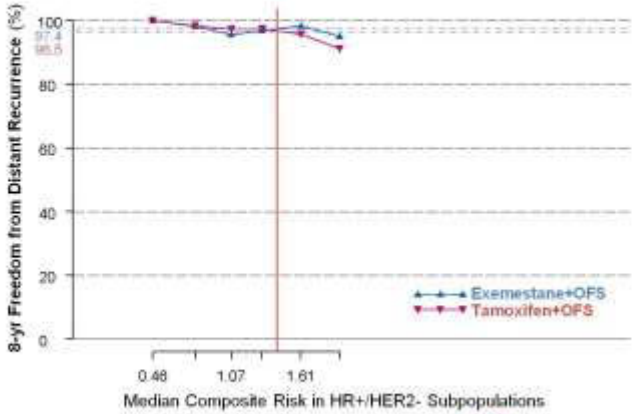
Characteristics by Cohort (HR+/HER2-)

		TEXT		SOFT	
Chemo-therapy	N=1276	Age<40	30%	N=1271	Age<40	49%
		LN+	69%		LN+	58%
		T-size>2cm	52%		T-size>2cm	46%
		PgR<50%	23%		PgR<50%	38%
		Grade 3	30%		Grade 3	28%
		Ki-67≥20%	42%		Ki-67≥20%	35%
No Chemo-therapy	N=991	Age<40	16%	N=1353	Age<40	9%
		LN+	21%		LN+	9%
		T-size>2cm	20%		T-size>2cm	13%
		PgR<50%	13%		PgR<50%	9%
		Grade 3	15%		Grade 3	9%
		Ki-67≥20%	27%		Ki-67≥20%	19%

Composite Risk and STEPP Analysis

- Combined standard clinico-pathologic features into a single value for each patient – a continuous, composite measure of recurrence risk "composite risk" *(Regan et al, JCO 2016)*
  - age (5-yr groups), nodal status (0, 1-3, ≥4), T size (≤2, >2 cm),
  - ER (<50%, ≥50%), PgR (<20%, 20-49%, ≥50%), tumor grade, Ki-67 (<14%, 14-19%, 20-25%, ≥26%) *[centrally-assessed]*
- Determined "composite risk" from a Cox model for DRFI
  - stratified by 4 cohorts and treatment assignment
- Analyzed by Subpopulation Treatment Effect Pattern Plot (STEPP)

STEPP of 8-yr Freedom from Distant Recurrence: TEXT No Chemotherapy

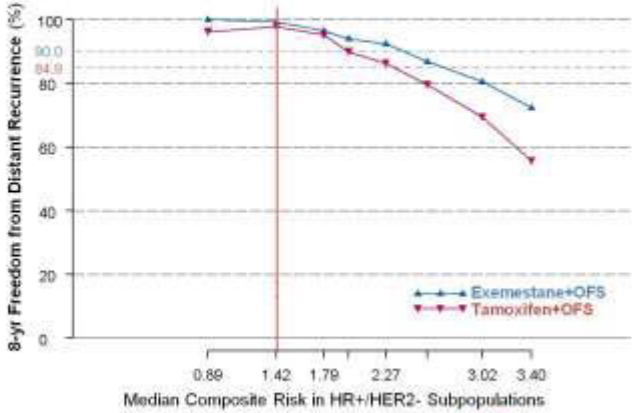


In the cohort, 8-yr %:
97.4% E+OFS
96.5% T+OFS

<1% E+OFS vs T+OFS, avg. improvement

Improvement ranged **2.5%** to **4%** at higher composite risks above overall median

STEPP of 8-yr Freedom from Distant Recurrence: TEXT Chemotherapy

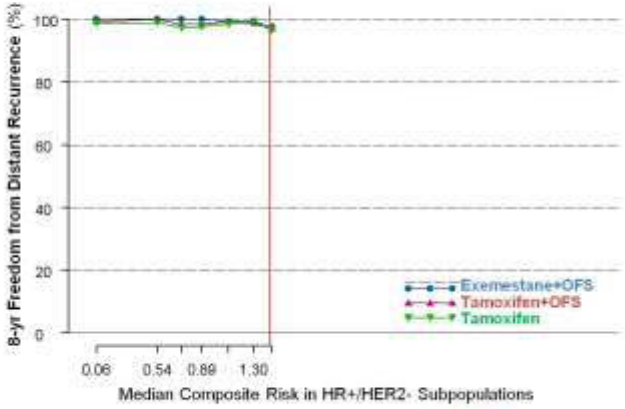


In the cohort, 8-yr %:
90.0% E+OFS
84.9% T+OFS

5.1% E+OFS vs T+OFS, avg. improvement

Improvement increases with increasing composite risk, to **15%** at highest composite risks

STEPP of 8-yr Freedom from Distant Recurrence: SOFT No Chemotherapy

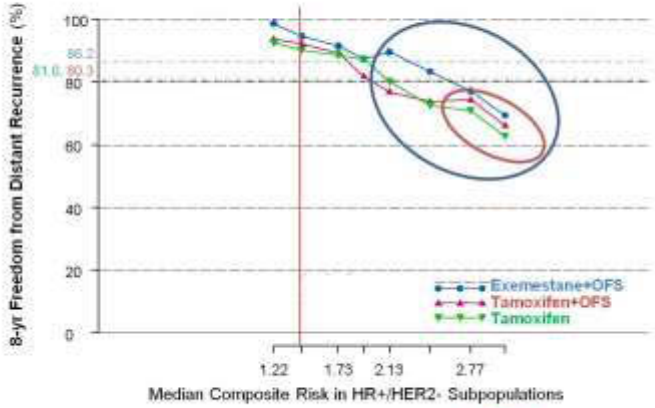


In the cohort, 8-yr %:
99.3% E+OFS
98.3% T+OFS
98.0% T

1.3% E+OFS vs T, avg. improvement ranged **1** to **2.5%**

<1% avg. improvement T+OFS vs T

STEPP of 8-yr Freedom from Distant Recurrence: SOFT Prior Chemotherapy



In the cohort, 8-yr %:
86.2% E+OFS
80.3% T+OFS
81.0% T

5.2% E+OFS vs T, avg. improvement, max **10%** for higher composite risks

T+OFS vs T, max **3.5%** at highest composite risks

Conclusions

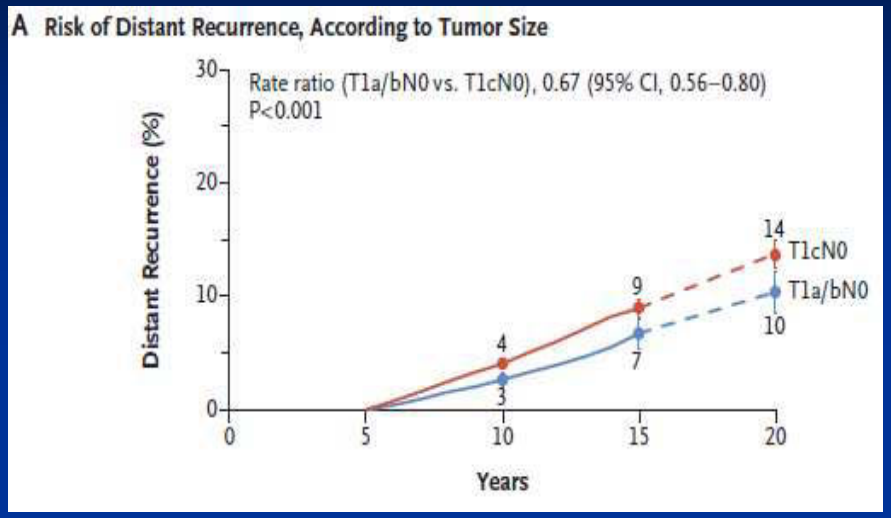
Among premenopausal women in SOFT & TEXT with HR+/HER2- cancers, magnitude of absolute improvement in 8-yr freedom from distant recurrence varied widely according to *risk of recurrence*:

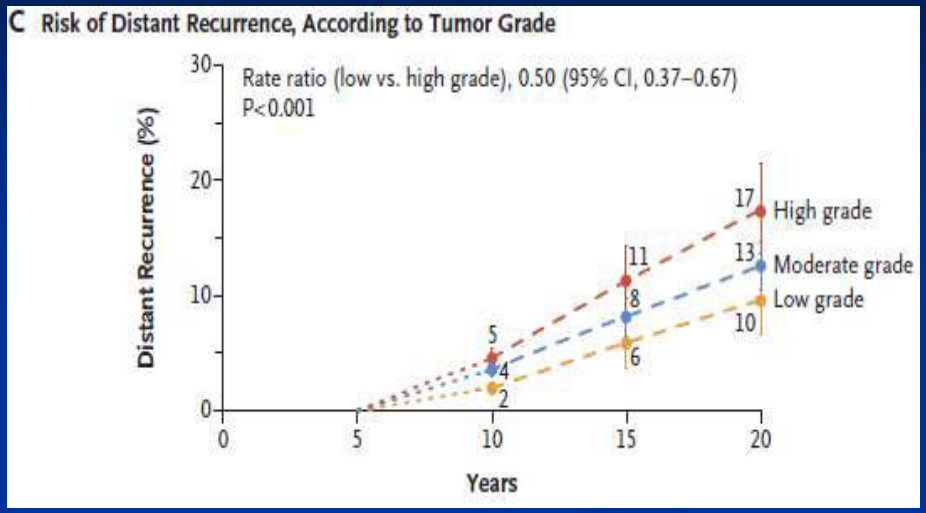
- Those at higher risk may experience 10-15% improvement with E+OFS vs T+OFS or T alone
- Improvement with E+OFS may be 4-5% for patients at intermediate risk, most of whom also received chemotherapy
- For those at low risk, potential benefit of escalating endocrine therapy from T-alone may be minimal, as >97% of these women were without distant recurrence at 8 years

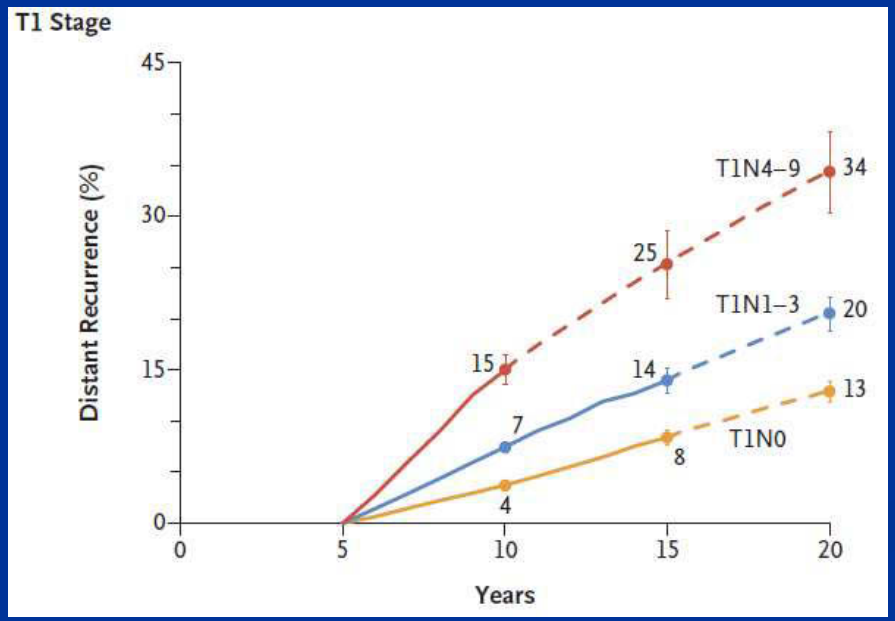
Extending Duration of Therapy

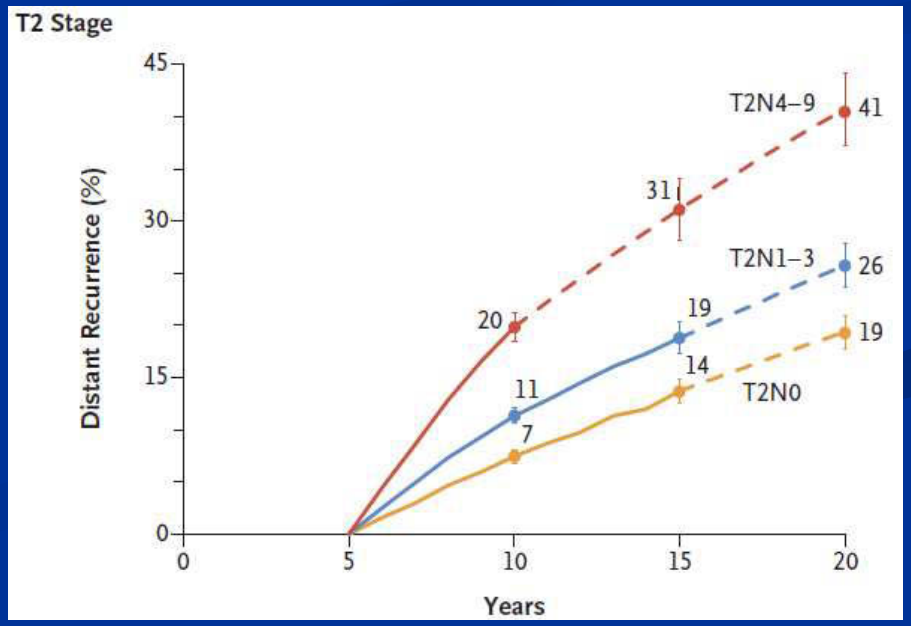
- Meta-analysis, 88 trials, 62,923 patients, ER positive
- Patients that are disease free at 5 years

Extending Duration of Therapy





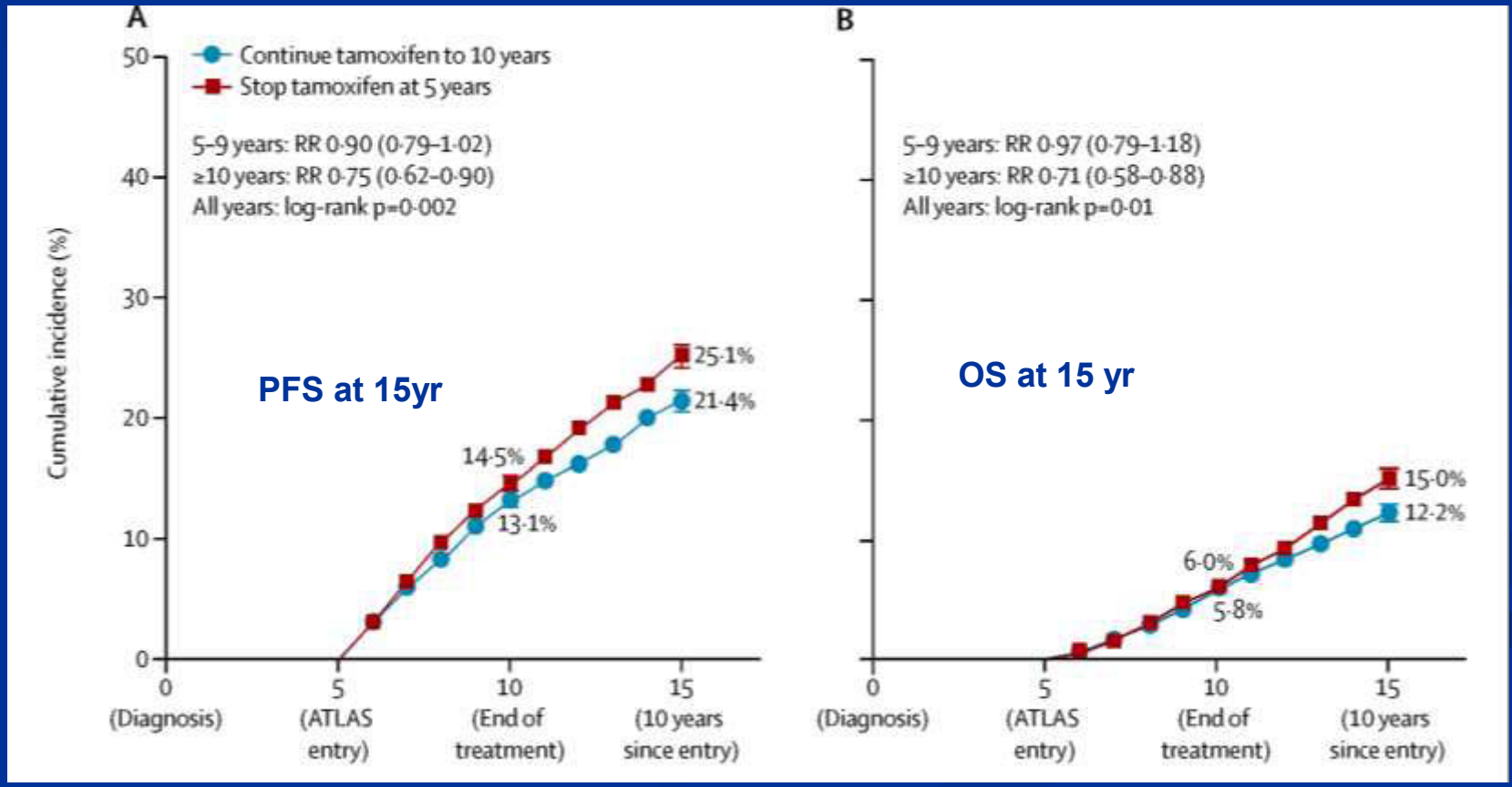




Extending Duration of Endocrine Therapy

ATLAS Trial (Adjuvant **T**amoxifen, **L**onger **A**gainst **S**horter)

5 vs 10 year of Tamoxifen, 6846 patients, ER positive



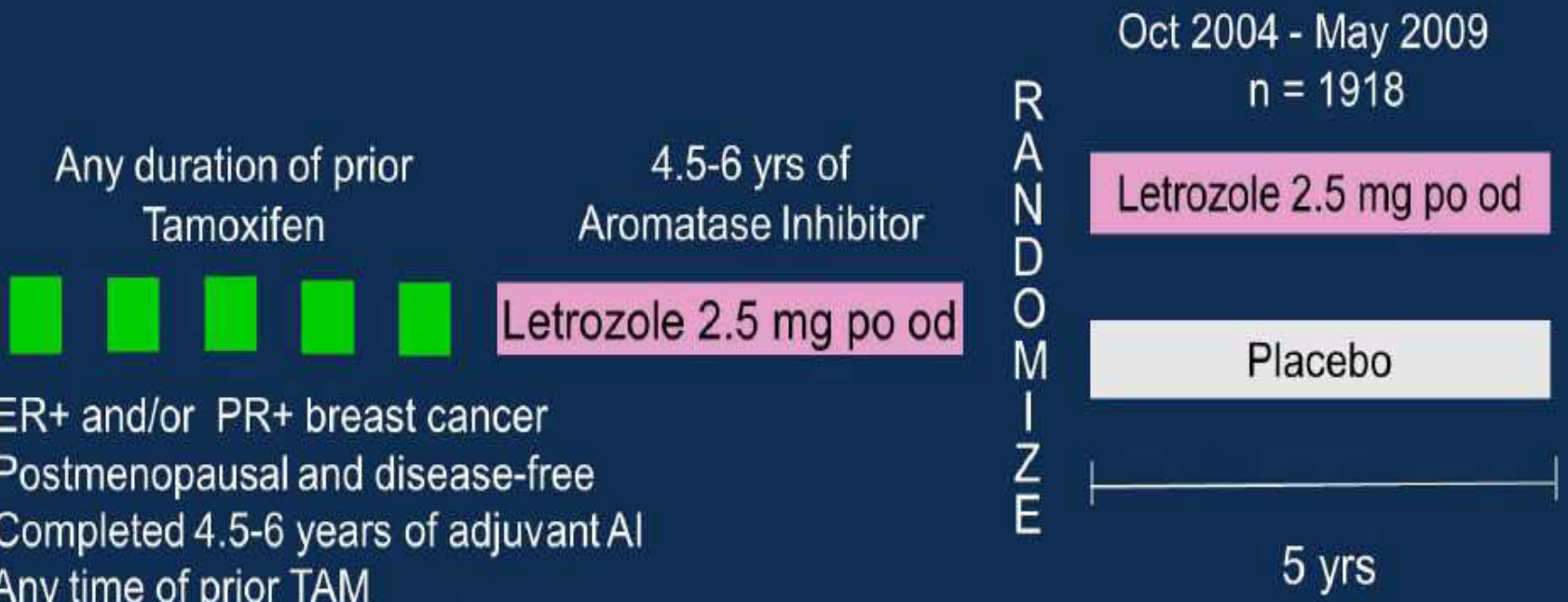
Extending Duration of Endocrine Therapy

aTTom Trial (adjuvant **T**amoxifen **T**reatment **o**ffers **m**ore)

- 5 yr versus 10 years of Tamoxifen, 6,953 patients
- Time dependent improvement in recurrence and breast cancer related mortality
  - RR 0.75 for PFS after year 9
  - RR 0.86 for Breast Cancer related mortality after year 9
- At Year 15
  - Absolute reduction of recurrence was 4%
  - Absolute reduction of breast cancer mortality was 2%

MA.17R Trial Schema and Design

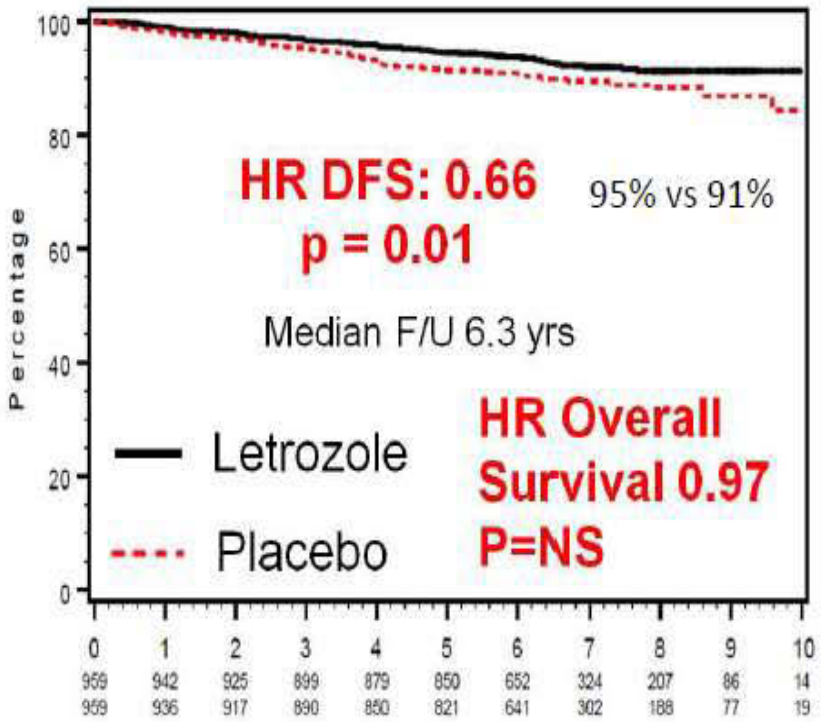
AI x 5 yrs - Following Prior 5 years of AI - preceded or not by Tamoxifen



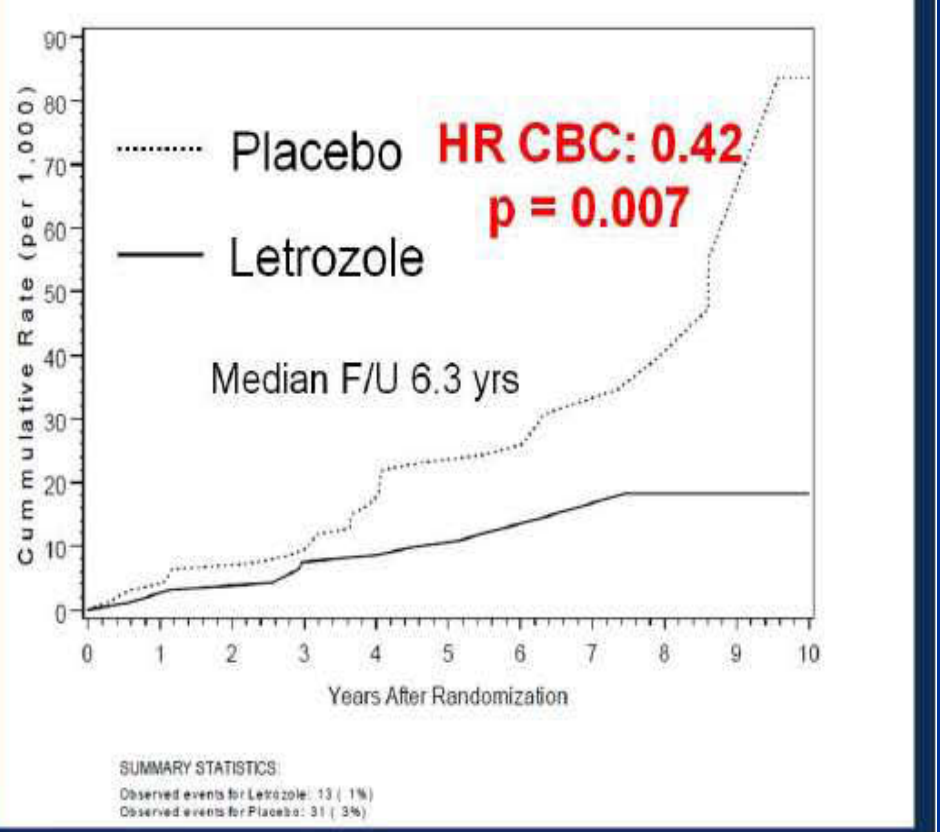
- ER+ and/or PR+ breast cancer
- Postmenopausal and disease-free
- Completed 4.5-6 years of adjuvant AI
- Any time of prior TAM
- Minimum life expectancy ≥5 years (no exclusion for age alone)

MA.17R – Improved Outcomes with Letrozole for 10 Years over 5 years

Disease-Free Survival



Contralateral Breast Cancer



Extending Duration of Endocrine Therapy

- **NSABP B42 (SABCS 2016)**
  - 5 vs 10 years of AI
  - No improvement in OS
  - 28% reduction in cumulative risk of disease recurrence
  - 29% reduction in recurrence/new cancer in opposite breast
- **ABCSG 16 (SABCS 2017)**
  - 7 vs 10 year of AI (2 vs 5 after initial 5 years)
  - 3,484 postmenopausal women
  - At 6/2016 cutoff, DFS was 78% in both arms
  - No Difference in OS, contralateral new breast cancer

Extending Duration of Endocrine Therapy

Extend AI therapy beyond 5 yrs

- Good initial tolerance to AI
- Excellent bone health
- Young age
- Higher risk disease by clinical/pathologic features, including high grade, node positive
- Higher risk by genomic testing
- Patient preferences

Stop AI therapy at 5 yrs

- Difficult tolerance to AI's (i.e. poor bone health, musculoskeletal symptoms)
- Lower risk by clinical/pathologic features
- Lower risk by genomic testing
- Patient preferences

Side Effects-Tamoxifen

- Most people do not experience all of the side effects listed
- Often predictable in terms of their onset and duration
- Almost always reversible and go away after treatment is stopped
- Multiple options to help minimize or prevent side effects
- No relationship between the presence or severity of side effects and the effectiveness of the medication

Side Effects-Tamoxifen

- Hot flashes
- Swelling (fluid retention in feet, ankles, or hands)
- Loss of libido
- Nausea
- Menstrual irregularities
- Vaginal bleeding
- Weight Gain (esp younger patients)
- Mood changes (anxiety and/or depression)

Side Effects-Tamoxifen

- Rare but Serious
  - Blood Clots (Deep Venous Thrombosis and Pulmonary Embolus)
  - Development of Uterine cancer
    - Uterine cancer related mortality 1.1% (10yr group) vs 0.6% (5 yr group)
    - Every endometrial cancer death that occurs as a side effect of long-term tamoxifen, 30 deaths from breast cancer are prevented

Side Effects-AI's

- Hot Flashes
- Muscle/Joint pain
- Decreased energy
- Mood disturbances, Depression and Insomnia (Trouble sleeping)
- Osteoporosis (Weak bones) and Fractures
- Vaginal Dryness

Side Effects-AI's

- Rash
- Headache
- Peripheral edema and lymphedema (fluid build-up)
- Dyspnea (difficulty breathing)
- Increased cough
- High blood pressure
- Stomach upset, Sore throat, Cough
- Nausea and Vomiting
- Cardiovascular Events

Side Effects-AI's

- 3 options (Anastrozole, Letrozole, Exemestane)
- Stopping and Switching first option
  - Same S/E on Paper—individual response and tolerance of a drug for one person is VERY different from another person

Integrative Oncology and S/E

- Use of complementary and integrative therapies in collaboration with conventional oncology care
- Complementary therapies include
  - meditation
  - yoga
  - natural products
- Society for Integrative Oncology (SIO) Guidelines now Endorsed by ASCO also
  - Concern when complementary therapy is not disclosed or used instead of conventional effective therapies

CA CANCER J CLIN 2017;67:194–232

Clinical Practice Guidelines on the Evidence-Based Use of Integrative Therapies During and After Breast Cancer Treatment

Heather Greenlee, ND, PhD, MPH[1,2]; Melissa J. DuPont-Reyes, MPH, MPhil[3]; Lynda G. Balneaves, RN, PhD[4]; Linda E. Carlson, PhD[5]; Misha R. Cohen, OMD, LAc[6,7]; Gary Deng, MD, PhD[8]; Jillian A. Johnson, PhD[9]; Matthew Mumber, MD[10]; Dugald Seely, ND, MSc[11,12]; Suzanna M. Zick, ND, MPH[13,14]; Lindsay M. Boyce, MLIS[15]; Debu Tripathy, MD[16]

CA
A Cancer Journal for Clinicians

Society for Integrative Oncology Recommendations

- Anxiety/Stress Reduction: Music therapy, meditation, stress management, and yoga
- Depression/mood disorders: Meditation, relaxation, yoga, massage, and music therapy
- QOL: Meditation and yoga
- CINV: Acupressure and acupuncture

  - Lack of strong evidence for the use of ingested dietary supplements to manage breast cancer treatment-related adverse effects

Acupuncture

- Meta-analysis of Five trials involving 181 patients
  - Breast. 2017 Jun;33:132-138

- Significant pain reduction was observed after 6-8 weeks of acupuncture treatment
  - Significant decrease in the BPI worst pain score and WOMAC Index

Additional Options to help with S/E

- Bone Loss
  - Exercise, Calcium/ Vit D
  - Prolia or Bisphophate
- Hot Flashes
  - SSRI for Hot Flashes
  - Relizen (64 patient trial)
  - Black Cohosh

Additional Options to help with S/E

- Arthalgias
  - Exercise (J Clin Oncol. 2015 Apr 1; 33(10): 1104–1111)
    - Improvement in Worst pain, Pain severity and interference
  - Vitamin D (data not conclusive but tried anyway)
  - Glucosamine with chondroitin (https://www.ncbi.nlm.nih.gov/pubmed/23111941)

Conclusions

- Antiestrogen therapy is the cornerstone of systemic therapy for ER/PR positive breast carcinoma
- Significant effect on improving disease relapse/recurrence and Overall Survival
- Late relapses remain a challenge in this disease subset; longer duration of antiestrogen therapy and upfront use of AI's may be beneficial in the correct patient subset
- All drugs have their side effects that need to be balance against the absolute benefit
- Pharmaceutical and Non pharmaceutical options are available to improve tolerability to these drugs
  - extremely important to focus on QOL given extended duration use recommendation for these drugs

Thank you!