

Hormonal Therapies to Reduce Breast Cancer Recurrence

14th Annual Breast Cancer Update
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Let's start with a patient...

- Ms. L is a 60 year old female found to have an abnormal screening mammogram
- Subsequent biopsy confirmed invasive ductal right breast cancer
- No obvious evidence of regional or distant spread
- Underwent a right breast lumpectomy & axillary sentinel lymph node evaluation
- Findings
 - 2.5 cm tumor, ER+, PR+, her2/neu unamplified, with two axillary nodes negative for cancer

Ms. L

- After meeting with her breast surgeon & medical oncologist, informed of:
 - Stage IIA disease
 - Recommendation for ‘adjuvant’ therapy
 - Chemotherapy- YES
 - Radiation- YES
 - Hormonal therapy- YES
- After successful completion of chemo & radiation, she has many questions regarding hormonal therapy

Today's Agenda

- Breast cancer; reviewing the basics
- Hormonal therapy- A historical perspective
- Adjuvant hormonal therapy in 2011- Standard of care
- Toxicities from hormonal therapy
- Future areas of research

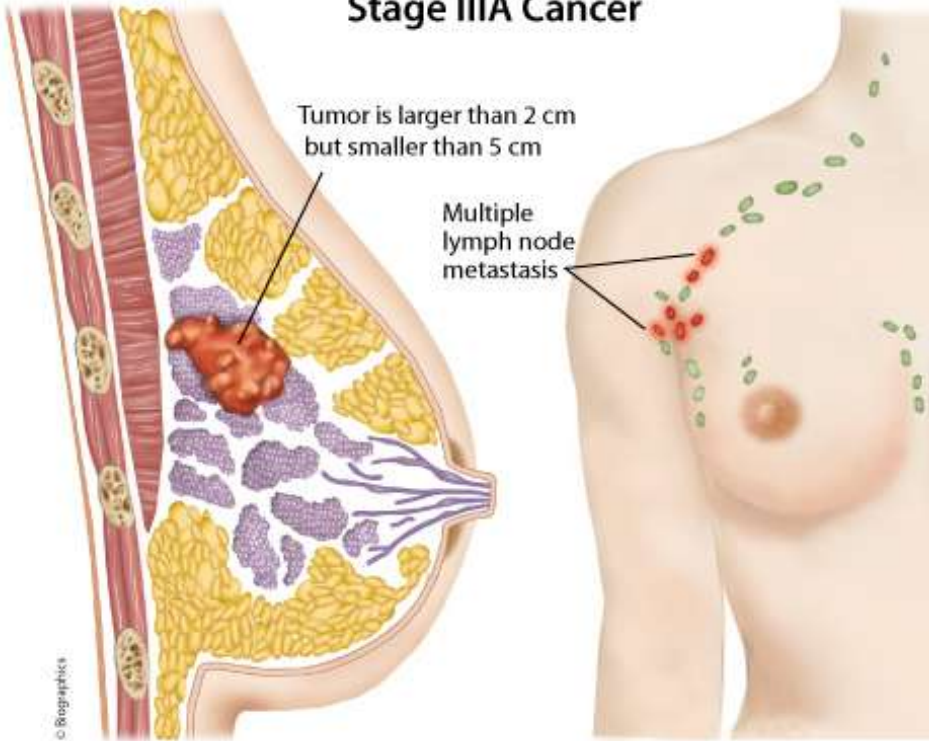
Breast Cancer: Staging

Breast Cancer: Staging

Stage IIIA Cancer

Tumor is larger than 2 cm but smaller than 5 cm

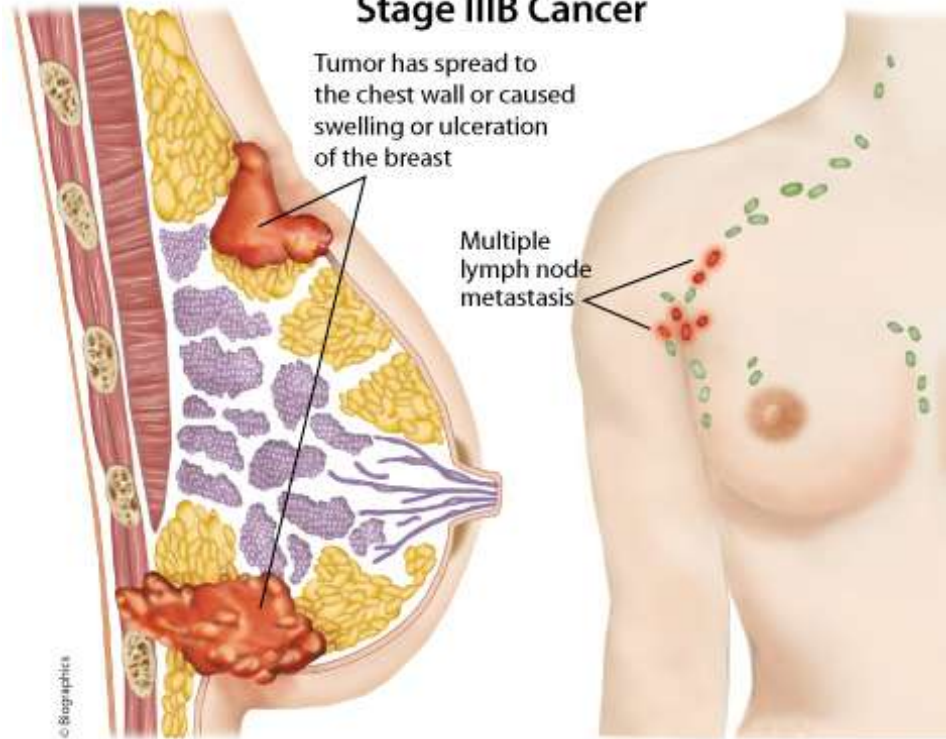
Multiple lymph node metastasis



Stage IIIB Cancer

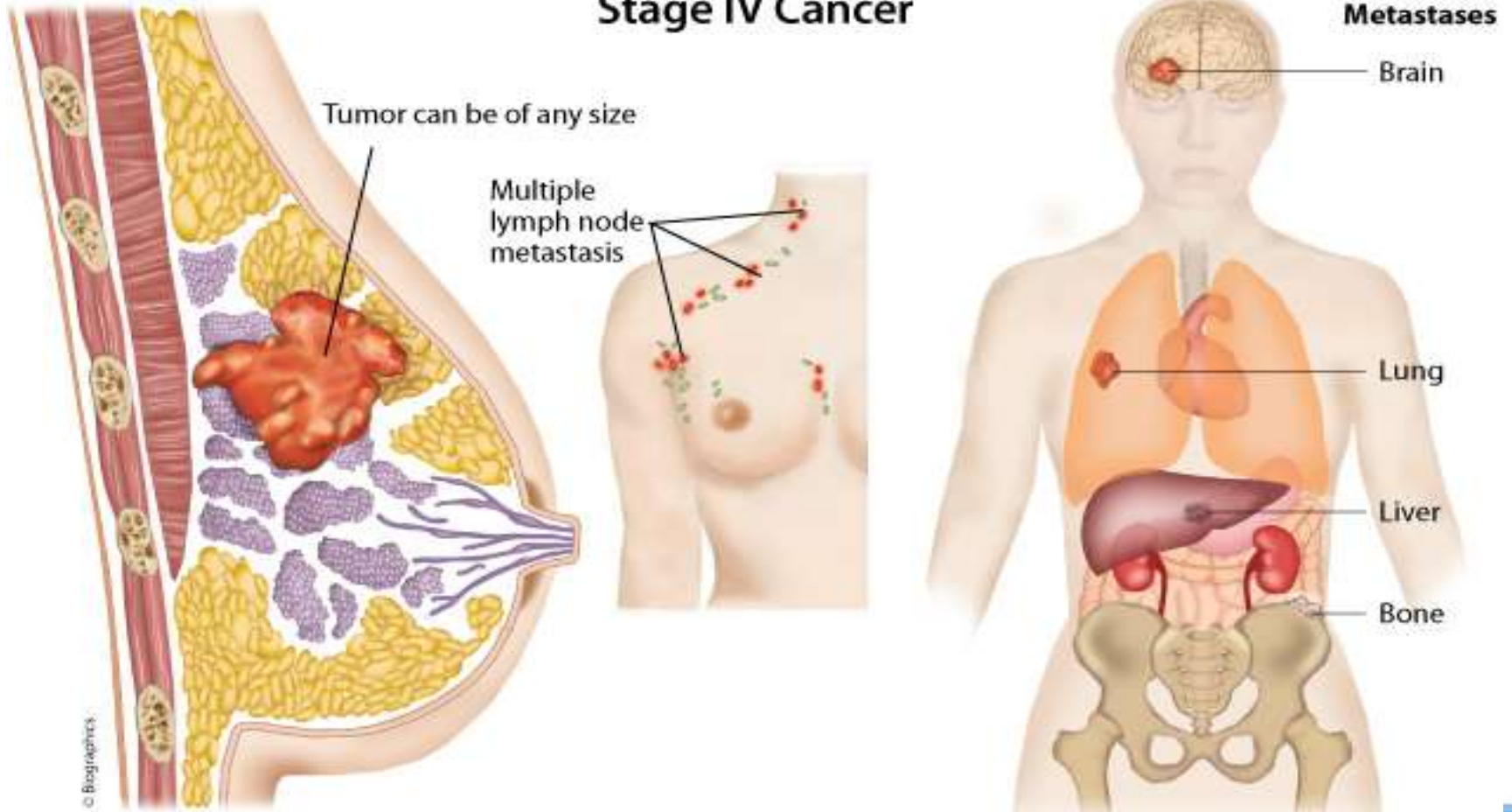
Tumor has spread to the chest wall or caused swelling or ulceration of the breast

Multiple lymph node metastasis

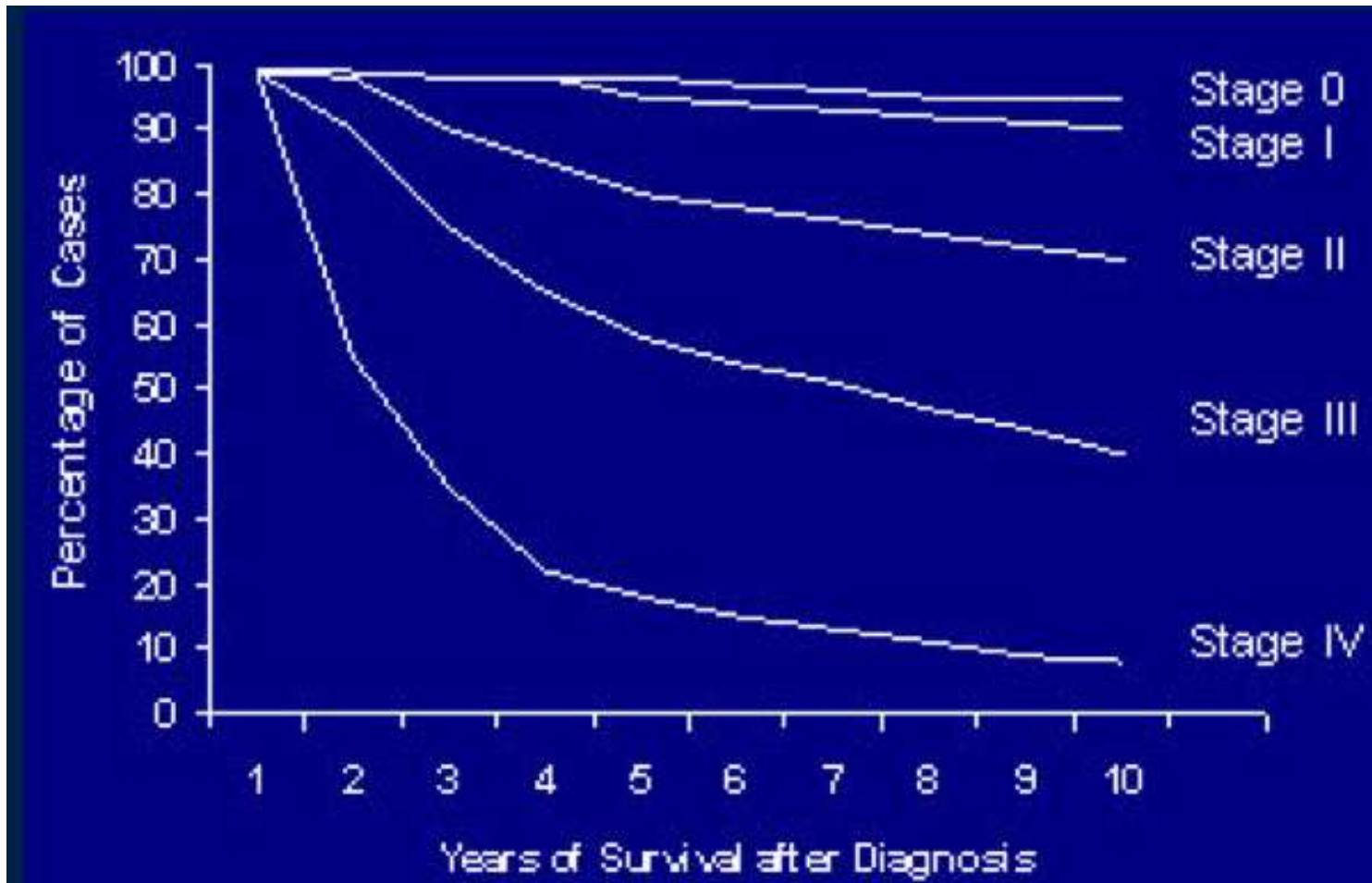


Breast Cancer: Staging

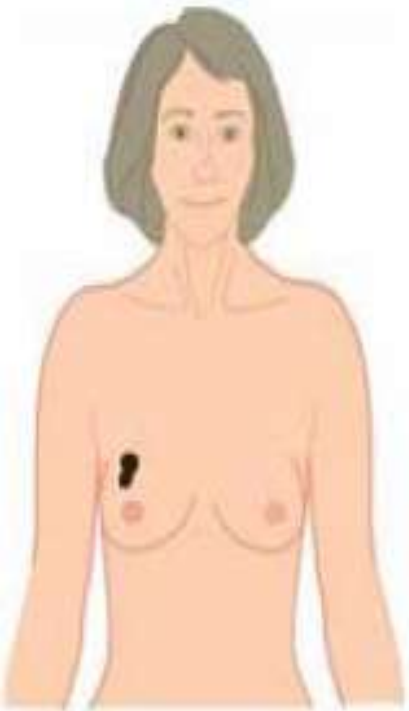
Stage IV Cancer



Effect of Stage on Survival



Micrometastasis



Prognostic Factors: Clinical

- Tumor size
- Tumor histologic factors
 - Grade
 - Lymphovascular invasion
- Axillary lymph node status
- Stage
- Hormone receptor status
- Patient age
- Risk calculators

Adjuvant! Online

Decision making tools for health care professionals

Adjuvant! for Breast Cancer (Version 8.0)

Patient Information

Age:

Comorbidity:

ER Status:

Tumor Grade:

Tumor Size:

Positive Nodes:

Calculate For:

10 Year Risk:

Adjuvant Therapy Effectiveness

Horm:

Chemo:

Hormonal Therapy:

Chemotherapy:

Combined Therapy:

No additional therapy:



59.2 alive in 10 years.
33.7 die of cancer.
7.1 die of other causes.

With hormonal therapy: Benefit = 9.0 alive.



With chemotherapy: Benefit = 11.4 alive.

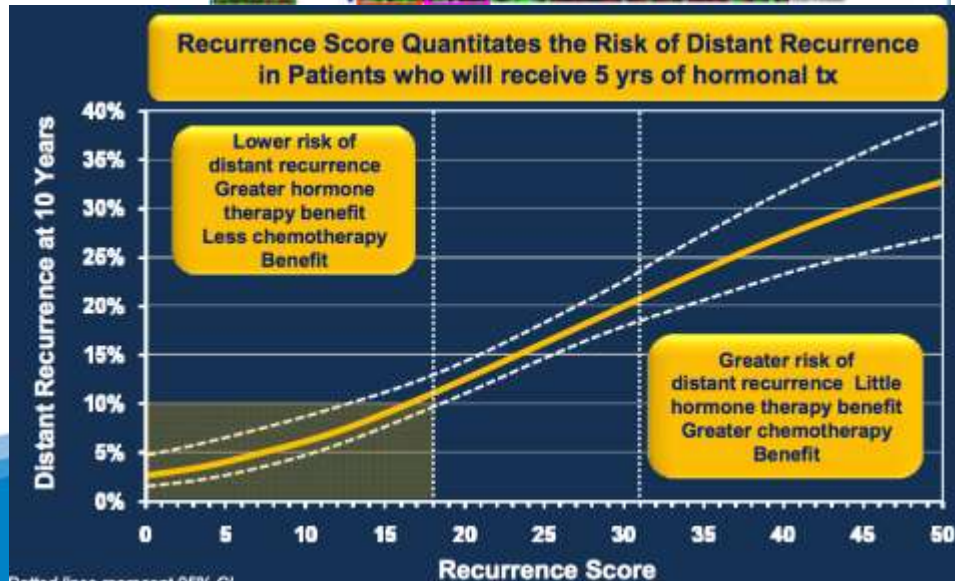
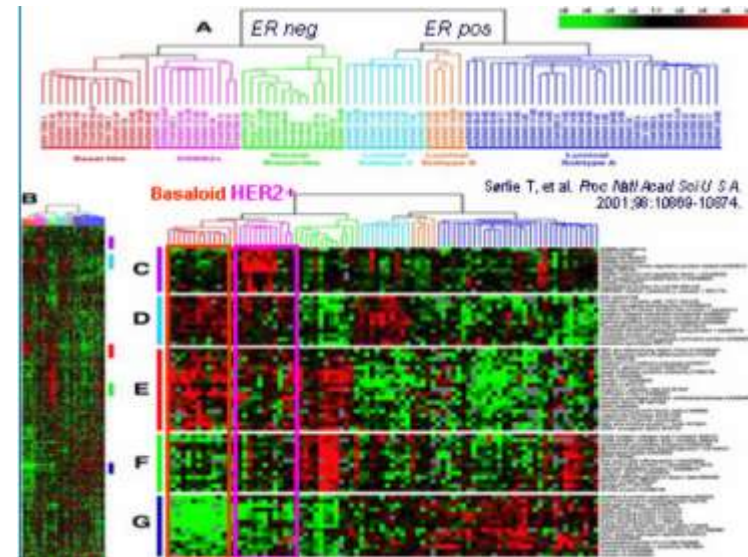


With combined therapy: Benefit = 17.5 alive.

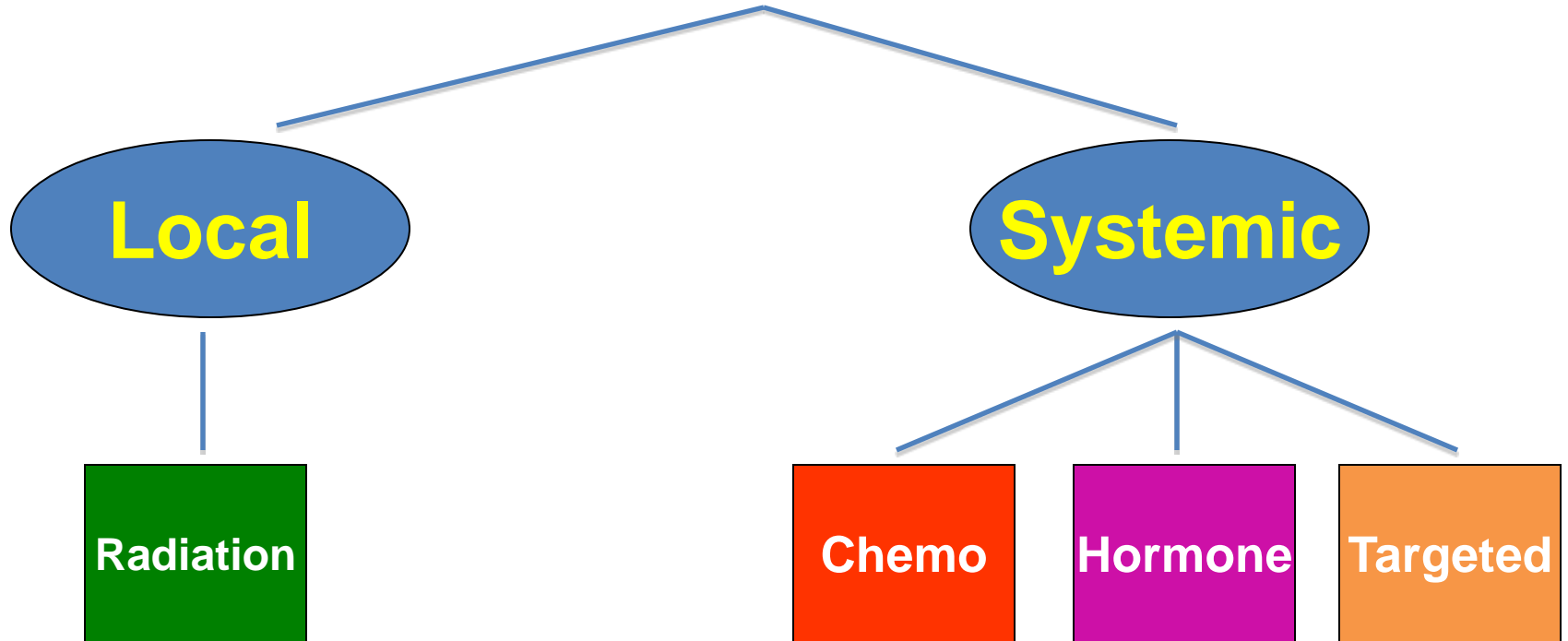


Prognostic Factors: Molecular Oncotype Dx

- Assess biology of your specific tumor
 - 21 breast cancer associated genes within the tumor sample
- Prognostic- estimates likelihood of future cancer relapse
- Predictive- estimates degree of benefit from adjuvant *chemotherapy*
- Indicated for early stage, LN negative, ER positive tumors



Adjuvant Therapy



Timing of Hormonal Therapy

S
U
R
G
E
R
Y

CHEMO

XRT

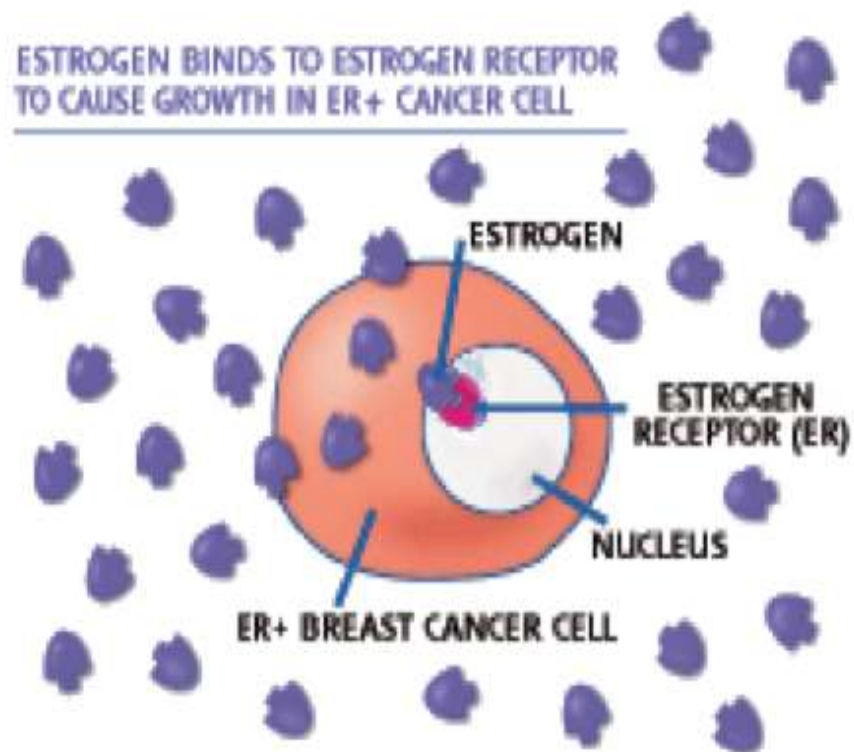
HORMONAL

A Historical Perspective

Hormonal Therapy

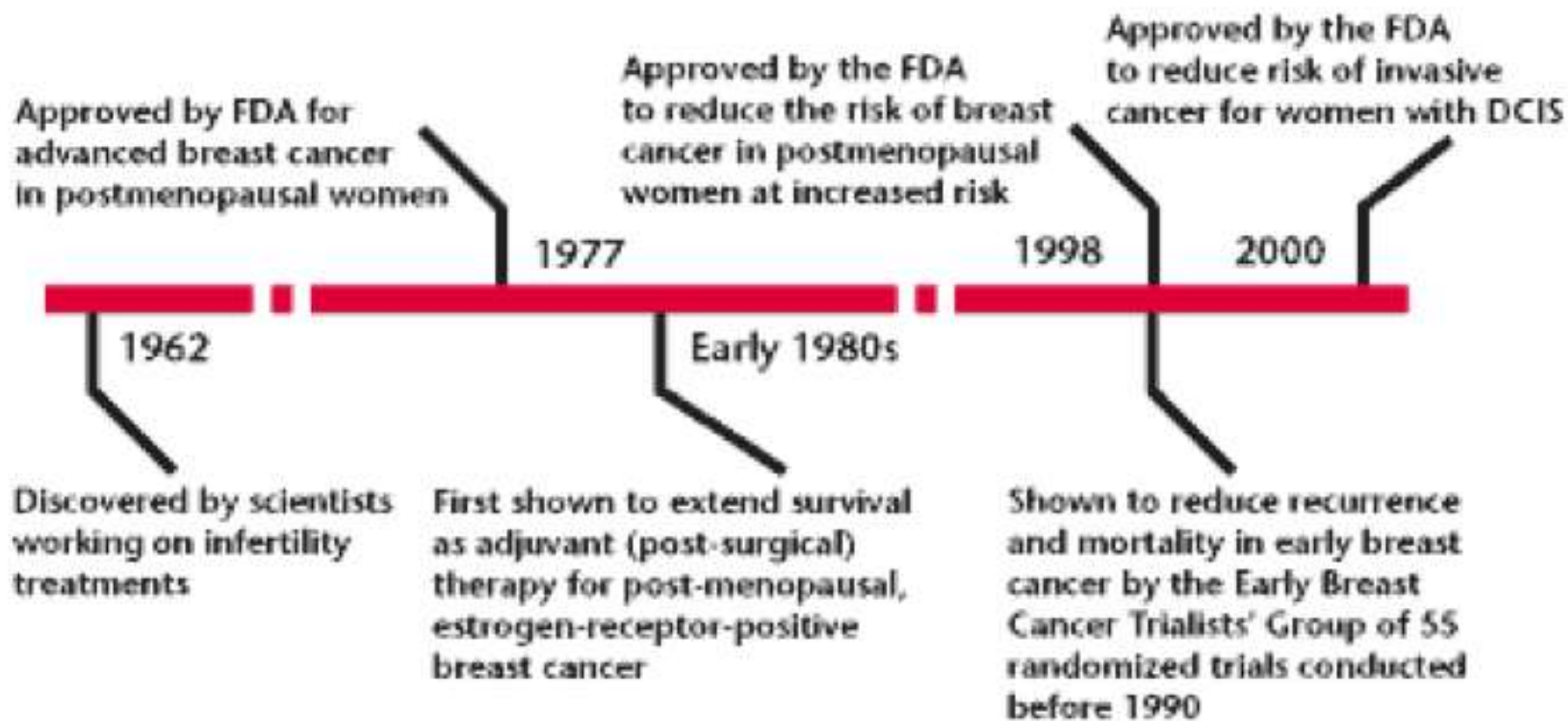
A historical perspective

- 1896: Sir George Beatson performs oophorectomy in women with advanced disease, leading to favorable response
- 1950's: Estrogen receptor discovered
- 1975-80: Estrogen receptor testing; correlates with response to hormonal therapy; pathophysiology is learned



~75% of breast cancers are ER+

Tamoxifen Timeline



Meet the 'key players'

	Mechanism of Action	Examples

Selective Estrogen Receptor Modulators (SERM)

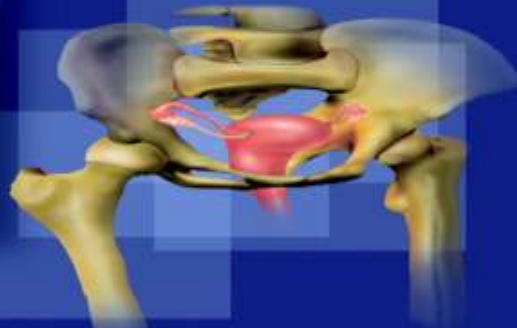
Tamoxifen

Reduces breast cancer incidence
(Antiestrogen)

Lowers circulating cholesterol
(Estrogen)

Maintains bone density
(Estrogen)

Increases endometrial cancer
(Estrogen)



Raloxifene

Reduces breast cancer incidence
(Antiestrogen)

Lowers circulating cholesterol
(Estrogen)

Maintains bone density;
Reduces fractures
(Estrogen)

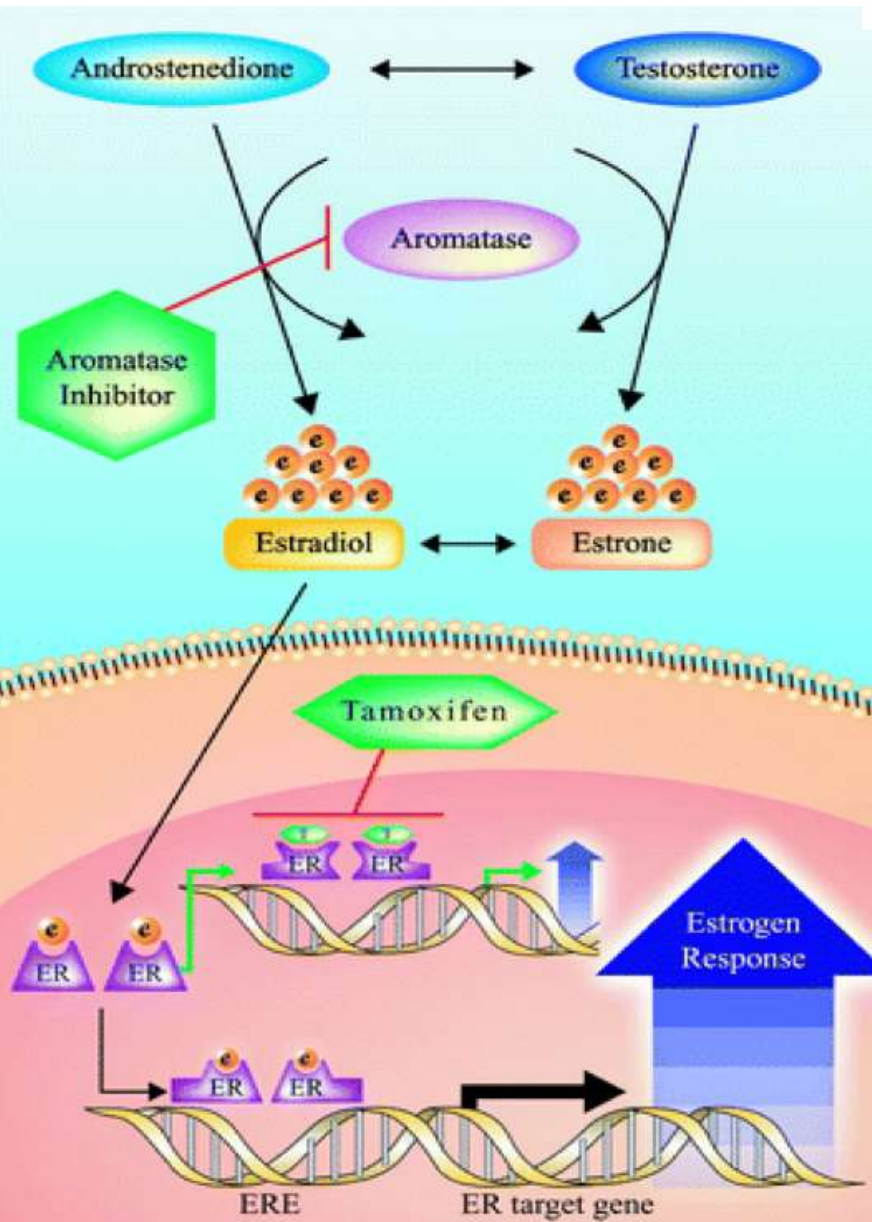
Reduces endometrial cancer
(Estrogen/Antiestrogen)

- Mixed agonist & antagonist activity, depending on the target tissue

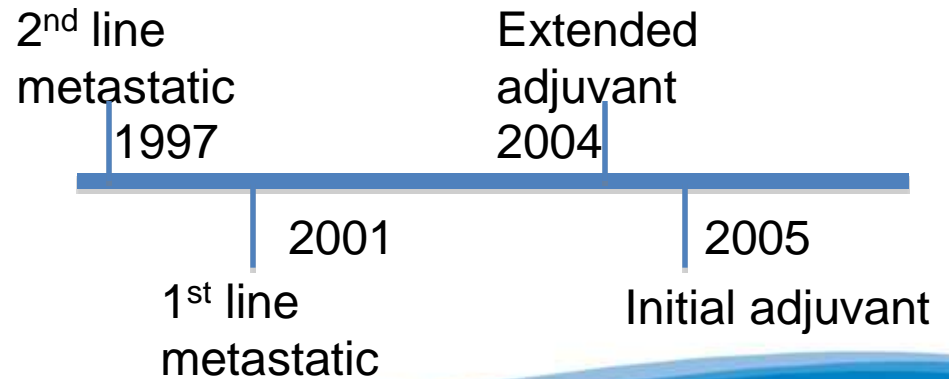
Meet the 'key players'

	Mechanism of Action	Examples
SERM	Inhibit Estrogen receptor	Tamoxifen, Raloxifene

Aromatase Inhibitors



- Markedly suppress plasma estrogen levels
 - Letrozole (Femara)
 - Anastrozole (Arimidex)
 - Exemestane (Aromasin)



Meet the 'key players'

	Mechanism of Action	Examples
SERM	Inhibit Estrogen receptor	Tamoxifen, Raloxifene
Aromatase Inhibitors	Inhibit Estrogen synthesis	Anastrozole, Letrozole, Exemestane

New treatments making a difference

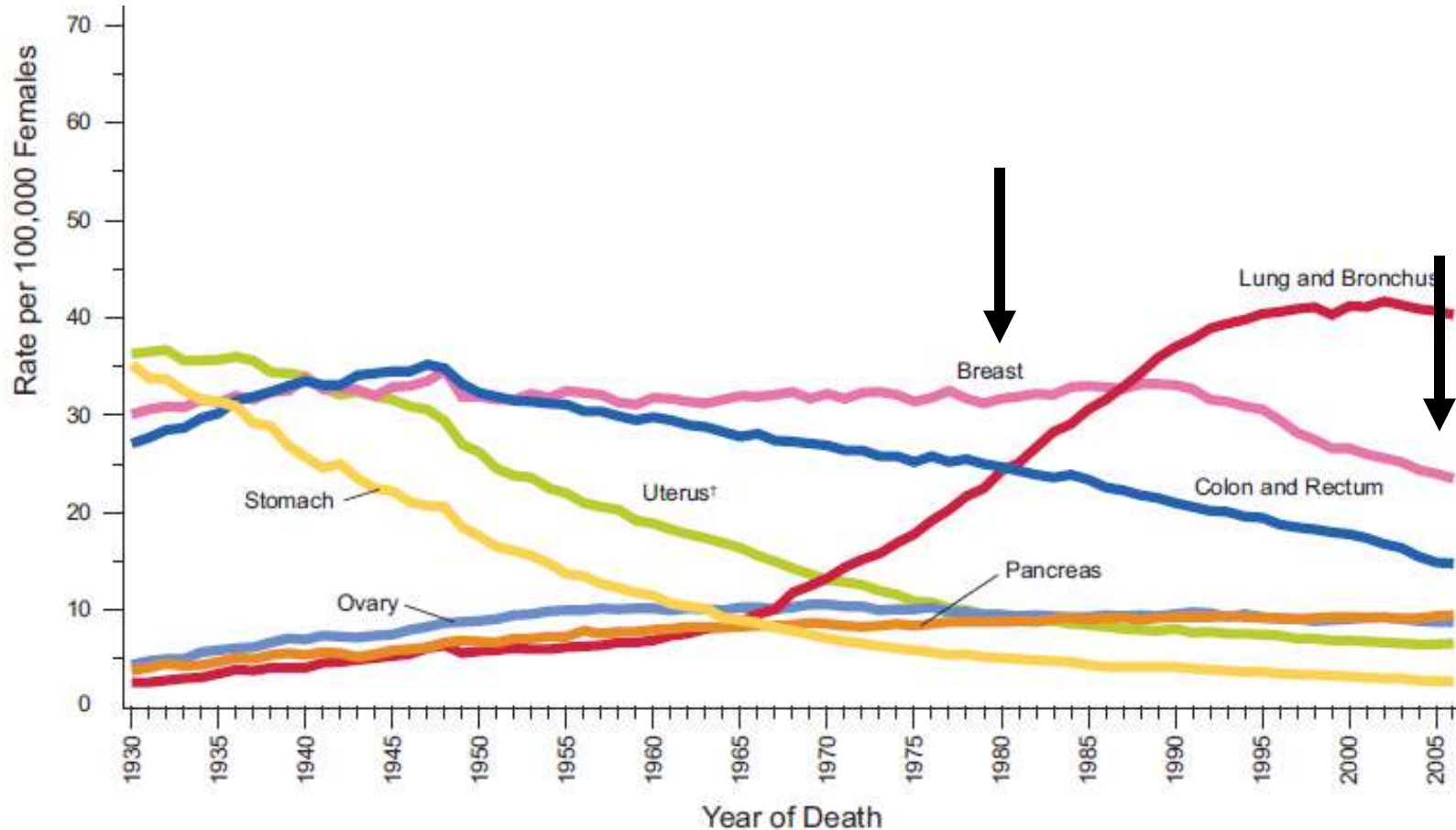
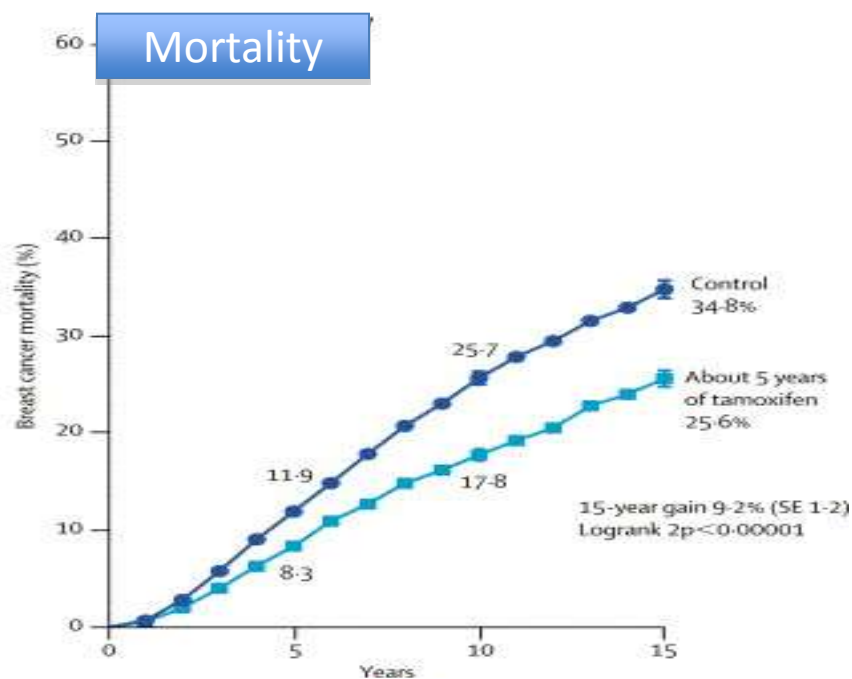
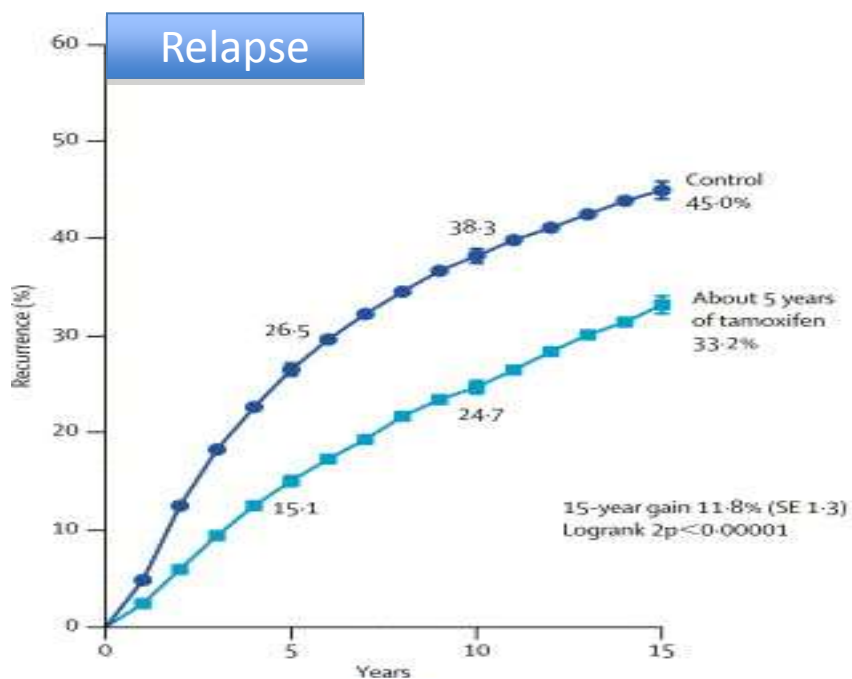


FIGURE 5. Annual Age-Adjusted Cancer Death Rates* Among Females for Selected Cancers, United States, 1930 to 2006.

Adjuvant Hormonal Therapy in 2011; Standard of Care

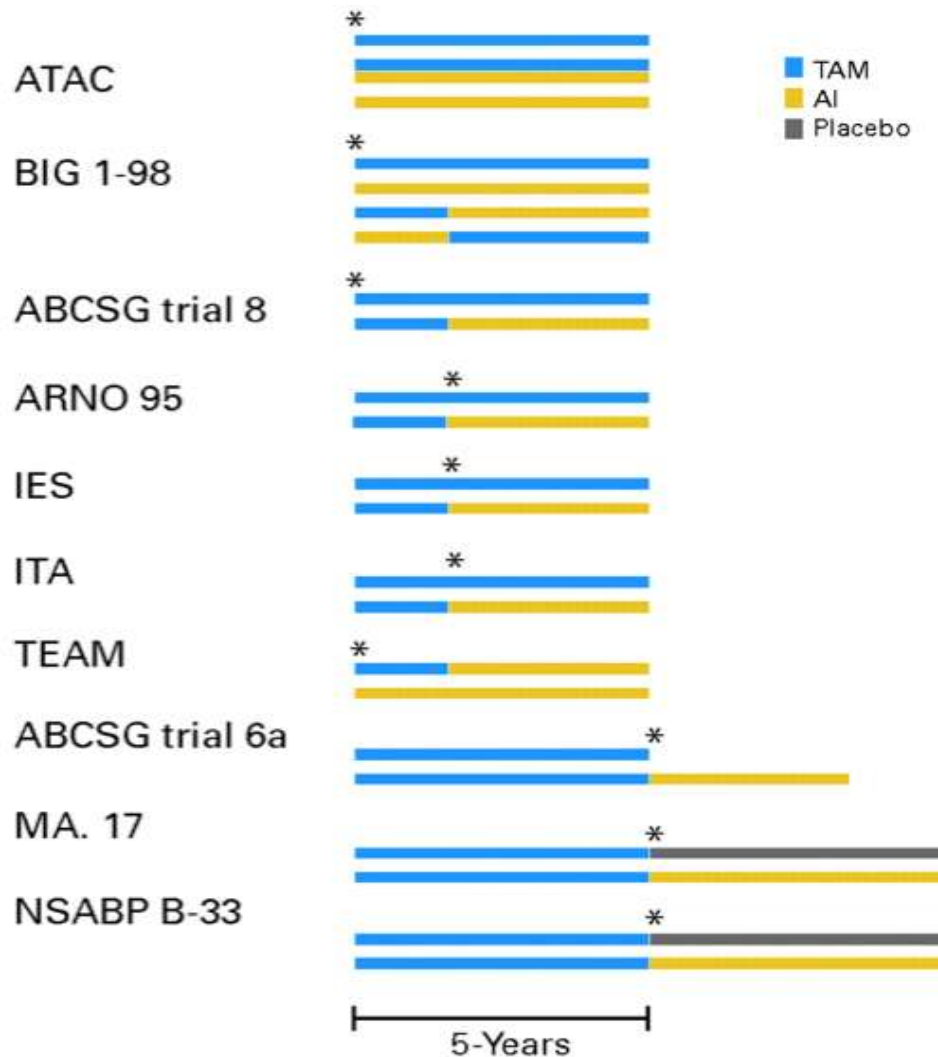
Postmenopausal women

Tamoxifen x 5 years Becomes the standard of care



- Women taking Tamoxifen experienced a:
 - 41% reduction in risk of relapse
 - 34% reduction in risk of death
- Benefit exists regardless of lymph node status, age, chemotherapy

Aromatase Inhibitors- Strategies



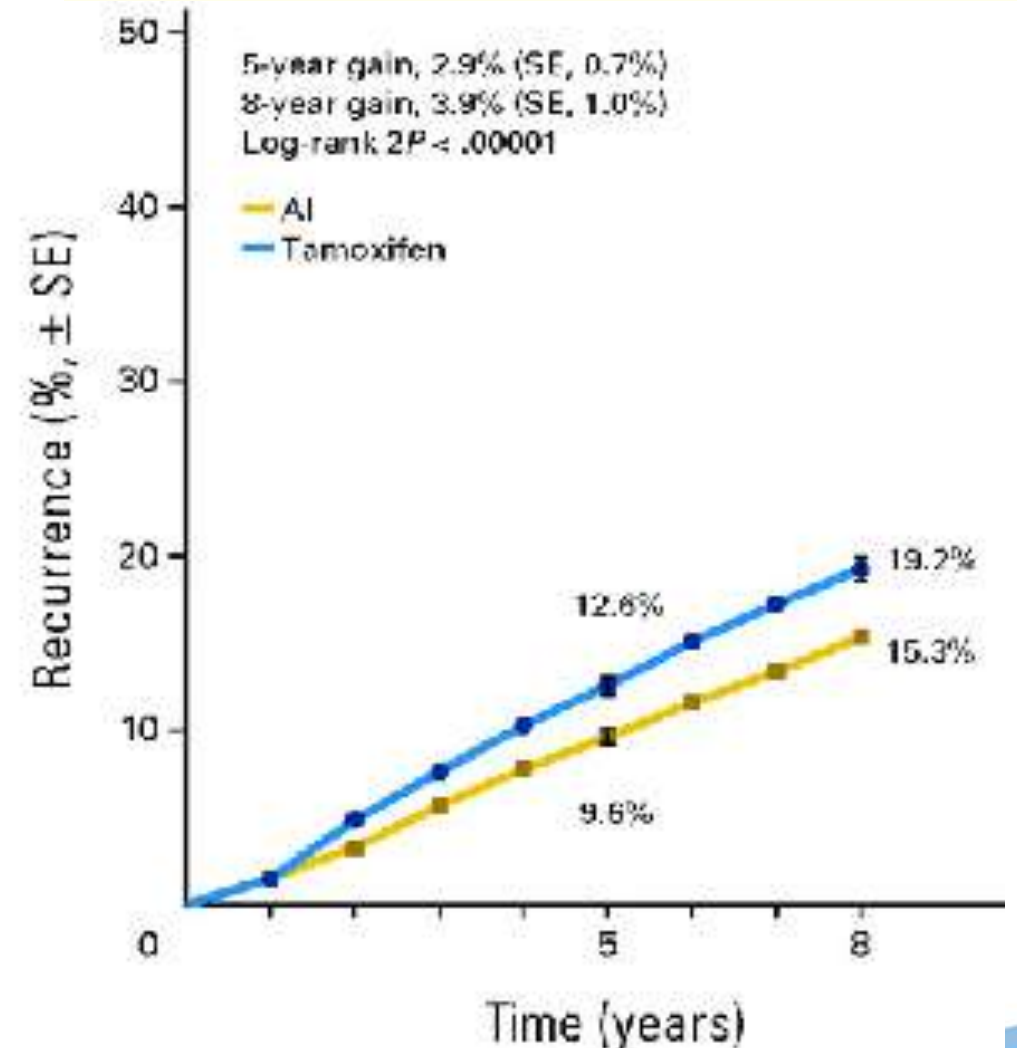
- **Initial**
 - Immediately after surgery
- **Sequential**
 - Following 2-3 yrs of Tamoxifen
- **Extended**
 - Following 5 yrs of Tamoxifen

Tamoxifen (5 years)

Aromatase Inhibitor (5 years)

INITIAL

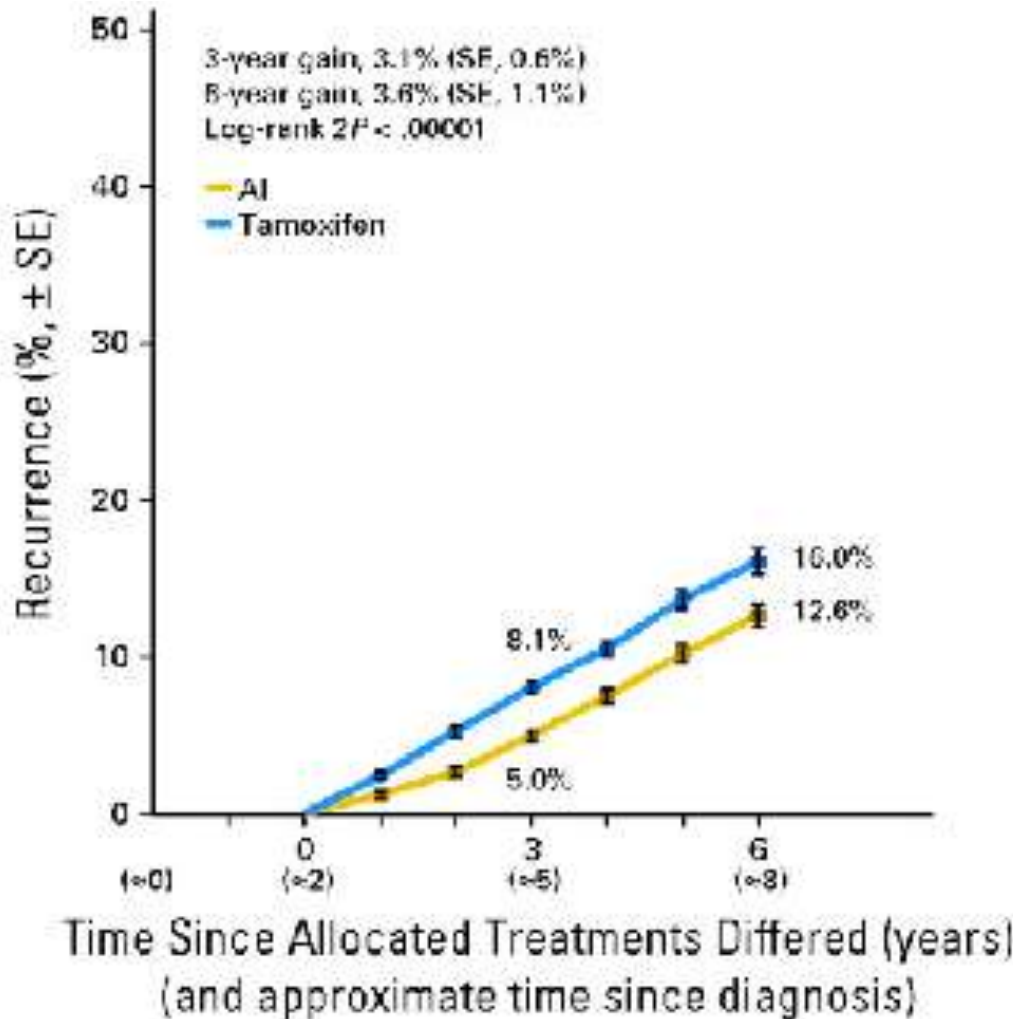
- 2 trials; >9800 women
- AI reduces risk of relapse by ~23%
- Benefit continues even after drug stopped
- Results confirmed at recent '10 yr update'



Tamoxifen Aromatase Inhibitor

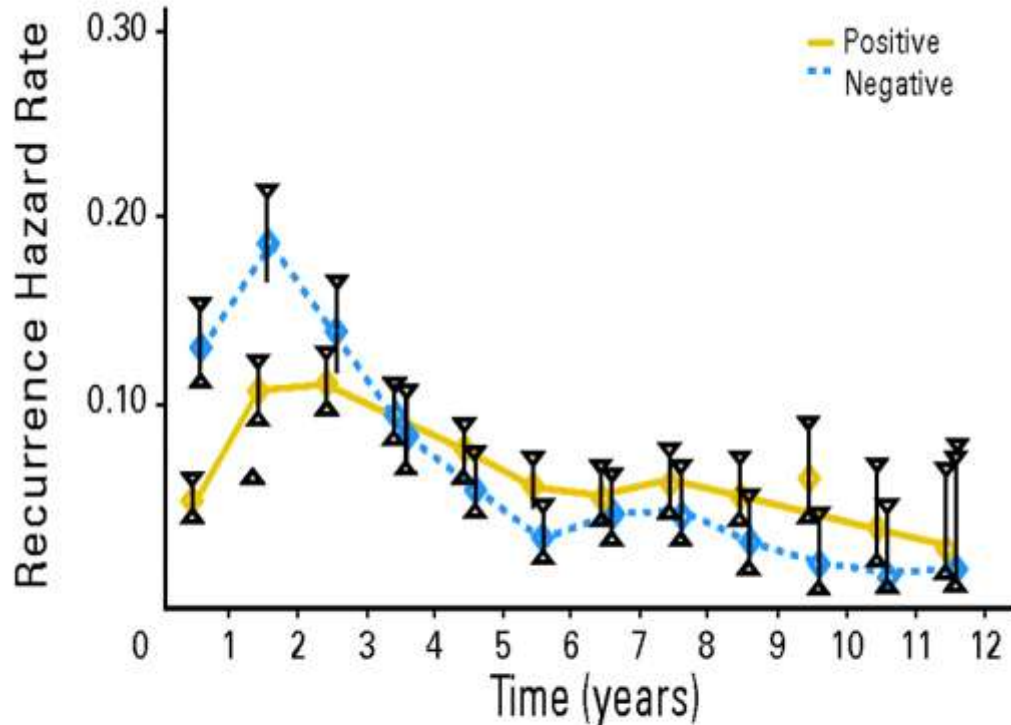


SEQUENTIAL



- 4 trials; >9000 women
- 29% reduction in risk of relapse
- Reduction in mortality risk (small, but statistically significant)

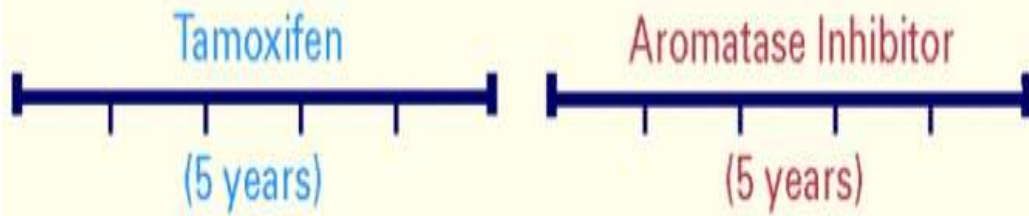
Natural History of ER+ Breast Cancer



No. at risk

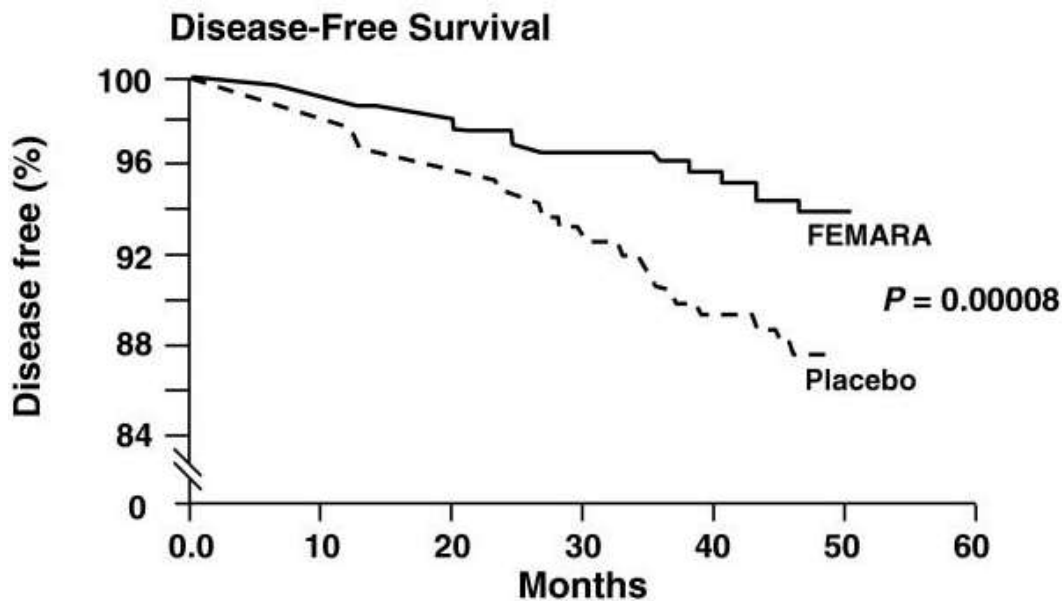
Positive	2,257	2,096	1,857	1,642	1,462	1,313	1,166	961	717	506	319	193
Negative	1,305	1,108	910	784	711	647	562	457	361	290	203	130

- ER+ tumors have a constant recurrence risk over time
- >50% of recurrences occur between 6-15 yrs after diagnosis
- *Extended* therapy may reduce risk of late relapses



EXTENDED

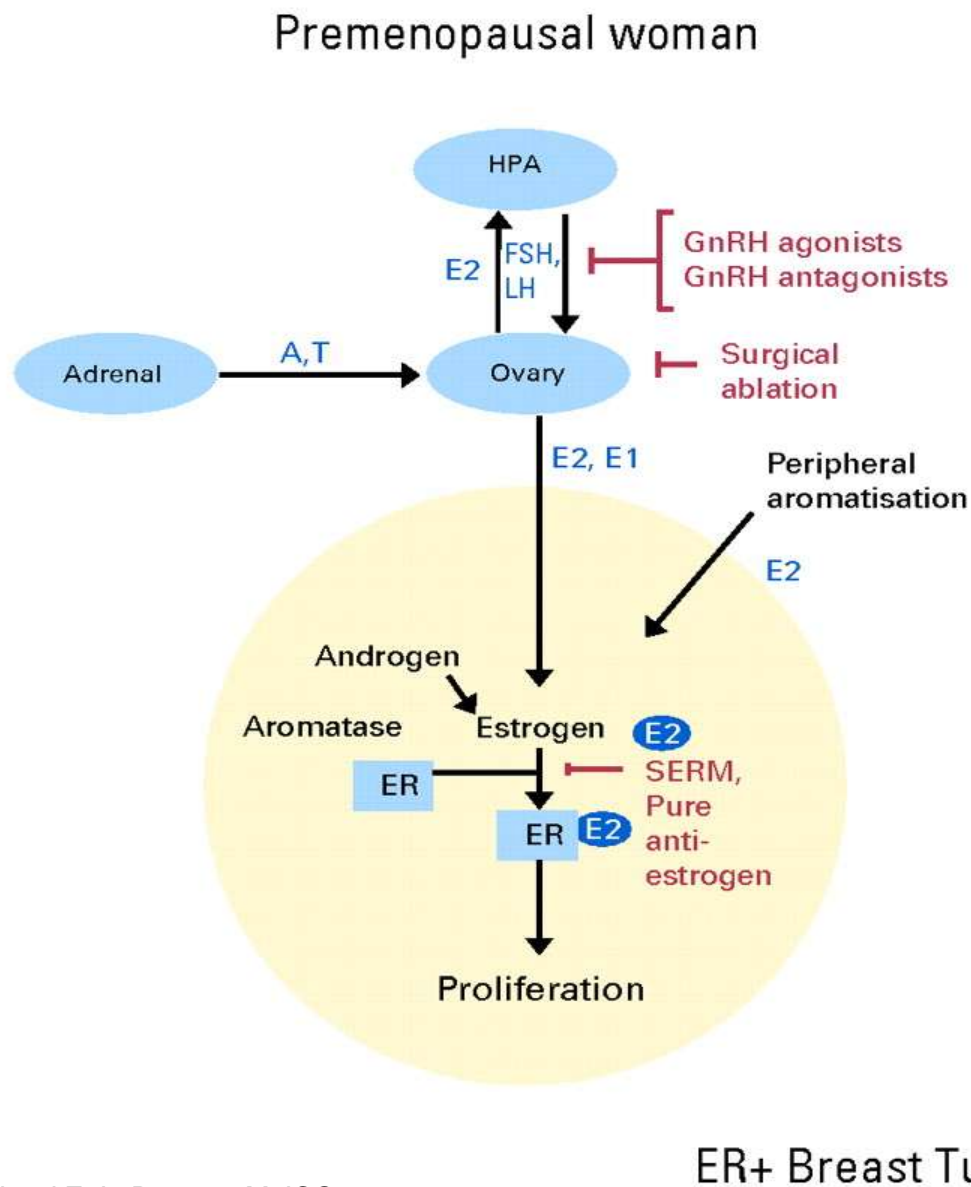
- 42% reduction in risk of relapse associated with continued hormonal therapy



Adjuvant Hormonal Therapy in 2011; Standard of Care

Premenopausal women

Differences in Estrogen production leads to different treatment approaches for pre vs postmenopausal women



Premenopausal Women are treated differently!

- Tamoxifen x 5 yrs considered a standard of care
- Addition of Ovarian suppression therapy in selected situations
- No role for aromatase inhibitors outside of investigational setting

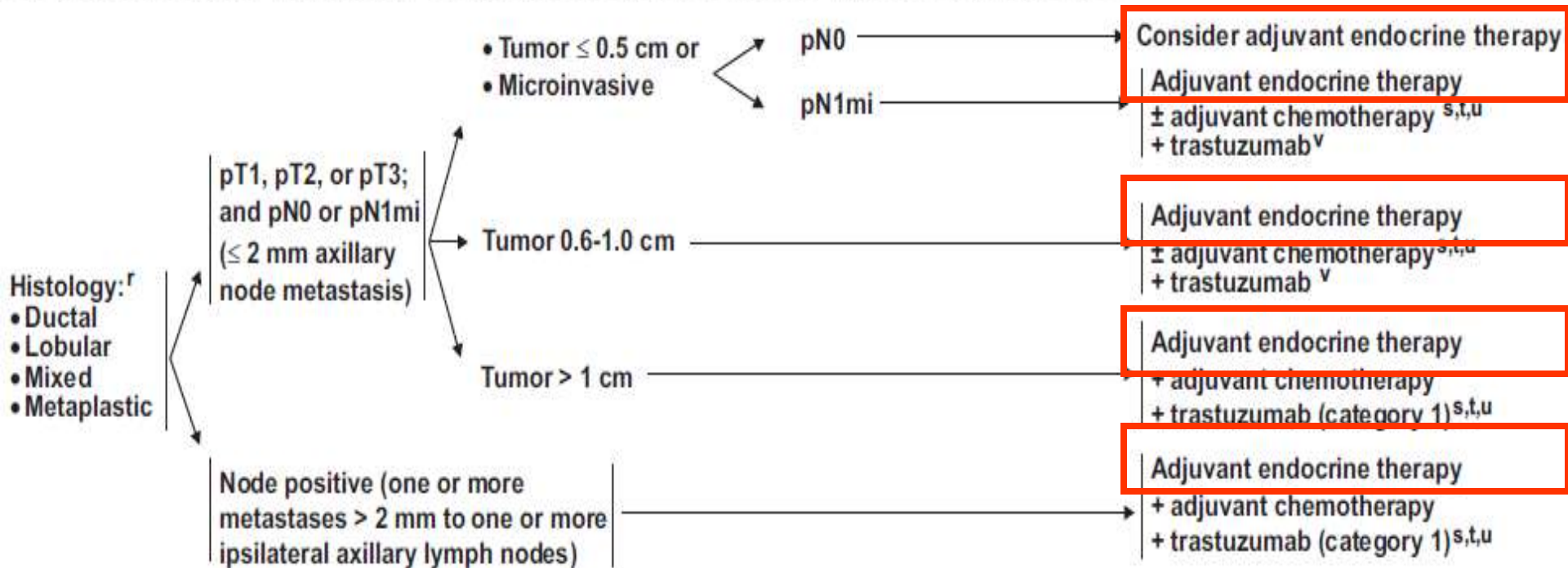
Definition of Menopause

Because it matters!

- Any **one** of the following criteria must be met
 - Age \geq 60
 - Age $<$ 60 with NO menses for 12 or more months, in absence of chemo/hormonal therapy, & FSH/estradiol levels in postmenopausal range
 - If taking Tamoxifen, and age $<$ 60, then FS/estradiol levels in postmenopausal range
- Chemotherapy induced amenorrhea \neq menopause!

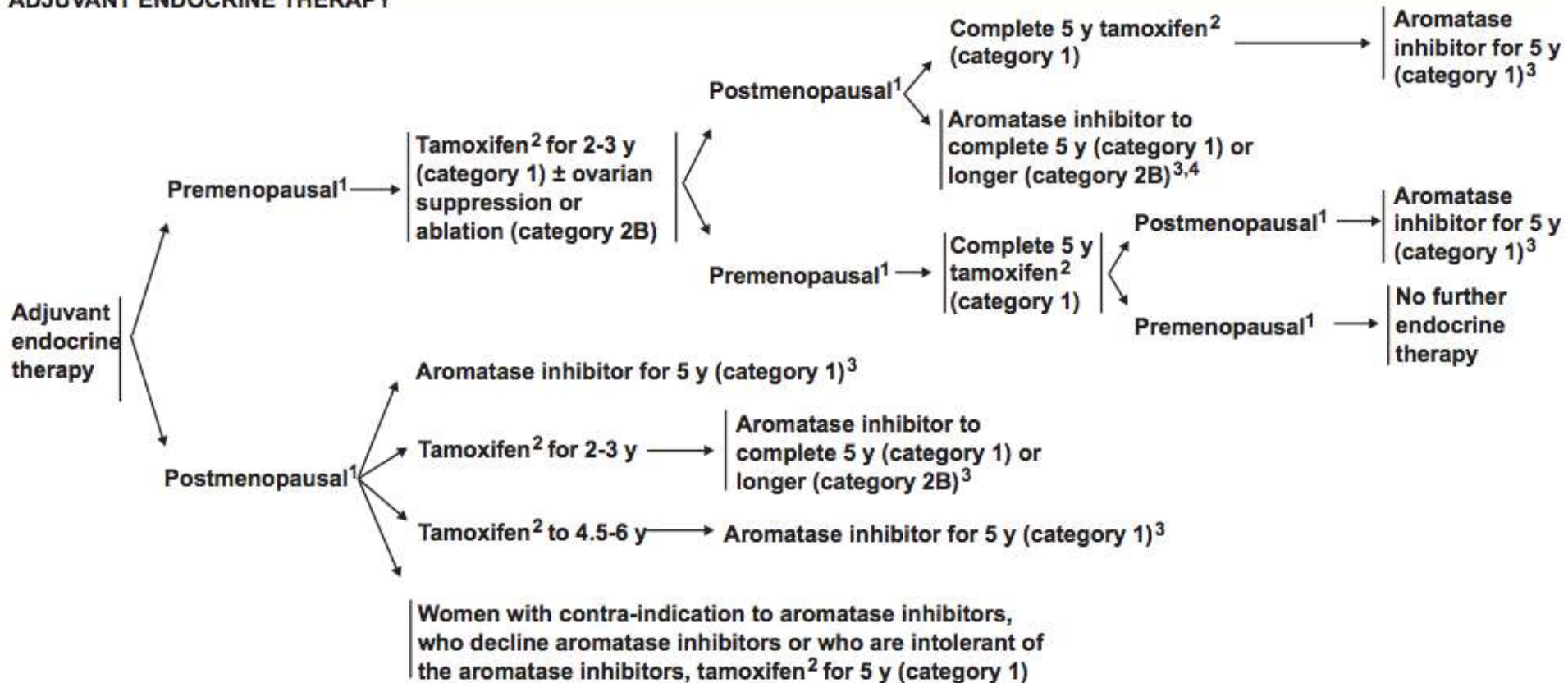
Who should get it?

SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR POSITIVE - HER2 POSITIVE DISEASE^b



What should they get?

ADJUVANT ENDOCRINE THERAPY



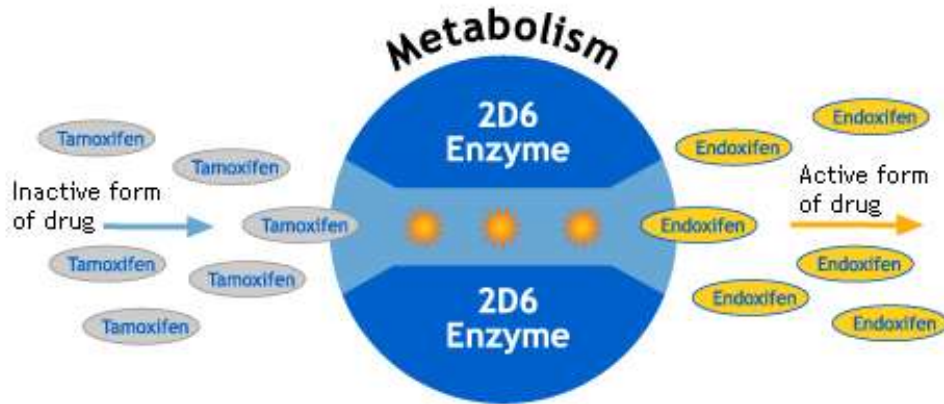
National Practice Guidelines

ASCO 2010

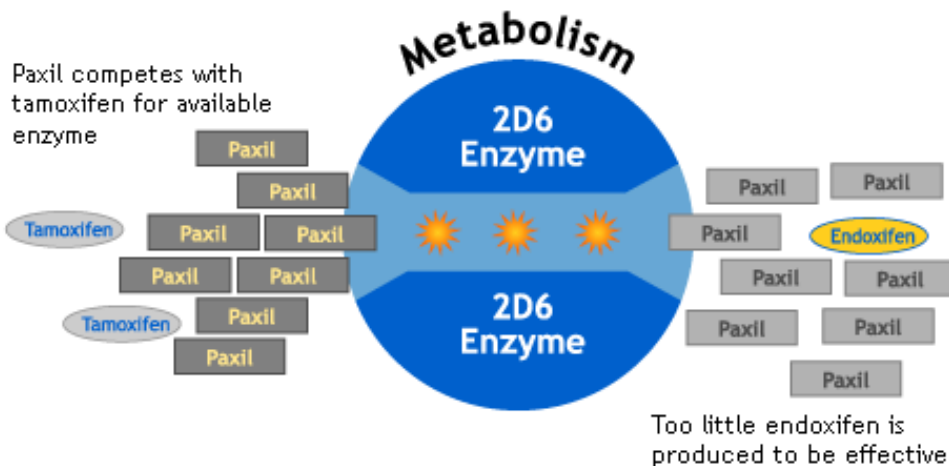
- **AI should be incorporated into adjuvant course**
 - Either initial or sequential
 - Maximum AI duration of 5 yrs
- **If initial Tamoxifen, then switch to AI**
 - After 2-3 yrs (preferred)
 - After 5 yrs
- **AI's may be used interchangeably**
- **Note specific populations**
 - Premenopausal; Tamoxifen x 5 yrs
 - Male; Tamoxifen x 5 yrs
 - Caution with CYP2D6 inhibitors

Tamoxifen: Potential drug interactions “CYP2D6”

Normal Tamoxifen Metabolism



Tamoxifen-Paxil Traffic Jam



Strong CYP2D6 Inhibitors	Moderate CYP2D6 Inhibitors	
bupropion (Wellbutrin®, Aplenzin®, Zyban®) chlorpromazine (Thorazine®) cinacalcet (Sensipar®) delavirdine (Rescriptor®) fluoxetine (Prozac®, Sarafem®, Symbyax®) paroxetine (Paxil®, Pexeva®) quinidine (Quinidex®) quinine (Qualaquin®) ritonavir (Norvir®, Kaletra®) ropinirole (Requip®) terbinafine (Lamisil®)	amiodarone (Cordarone®, Pacerone®) chloroquine (Aralen®) cimetidine (Tagamet®) clomipramine (Anafranil®) clozapine (Clozaril®, FazaClo®) desipramine (Norpramin®) diphenhydramine (Benadryl®) dronedarone (Multaq®) duloxetine (Cymbalta®) haloperidol (Haldol®) imipramine (Tofranil®) isoniazid (Rifater®, IsonaRif®, Rifamate®)	ketoconazole (Nizoral®) methadone (Dolophone®, Methadose®) methimazole (Northyx®) nicardipine (Cardene®) pyrimethamine (Daraprim®) sertraline >50 mg (Zoloft®) thioridazine (Mellaril®) ticlopidine (Ticlid®) tranylcypromine (Parnate®)

Toxicities of Hormonal Therapy

Toxicity Profile

More with Tamoxifen

More with AI's

- ↑ Hot flushes
- ↑ Ischaemic cerebrovascular event

- ↑ Ischemic cardiovascular event
- ↑ cholesterol

- ↑ Venous thromboembolic event

- ↑ Endometrial cancer
- ↑ Vaginal bleeding
- ↑ Vaginal discharge

- ↑ Bone fractures
- ↑ Musculoskeletal disorder



AI's: Arthralgias



- Related to estrogen deprivation
- Joint pain & stiffness-mild to moderate in most cases
 - Risk factors include
 - Prior joint problems
 - Young age
 - Prior taxane/growth factors
- 25-35% of women
 - Probably more common than that!
- Often improves over time with continued therapy
- Evaluation & Management
 - Exclude other causes
 - Lifestyle modifications
 - Medical therapy
 - Alternative anti-estrogen

AI's: Bone Health

What is the problem?



- AI's increase risk of bone loss, osteoporosis and fracture vs Tamoxifen
- Estrogen deficiency leads to increased bone breakdown
- Risk factors for osteoporosis:
 - Advanced age/female
 - Alcohol/Cigarettes
 - Personal/Family history of fracture
 - Immobility
 - corticosteroid use

AI's: Bone Health

What can we do about it?

- Bone mineral density (DEXA) monitoring recommended at baseline and every 1-2 yrs on AI therapy
- Lifestyle measures
 - Calcium 1200-1500 mg daily
 - Vit D3 800 IU daily
 - Weight bearing exercise
 - Limit alcohol
 - Stop smoking
- Consider medical therapy for osteoporosis, or osteopenia with other risk factors

Hot Flashes



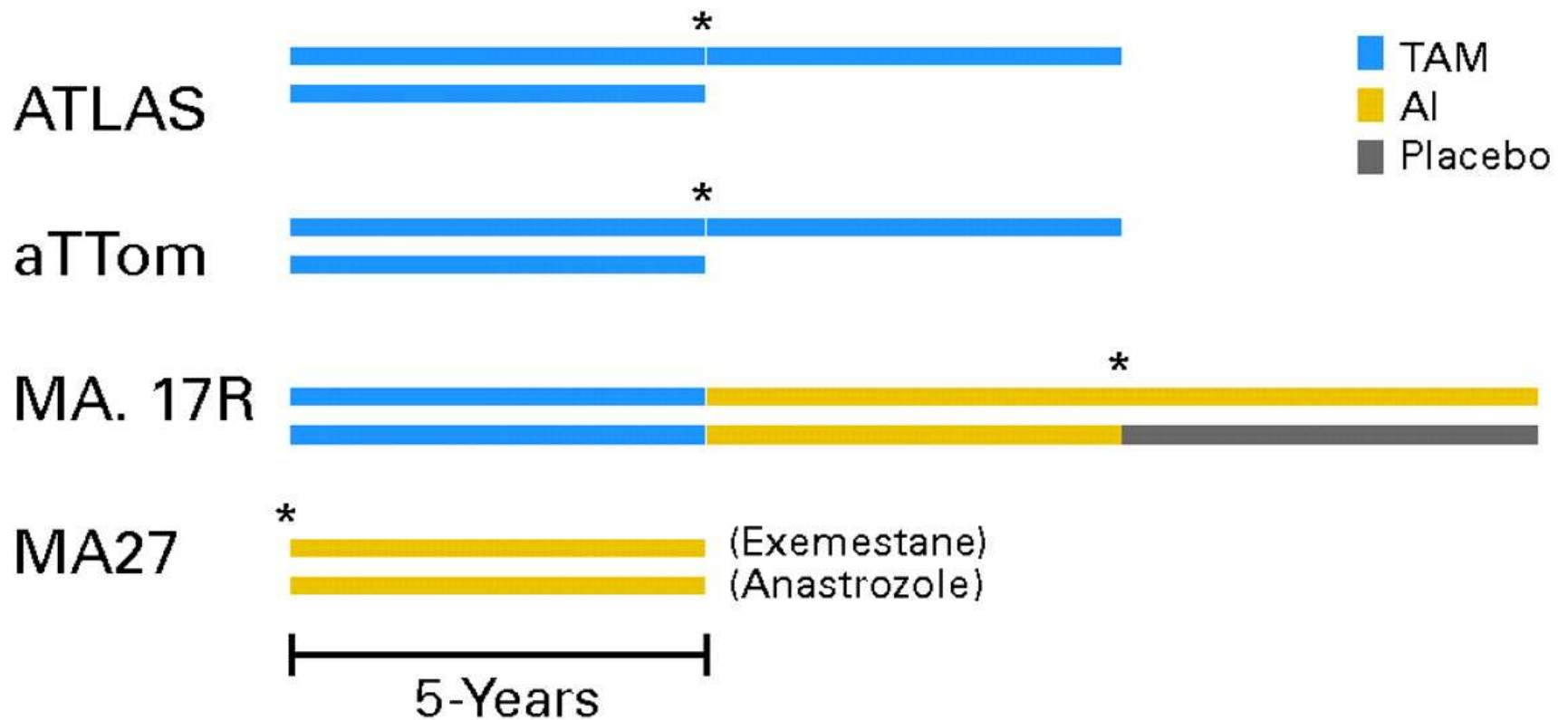
- Up to 80% of women on Tamoxifen
 - Severe in 30%
- Antiestrogenic effect on CNS → thermoregulatory dysfunction
- Think about
 - Selective Serotonin Reuptake Inhibitors (SSRI's)
 - Venlafaxine, Escitalopram
 - Gabapentin, Clonidine
- Do **NOT** think about
 - Estrogen
- What probably does not help (and may be harmful!)
 - Black cohosh, soy, primrose oil, red clover, flaxseed

Future Areas of Research

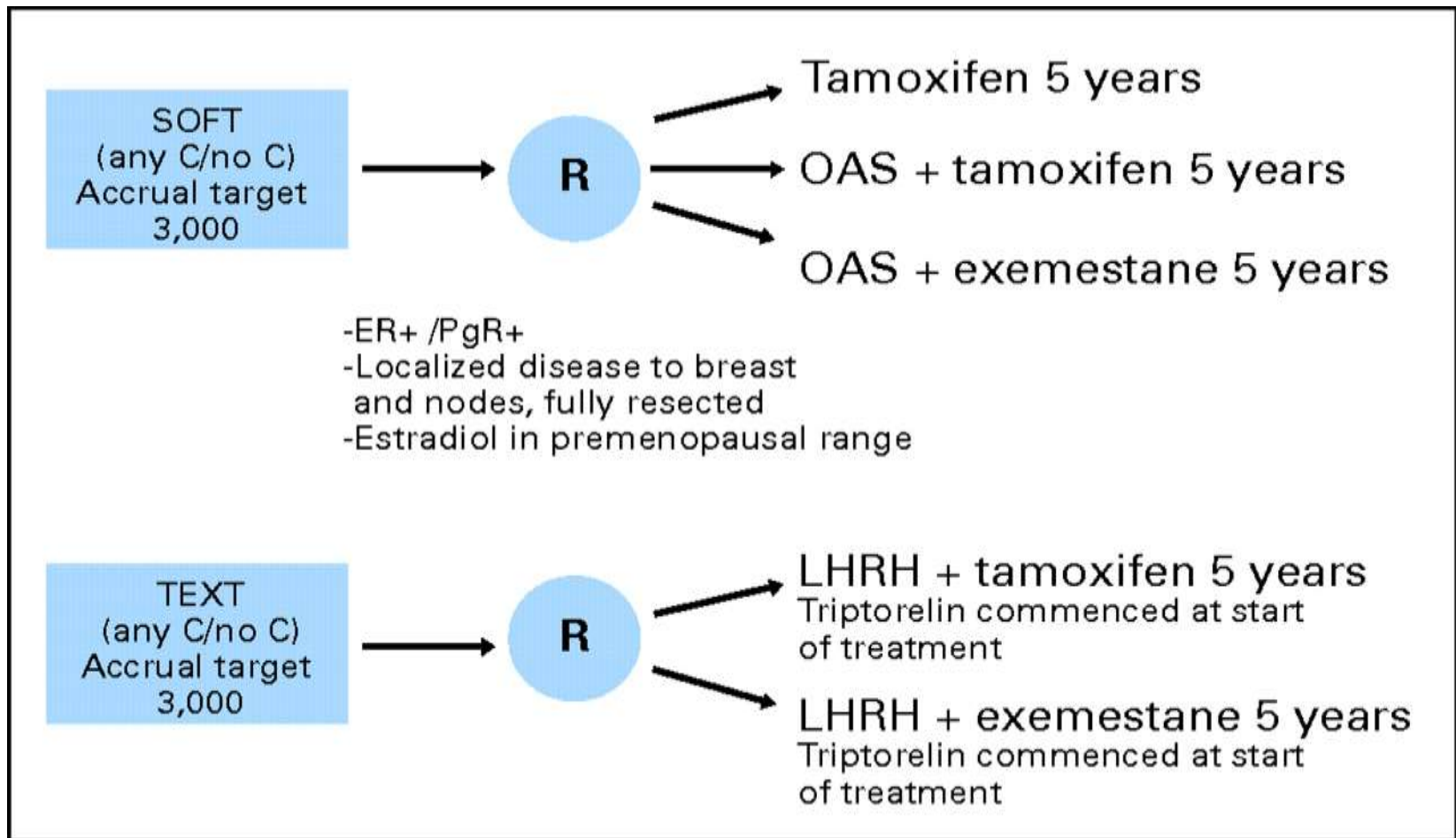
Future areas of research

- Long term effects of AI's
- Comparison of AI's against one another
- Interventions to minimize toxicities
- Biomarker development to guide treatment
- Further analysis of drug metabolism & pharmacogenetics to predict benefit
- Clarification of optimal premenopausal strategy

Clinical trials: Postmenopausal



Clinical Trials: Premenopausal



Back to Ms. L

- Baseline bone density normal
 - Initiates calcium/vitamin D, & lifestyle measures
- Anastrozole 1 mg orally daily initiated, planned treatment duration of 5 years
- Mild hot flashes
- Mild arthralgias requiring occasional analgesics
- Continued close follow-up with family physician

Thank you!