Everything you ever wanted or needed to know about Breast Cancer

(Well, not really….)

Cell 616
Advanced Topics in Cancer Biology

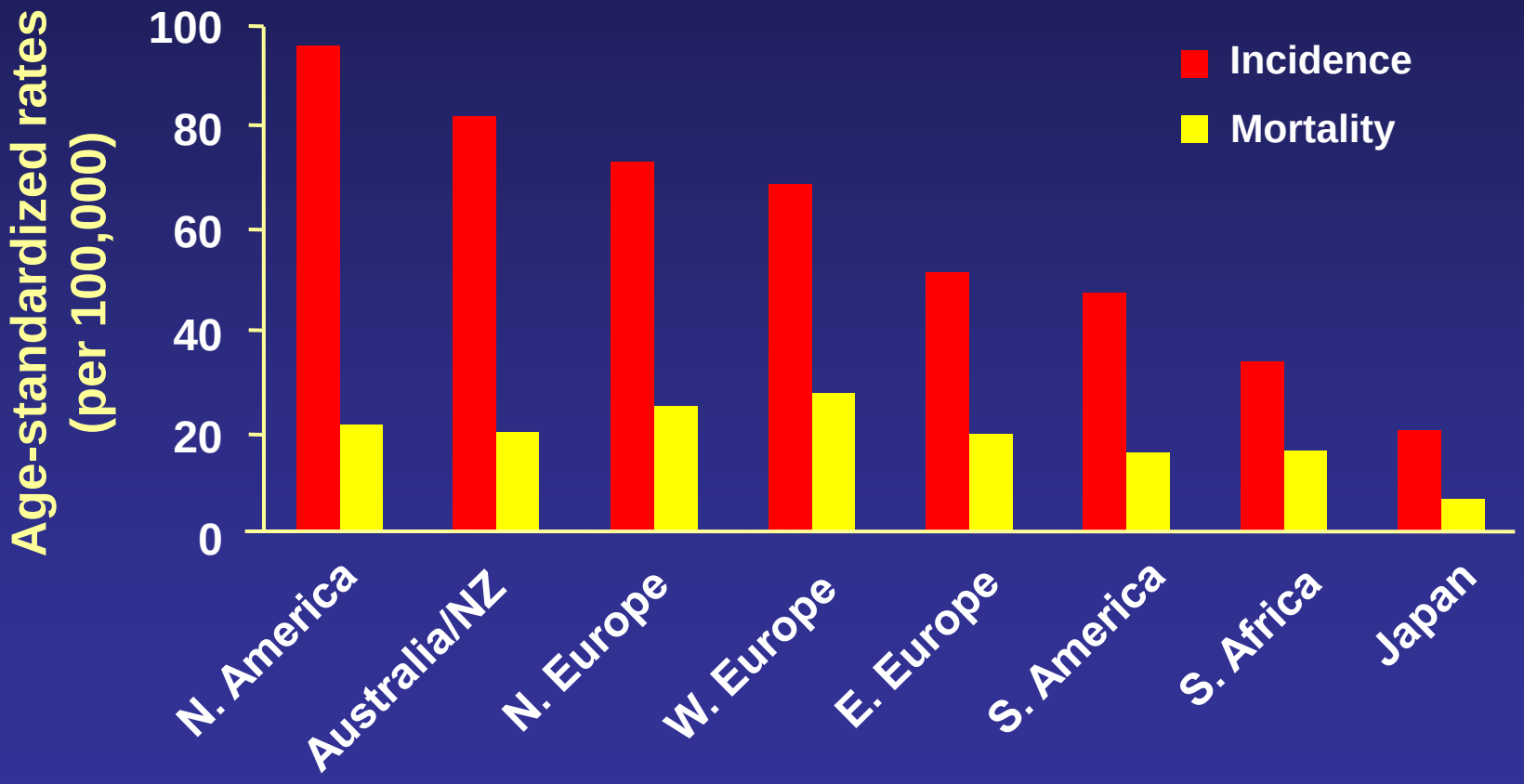
Stephen Y. Chui, M.D.
Assistant Professor of Medicine
Division of Hematology and Medical Oncology
Acting Breast Cancer Clinical Research Director
Oregon Health & Science University

Outline

- Epidemiology
- Breast cancer screening and detection
- Prognosis and Treatment of Early ("potentially curable") Breast Cancer according to:
  - Anatomic size
  - HER2 status
  - Hormone receptor status
  - Genomic analysis

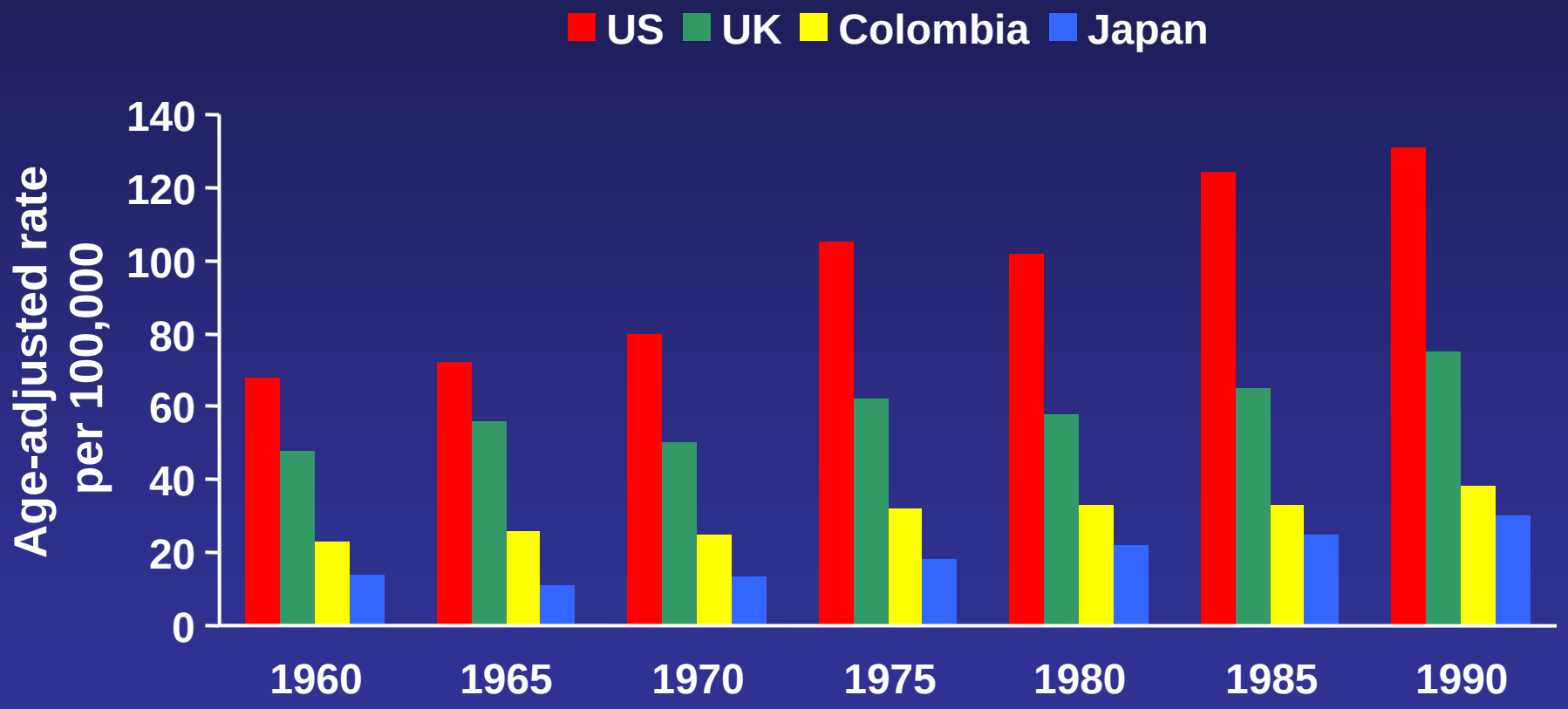
Breast cancer incidence and epidemiology

Incidence and Mortality of Breast Cancer Worldwide in 2000



Adapted with permission from GLOBOCAN 2000.

The Incidence of Breast Cancer is on the Increase Worldwide



SEER Cancer Statistics Review 1973-1999. NCI, 2001. Available at: www.seer.cancer.gov.
Parkin et al. *Eur J Cancer.* 2001;37(suppl 8):S4.

BREAST CANCER IS COMMON

- > 220,000 cases/yr in USA alone
- #1 life threatening cancer in women
  - 1 in 8 lifetime risk
- #2 cancer mortality (after lung cancer)
  - 40,000 deaths annually
  - 1 in 30 women will die from breast cancer

Age as a Risk Factor for Breast Cancer

	RISK
By age 30	1 out of 2,000
By age 40	1 out of 233
By age 50	1 out of 53
By age 60	1 out of 22
By age 70	1 out of 13
By age 80	1 out of 9
Lifetime risk	1 out of 8

NCI Surveillance, Epidemiology and End Results, 1995-1997

Breast cancer risk factors (1)

Controllable

- Alcohol intake
- Being overweight
- Oral contraceptives (very slight)
- Use of postmenopausal hormone replacement therapy
- Sedentary lifestyle
- Exposure to large amounts of radiation

Uncontrollable

- Getting older
- 1st degree relative with breast cancer
- A previous breast biopsy showing atypical changes
- Younger age at the time of starting menses
- Older age at the time of menopause (>55 years)

www.bcra.nci.nih.gov/brc

Breast cancer risk factors (2)

"Controllable"

- Never having children
- 1st child at >30 years of age

Uncontrollable

- Having an inherited mutation in the breast cancer genes (BRCA 1 or 2)

www.bcra.nci.nih.gov/brc

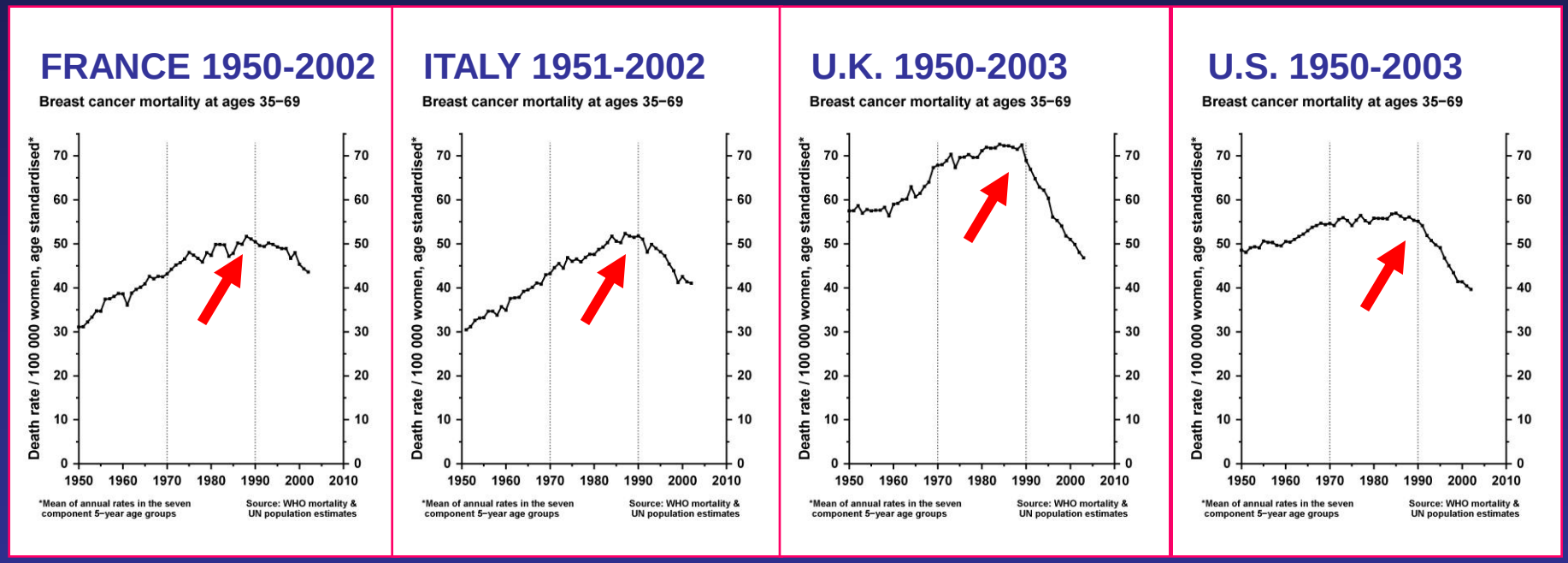
Breast Cancer Risk Factors

- Risk Factors do not cause breast cancer but are associated with an increased chance of getting breast cancer

New cancer diagnoses in U.S. 2008:

Breast cancer:	**182,460**
Prostate cancer	186,320
Lung cancer:	215,020
Colorectal cancer	108,070
Testicular cancer:	8,090
Pancreatic cancer:	37,680
Hodgkin Lymphoma:	8,220
Non-Hodgkin Lymphoma:	66,120
Acute Myeloid Leukemia:	13,290

Breast Cancer Mortality Rates Have Been Decreasing Since The Early 1990's



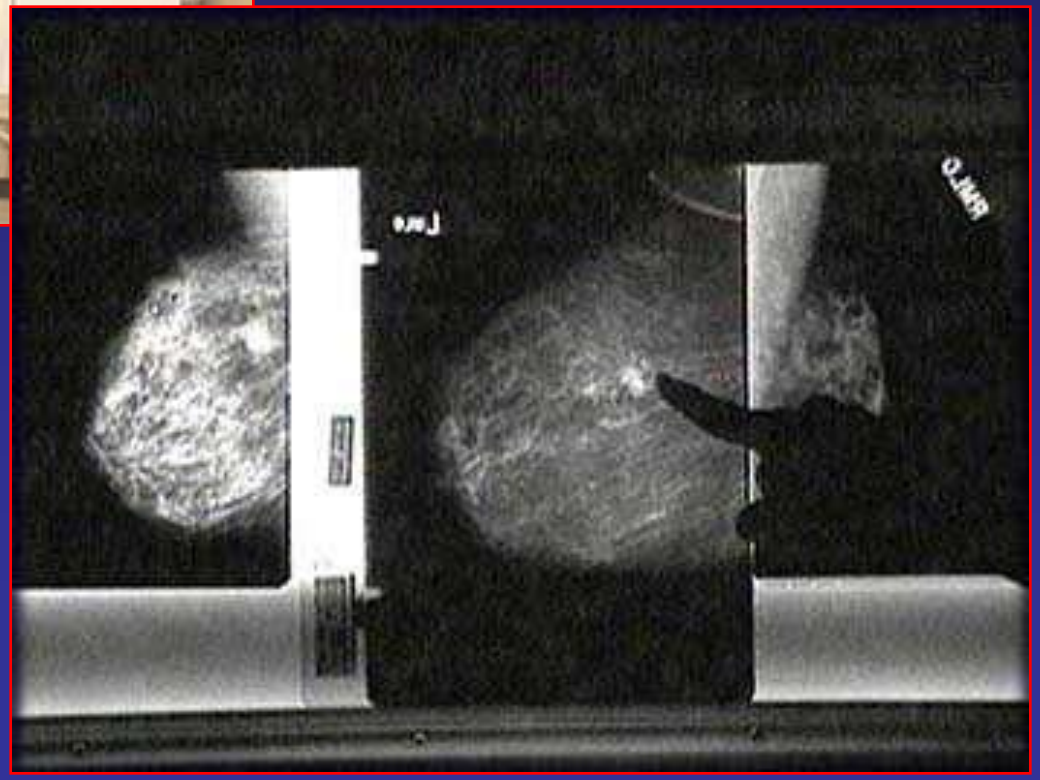
25-30% ↓ in breast cancer mortality since 1990!

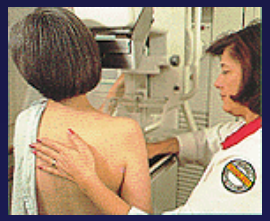
Early Breast Cancer Trialists' Collaborative Group (EBCTCG)
Lancet 365 (May 2005), 1687-1717

Breast cancer screening and detection

How is breast cancer detected?

- Physician/caregiver breast examination:
  LOUSY
- Breast self examination:
  EVEN WORSE
- **Screening mammography**





Mammograms are imperfect tests

- Sensitivity is 77-95% overall
  - 54-58% in women < 40
  - 81-94% in women > 65
    - Depends on lesion size, conspicuity, tissue density, patient age, hormone status, image quality, and interpretive skill of the radiologist
- Practice Makes Perfect:
  - Sensitivity 70.3% for low volume MD
  - 78.6% for high volume radiologists

High breast density = lower sensitivity

- 10-29% lower in one study

Mammography benefits

- Meta-analysis:
  Breast cancer deaths ↓26% age 50-74
  Kerlikowske JAMA 1995;273:149
- Retrospective studies:
  - Breast cancer deaths ↓44% (Sweden)
    Tabar *Lancet* 2003;361:1405
  - Breast cancer deaths ↓19.9% (Netherlands)
    Otto *Lancet* 2003;361:1411

Screening recommendations

American Cancer Society (ACS) American College of Radiology (ACR) American College of Surgeons National Cancer Institute (NCI) American Medical Association (AMA) American College of Obstetricians and Gynecologists (ACOG) American Medical Women's Association	**Mammography beginning age 40**
American College of Physicians (ACP) Canadian Task Force on Periodic Health Examination (CTFPHE)	**Recommend *against* screening <50 yo**
American College of Preventive Medicine (ACPM) U.S. Preventive Services Task Force (USPSTF)	**Insufficient evidence to recommend screening <50 yo**

Screening Mammography

- Mammography National averages (CDC):
  - Overall 71% of women >40 years have had at least 1 mxr in last 2 yrs
  - Low-income women and women w/o health insurance were 58% and 50%
- Why don't women get mammograms?
  - Fear of radiation, anxiety that may not find CA, worry that CA might actually be detected, embarrassment, discomfort, pain

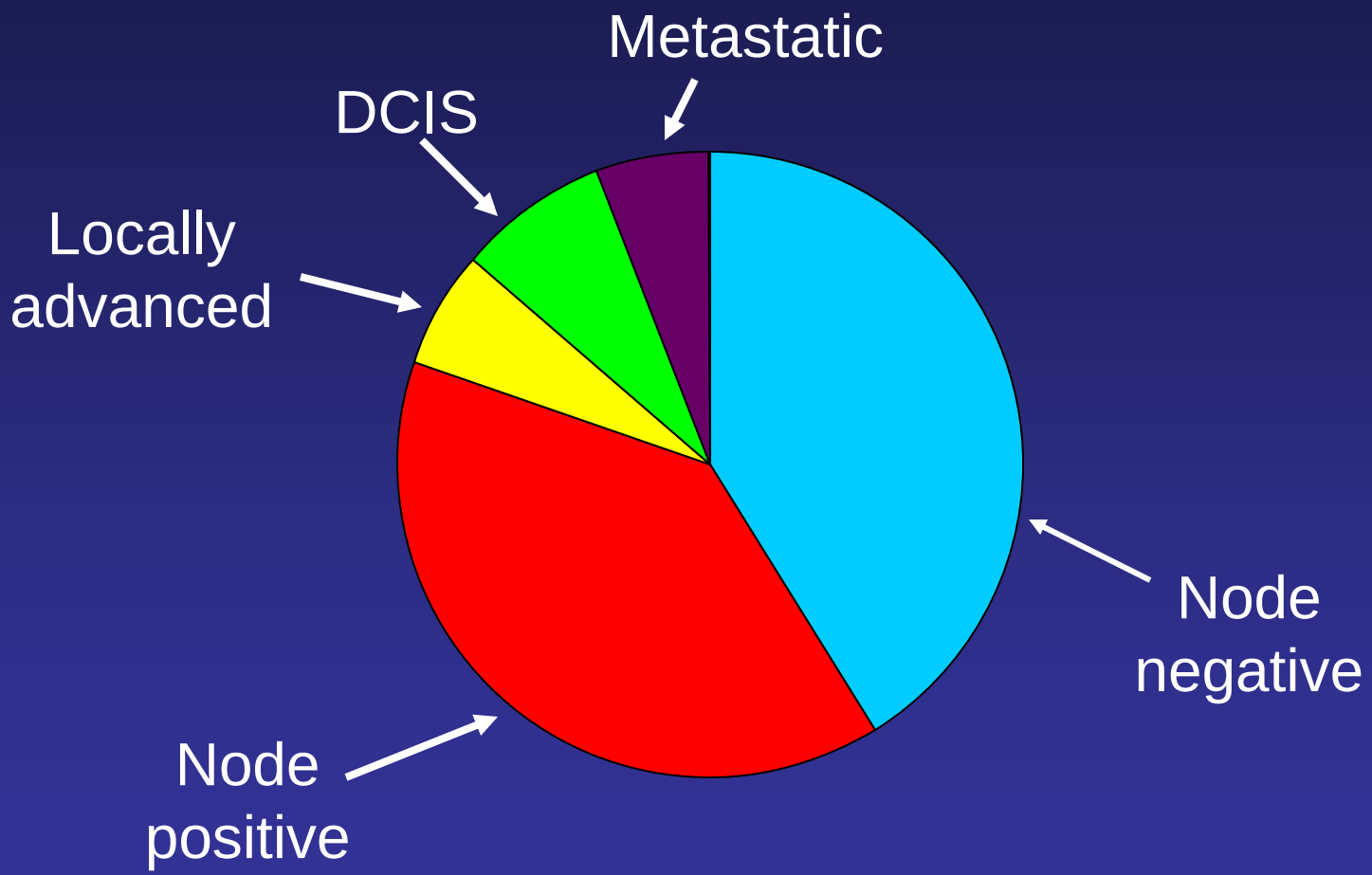
Factors that may discourage annual mammography among low-income women with access to free mammograms: a study using multi-ethnic, multiracial focus groups. Bobo JK, Psychol. Rep. Oct. 1999, 85(2).

Other screening tests for breast cancer

- **Breast MRI**
  - Can detect mammographically occult malignancies in high risk patients (particularly in dense breast parenchyma)
  - Expensive
  - Many false positives requiring additional imaging/biopsy
- **Breast ultrasound**
  - Poor (useless?) screening test
  - Good for distinguishing solid masses from cystic masses
- **Serum/blood tests**
  - Don’t exist!

Early (“*potentially curable*”)
versus
Metastatic *(“incurable”)*
Breast Cancer

Distribution of Disease at Presentation

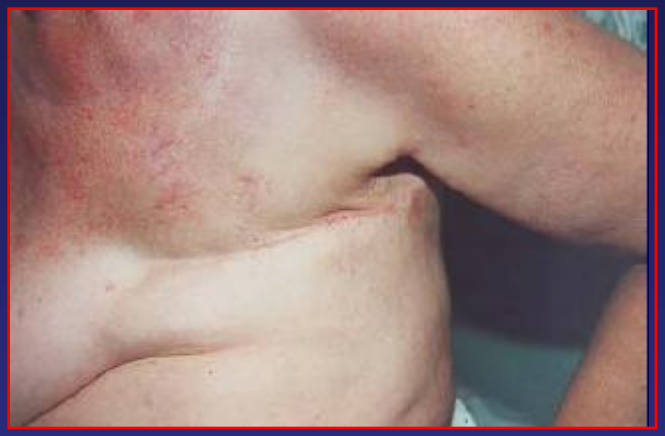


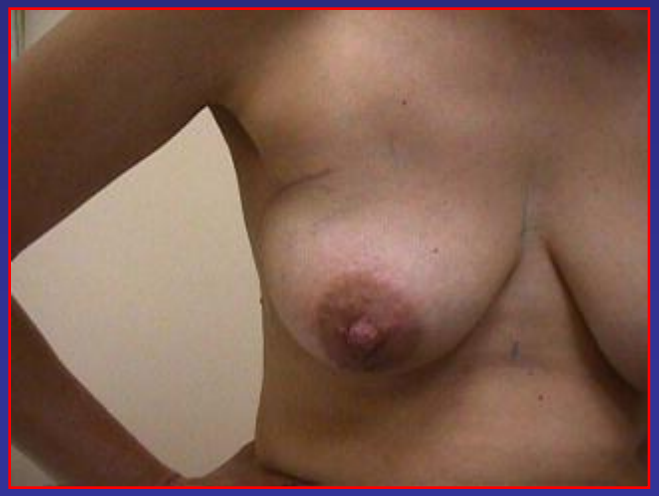
Breast Cancer Treatment

- **Early Breast Cancer** *(potentially curable):*
  - Loco-regional Therapy
    - Surgery
    - Radiation
  - Adjuvant Systemic Therapy
    - Chemotherapy
    - Hormone therapy
- **Metastatic Breast Cancer** *(incurable):*
  - Palliative

Loco-regional therapies for Early BC
Clinical paradigm shift

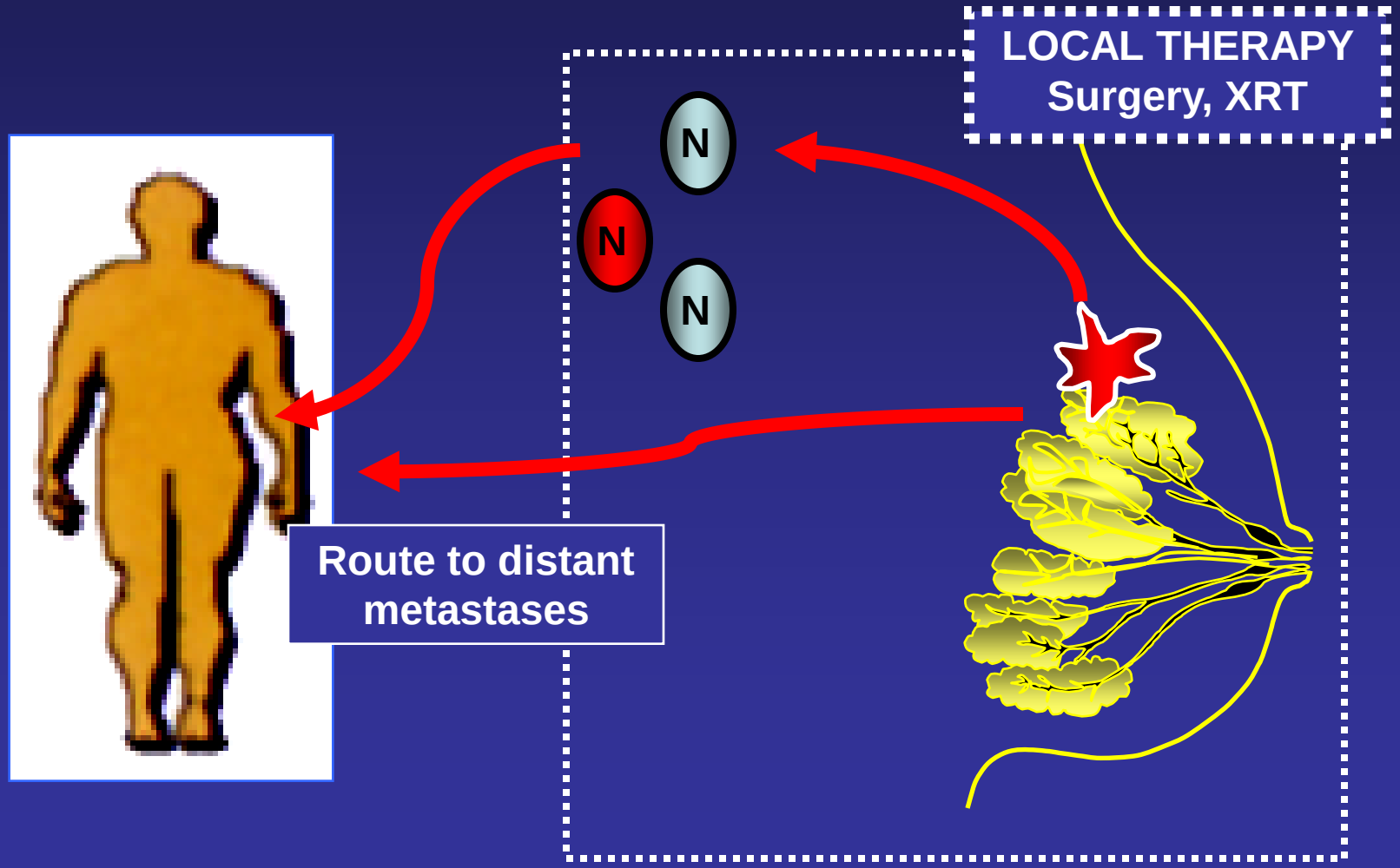
- Early-mid 1900's
  - Radical mastectomy
  - Axillary dissection
- 1980's
  - Wide local resection
  - Axillary dissection
  - External Beam Radiation Therapy
- 2000's
  - Wide local resection
  - Sentinel nodes
  - Partial breast irradiation???



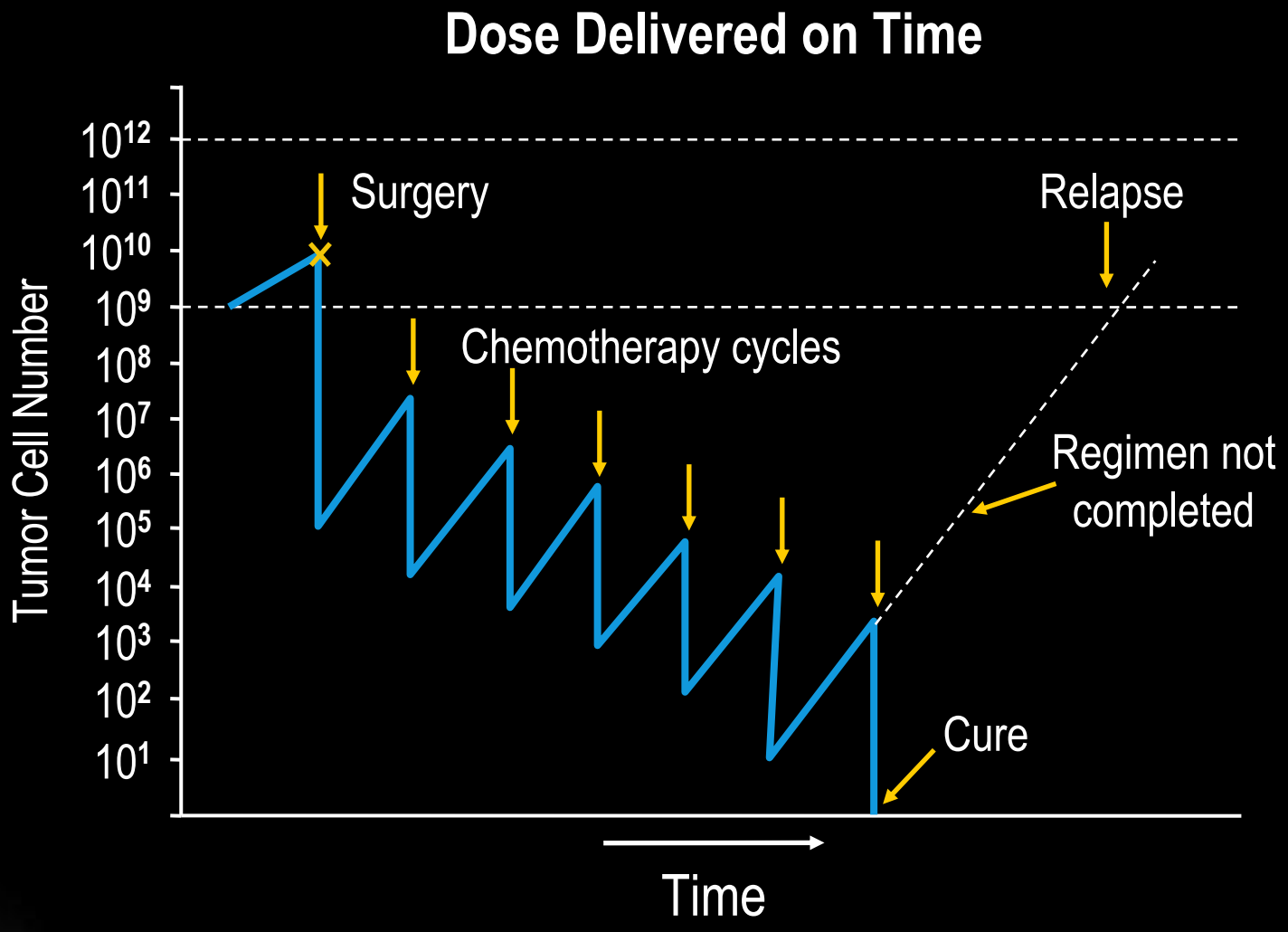


Adjuvant Systemic Therapy for Early Breast Cancer

- Eliminate micrometastatic disease



Theoretical Cure With Adjuvant Chemotherapy



Adapted from: Norton L. *Oncologist.* 2001;6(suppl 3):30-35.

The field of breast cancer is experiencing a major paradigm shift…

THE OLD WAY:

- Use **anatomic predictors** to risk-stratify patients
- **Treat the entire population** of breast cancer patients:
  Small relative benefits = Large absolute numbers

THE NEW WAY:

- Use **biologic factors** to risk-stratify patients
- **Individualize therapy** to each patient:
  Offer the most effective therapy(ies) for each tumor

How To Risk-Stratify and Make Treatment Decisions for Early Breast Cancer by Anatomic Size

(i.e. how "big" is the tumor?)

10-yr DFS Estimates with loco-regional therapy alone (No systemic adjuvant therapy) according to +ve nodes, 1º tumor size

# positive nodes	<1 cm	1-2 cm	2-3 cm	3-4 cm	4-5 cm	>5 cm
0	90	81	75	69	63	56
1-3	60	56	50	47	42	37
4-6	46	42	38	35	31	27
6-9	36	32	29	26	21	18
≥10	22	19	17	16	14	13

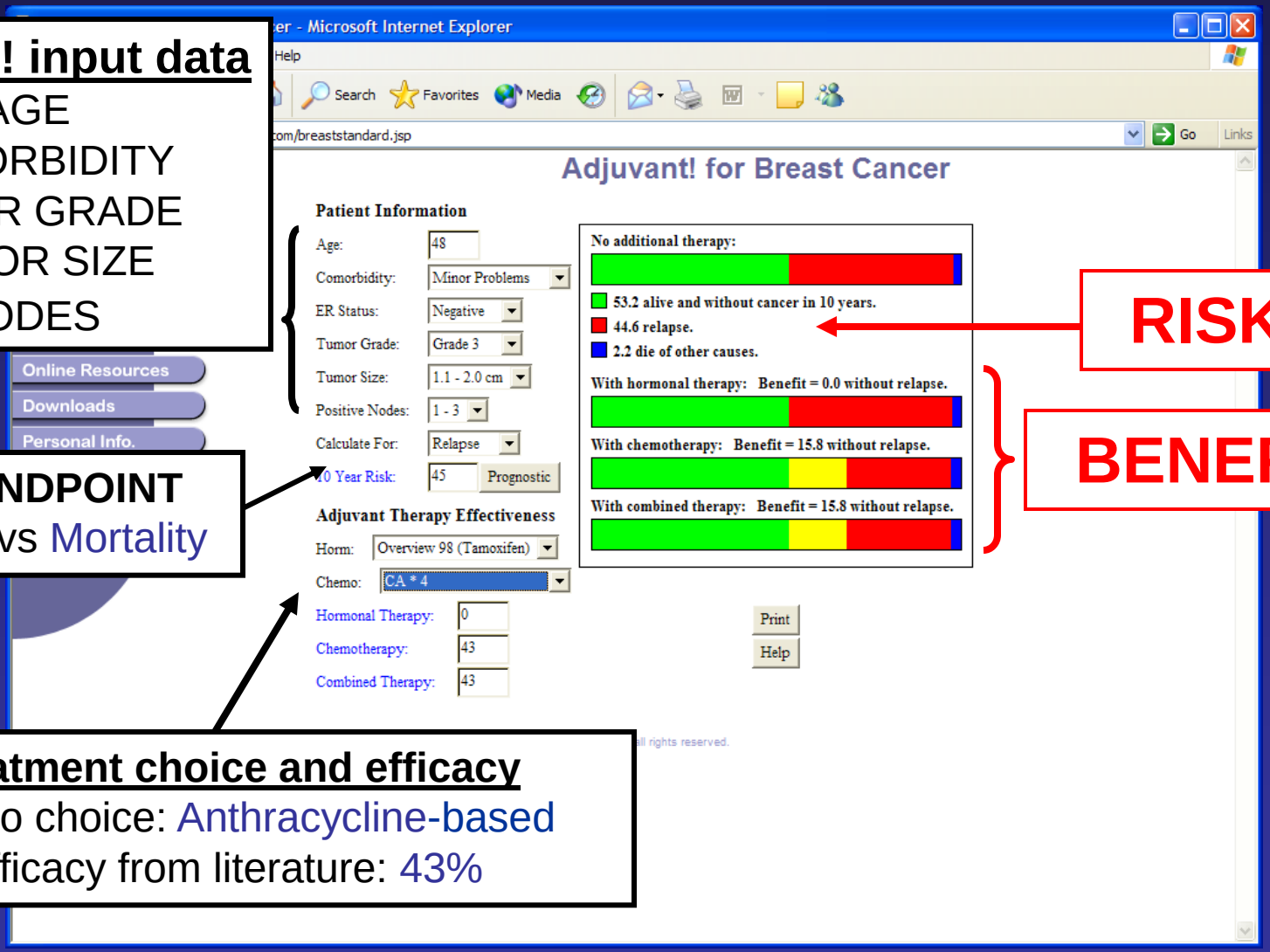
Values in body of table are percentages

Loprinzi JCO 2001;19(4)

Adjuvant!
www.adjuvantonline.com

Adjuvant! input data

AGE
COMORBIDITY
TUMOR GRADE
TUMOR SIZE
NODES



RISK

BENEFIT

10-yr ENDPOINT
Relapse vs Mortality

Treatment choice and efficacy
Chemo choice: Anthracycline-based
Efficacy from literature: 43%

Adjuvant! independent validation

British Columbia Cancer Agency

4083 women diagnosed with Stage I/II breast cancer 1989-1993.
Compare 10-yr predicted vs. observed breast cancer outcomes.

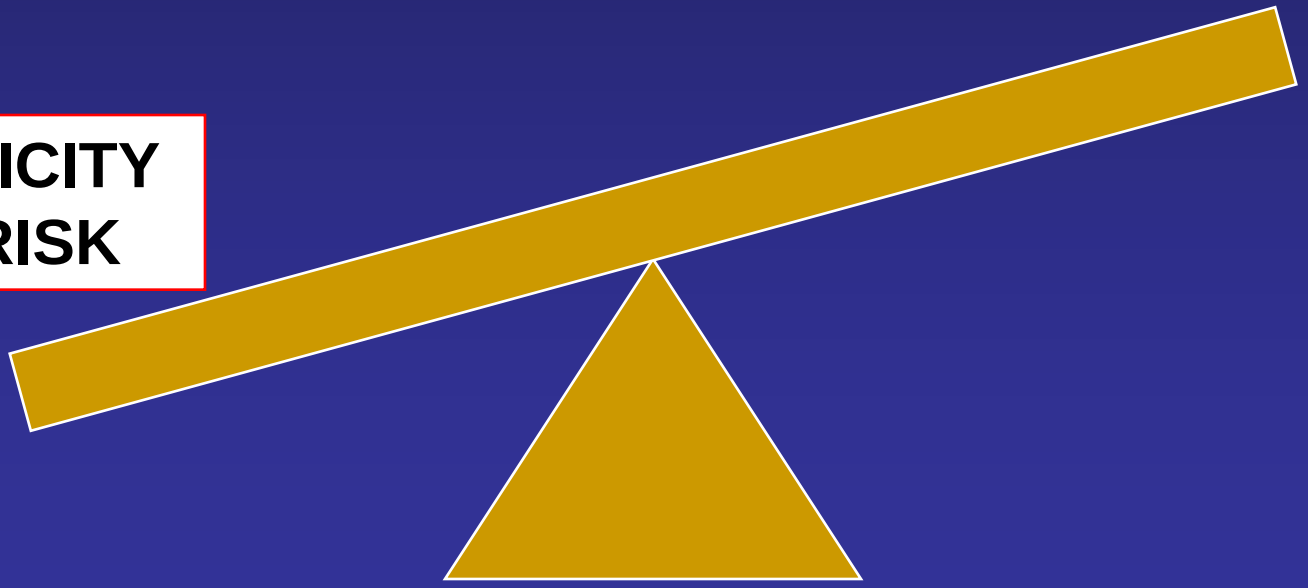
Predicted vs. Observed 10-yr Breast Cancer Specific Survival				
Adjuvant therapy	N	Predicted by Adjuvant!	BCOU Observed	Pred - Obs
No Rx	1842	**89.1%**	**90.0%**	**-1.0%**
TAM alone	1249	**81.2%**	**79.4%**	**1.8%**
Chemo alone	631	**74.6%**	**73.7%**	**+0.9%**
Chemo + TAM	371	**75.2%**	**70.6%**	**+4.6%**

Olivotto IA et al. ASCO 2004 abst #522

Balancing risks and benefits in adjuvant breast cancer treatment

REDUCTION IN BREAST CANCER RECURRENCE

TOXICITY & RISK



The Early Breast Cancer Trialists Collaborative Group i.e. “The Oxford Overview”

The basis for “Group Therapy” of early breast cancer

Breast Cancer

Public Health impact of Adjuvant Treatment

Annual Incidence in USA > 180,000

Candidates for Adjuvant Therapy > 100,000

Modest benefit (i.e. 2% @ 10 years) translates into a large absolute benefit (2,000 relapse free @ 10 years) *across the entire population*

EBCTCG - 2000

- All women on randomized trials begun before 1996 with survival main endpoint
- Tamoxifen
  50,000 tamoxifen
  (10,000 – 5 years vs none)
- Ovarian Ablation: 4900 + 4200 for Goserelin
- Chemotherapy
  28,000 polychemo

Lancet 2005

15 year followup for early invasive breast cancer

Treatment	Proportional Annual Recurrence Reduction
Tamoxifen x 5 yrs (HR+)	40% (+/- 3%)
Combination Chemo (CMF, AC, etc…)	24% (+/- 2%)
Ovarian Ablation (HR+ premenopausal or <50 yo)	31% (+/- 8%) [7% +/- 4% w/ chemo]

The impact of adjuvant therapy is proportional to the risk of relapse

33% reduction in annual risk of relapse

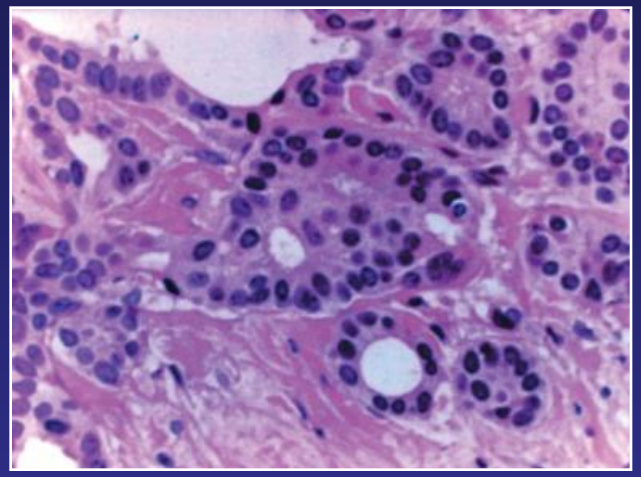
Adjuvant breast cancer chemotherapy regimens

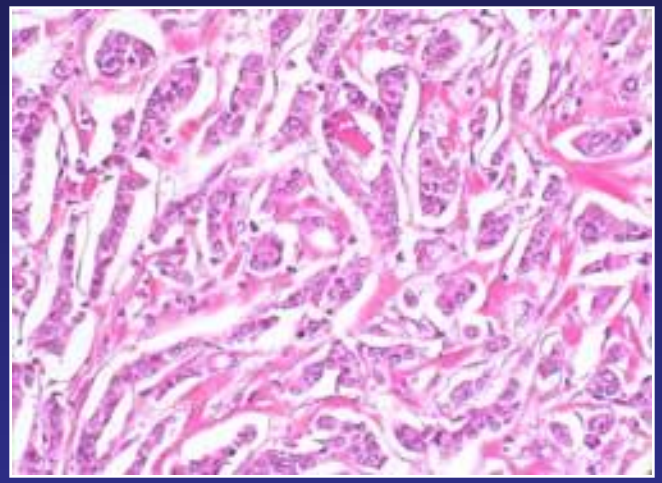
CMF	Cyclophosphamide + Methotrexate + 5-Flurouracil
AC	Doxorubicin (Adriamycin™) + Cyclophosphamide
AC-Taxol	AC + Paclitaxel
TAC	Docetaxel (Taxotere™) + Doxorubicin (Adriamycin™) + Cyclophosphamide
FAC/FEC	Fluorouracil + Doxorubicin or Epirubicin + Cyclophosphamide
TC	Docetaxel (Taxotere™) + Cyclophosphamide

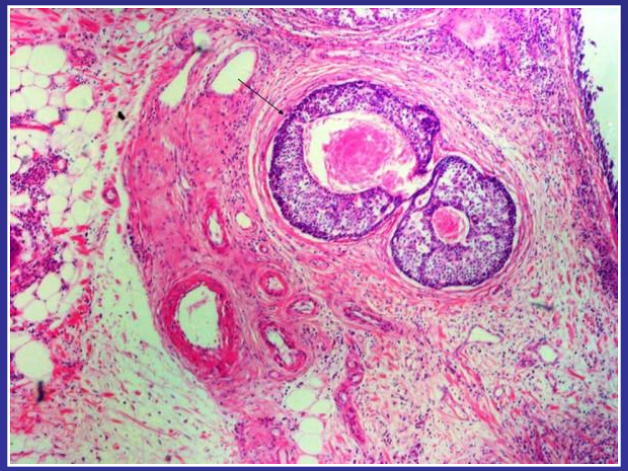
Can we be smarter about risk stratifying and treating breast cancer, by understanding the underlying *biology* of the tumor?

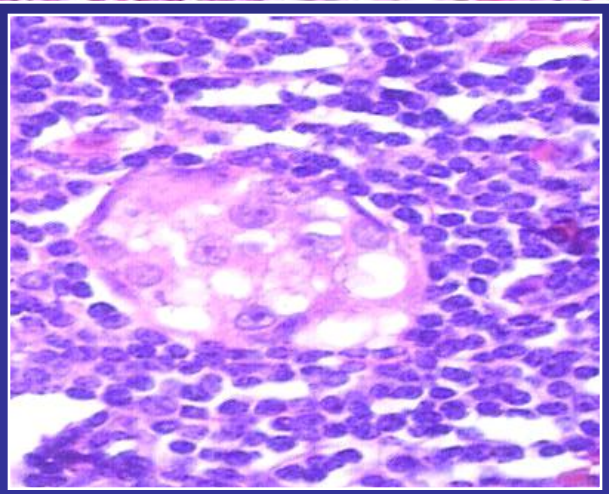
1. HER2-positive breast cancer
2. Hormone receptor-positive breast cancer

Risk stratification according to anatomy does NOT take into account the underlying biologic characteristics of the tumor







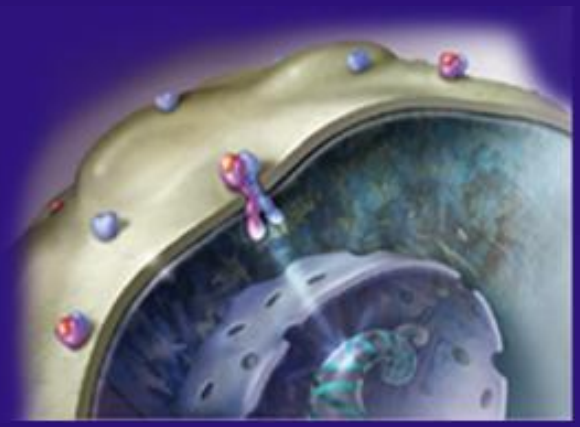


The HER2-positive subset of Breast Cancers

The HER2+ subtype of breast cancer and its clinical management

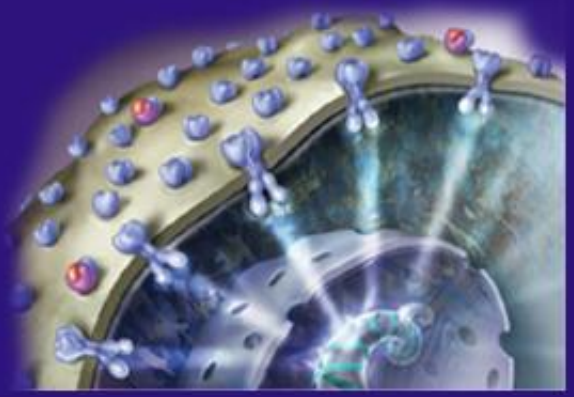
- HER2+ represents a distinct molecular subtype
- HER2+ tumors have a unique clinical behaviour (shorter DFS, more visceral and CNS metastases)
- HER2+ tumors exhibit a peculiar pattern of sensitivity to chemo and hormonal therapy
- HER2 targeting agents have dramatically changed the course of this disease and represent now the foundation of treatment in early and advanced disease

HER2 Overexpression in Breast Cancer

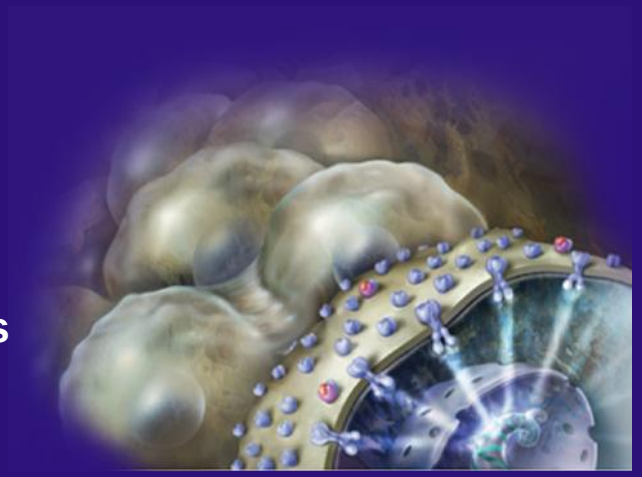


Normal (1X)
~20,000-50,000
HER2 receptors

HER2 is overexpressed in ~20% of breast cancers



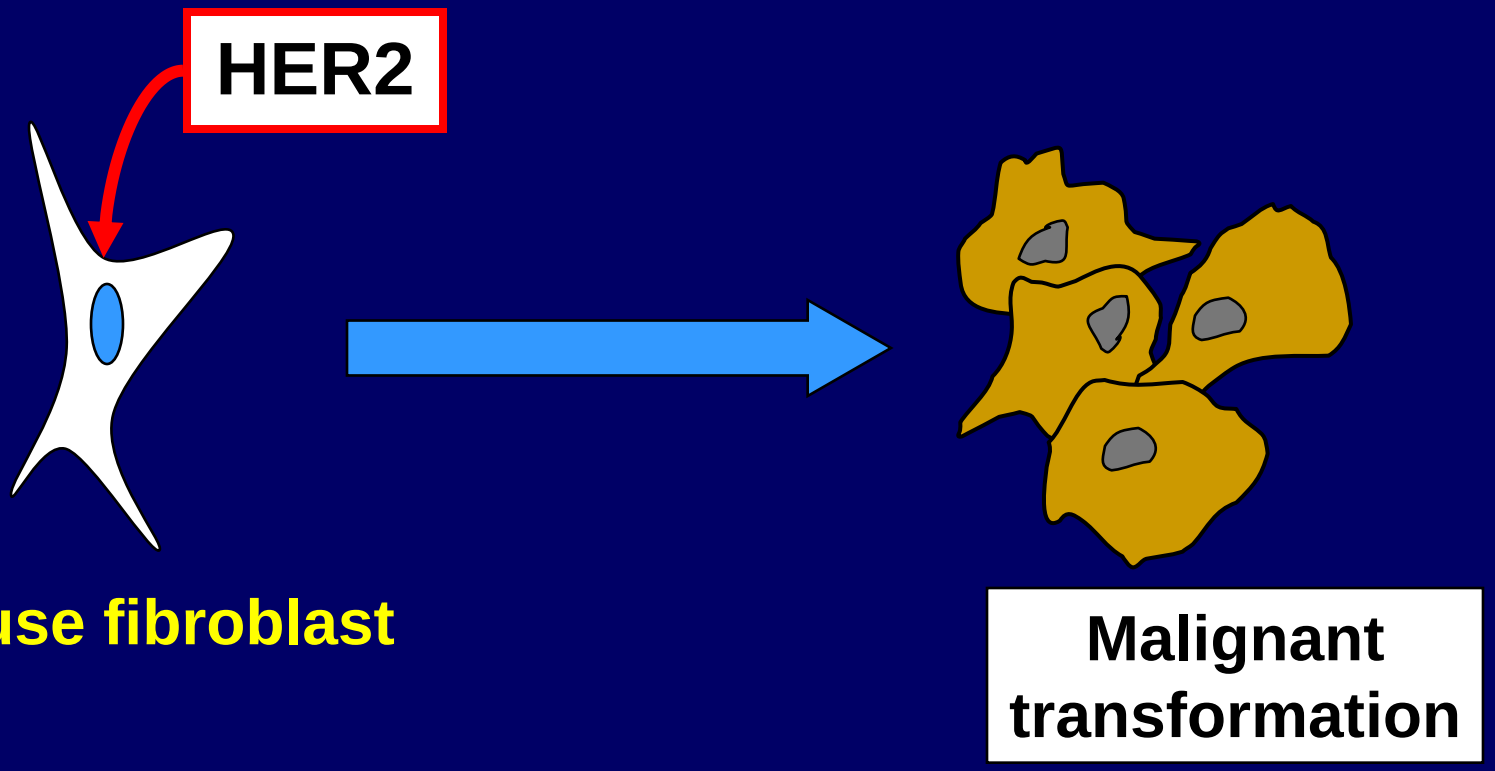
Overexpressed HER2 (10-100X)
Up to ~2,000,000 HER2 receptors



Cell-cycle progression
Survival & Treatment Resistance
Proliferation

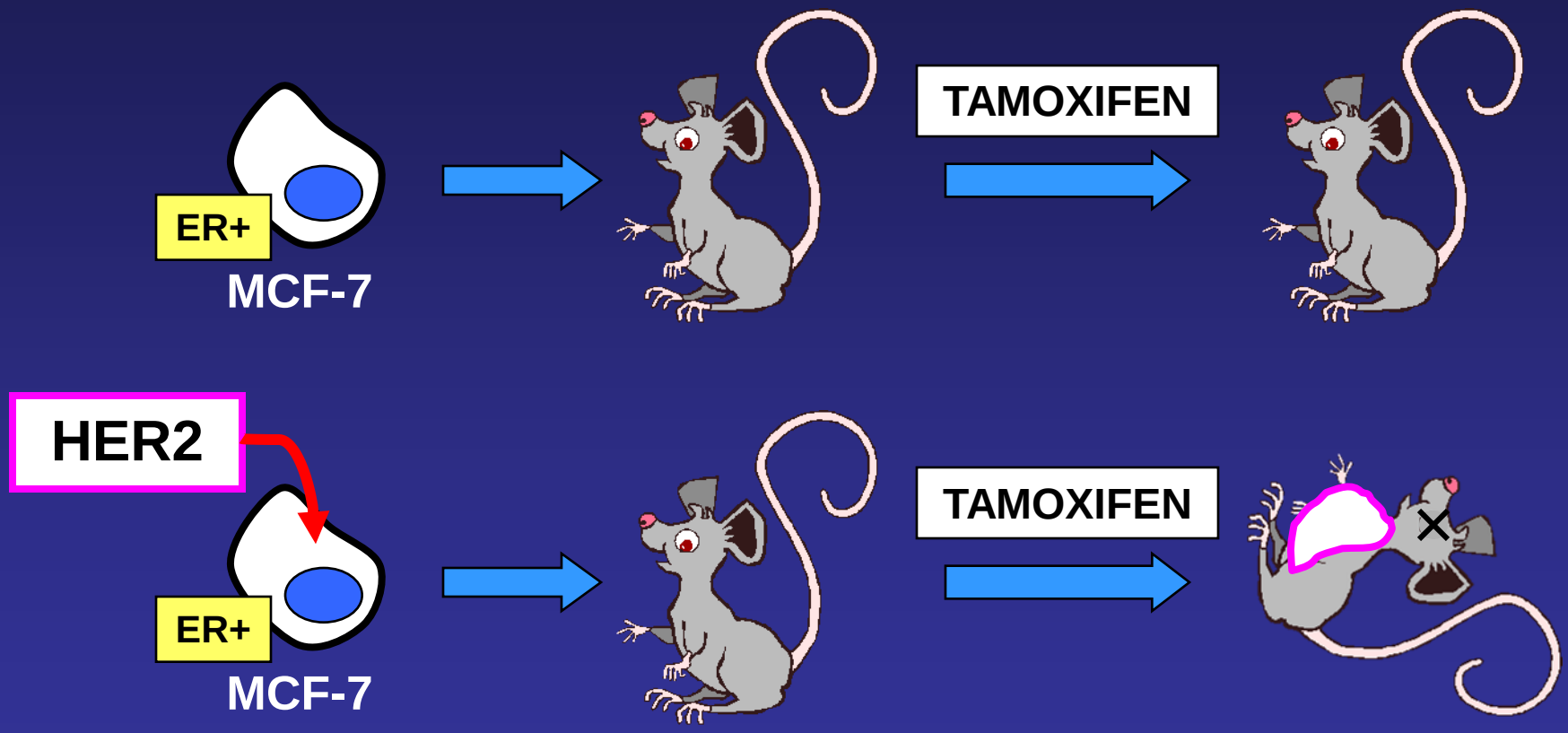
Pegram et al. *Cancer Treat Res*. 2000;103:57.
Ross and Fletcher. *Am J Clin Pathol*. 1999;112(suppl 1):S53.
Slamon et al. *Science*. 1987;235:177.

HER2 over-expression is sufficient to induce malignant phenotype



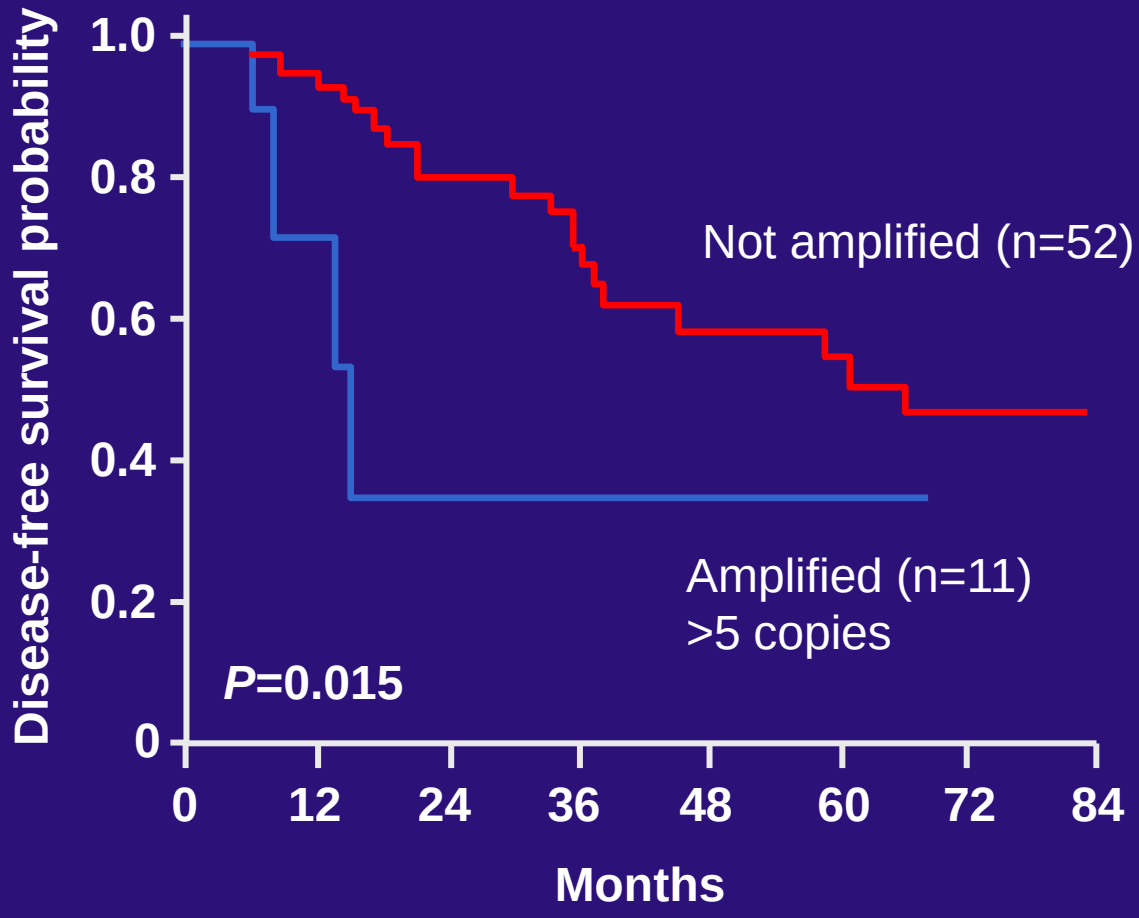
Chazin et al. Transformation mediated by the human HER-2 gene independent of epidermal growth factor receptor. Oncogene 1992;7(9):1859-66.

HER2 over-expression leads to hormone-independent growth



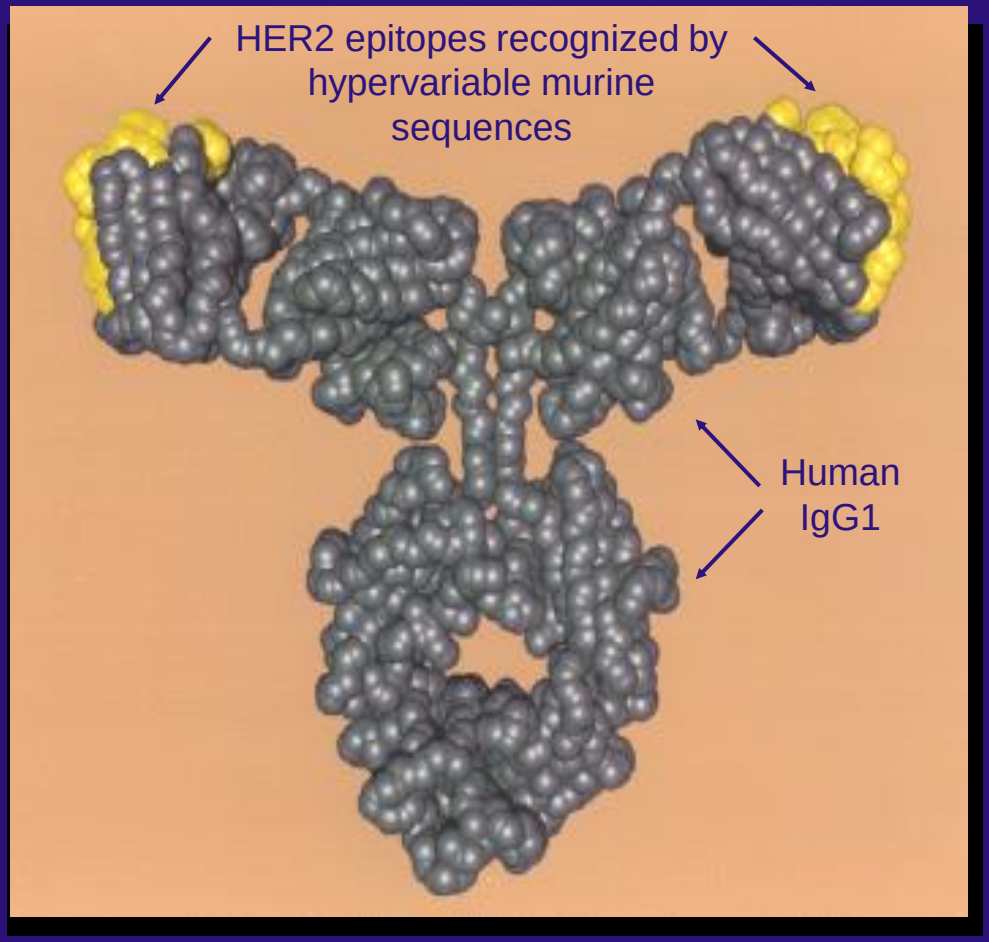
Benz et al. Estrogen-dependent, tamoxifen-resistant tumorigenic growth of MCF-7 cells transfected with HER2/neu. Breast Cancer Res Treat. 1992;24:85-95

HER2-Positive Breast Cancer



Slamon et al. *Science*. 1987;235:177.

Trastuzumab (Herceptin™): Humanized Anti-HER2 mAb



- Targets HER2 protein
- Selectively binds with high affinity ($K_d \leq 0.5$ nM)
- 95% human, 5% murine

Carter et al. *Proc Natl Acad Sci U S A*. 1992;89:4285.

Proposed mechanisms of trastuzmab action (1)

Internalization and degradation of HER2 receptor protein	Western blot shows trastuzumab downregulates HER2 protein in SKBR3 and MDA453 cells
Induces p27Kip1 levels and P27Kip1-CDK2 interaction, decreasing CDK2 activity	Western blot, immunoprecipitation, & kinase assay show that trastuzumab treatment of SKBR3 and BT474 cell lines increase P27Kip1 levels and interaction with CDK2, resulting in decreased CDK2 activity.
Blocks HER2 signaling via disruption of PI3K/Akt signaling pathway	Western blot shows that trastuzumab decreases phospho-Akt levels and AKt kinase activity. Trastuzumab increases membrane localization of PTEN (P13K/Akt-inhibiting molecule)
Reduces angiogenesis	Trastuzumab treatment of breast ca xenografts reduces levels of VEGF, induces TSP1, and decreases microvessel growth

Proposed mechanisms of trastuzmab action (2)

Immune effects: Stimulation of natural killer cells and activation of ADCC

Lymphoid infiltration of tumor noted in pts who receive preop trastuzumab, and level of lymphocyte infiltration correlated with response to therapy.

The Fc domain of trastuzumab IgG1 binds the Fc gamma receptor of NK cells, activating NK cell-mediated lysis.

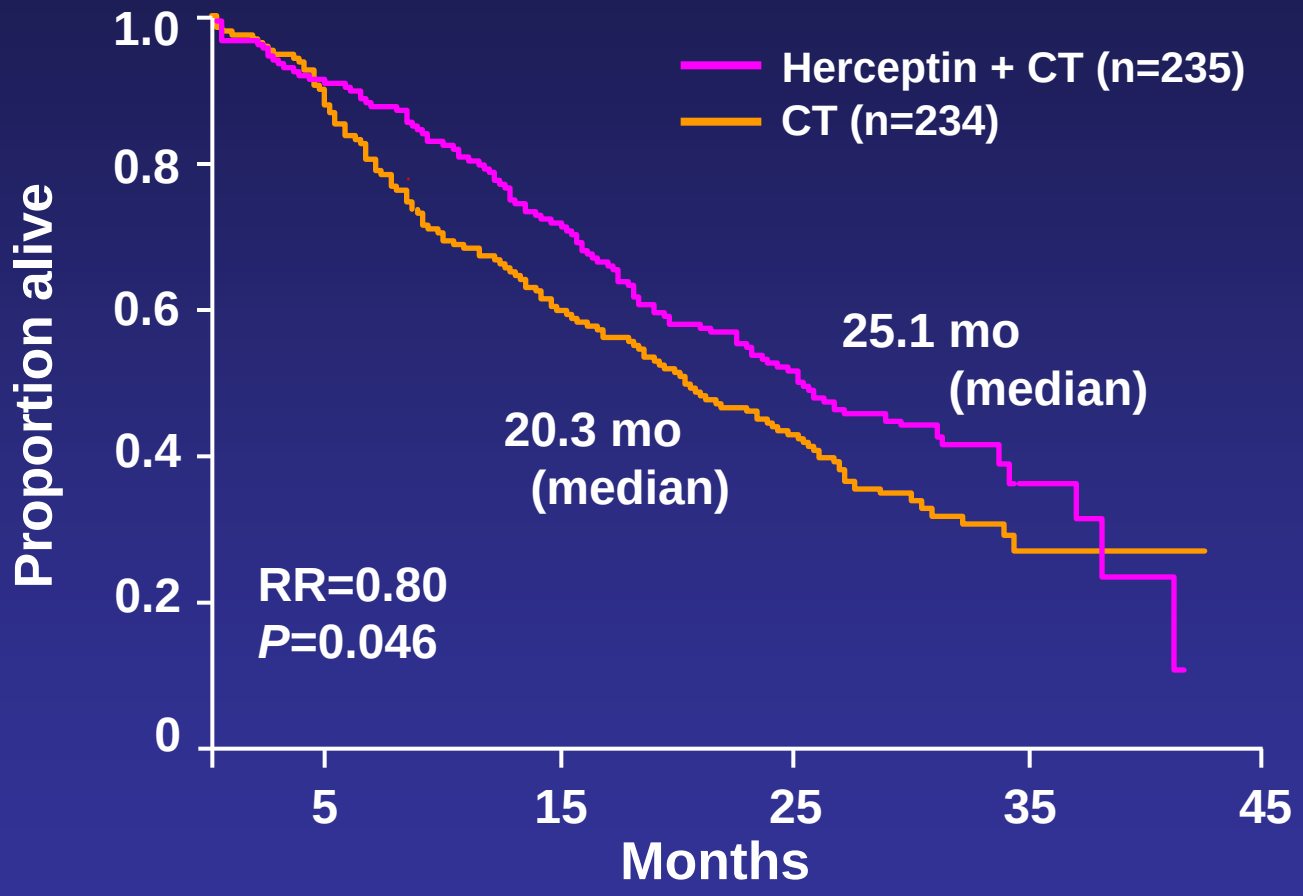
Inhibits HER2 extracellular domain proteolysis

Trastuzumab inhibits basal and activated HER2 ECD cleavage in vitro. ECD levels decline in pts who respond to trastuzumab + docetaxel.

Inhibits DNA repair

Trastuzumab partially inhibits repair of DNA adducts in vitro after treatment with cisplatin and radiation.

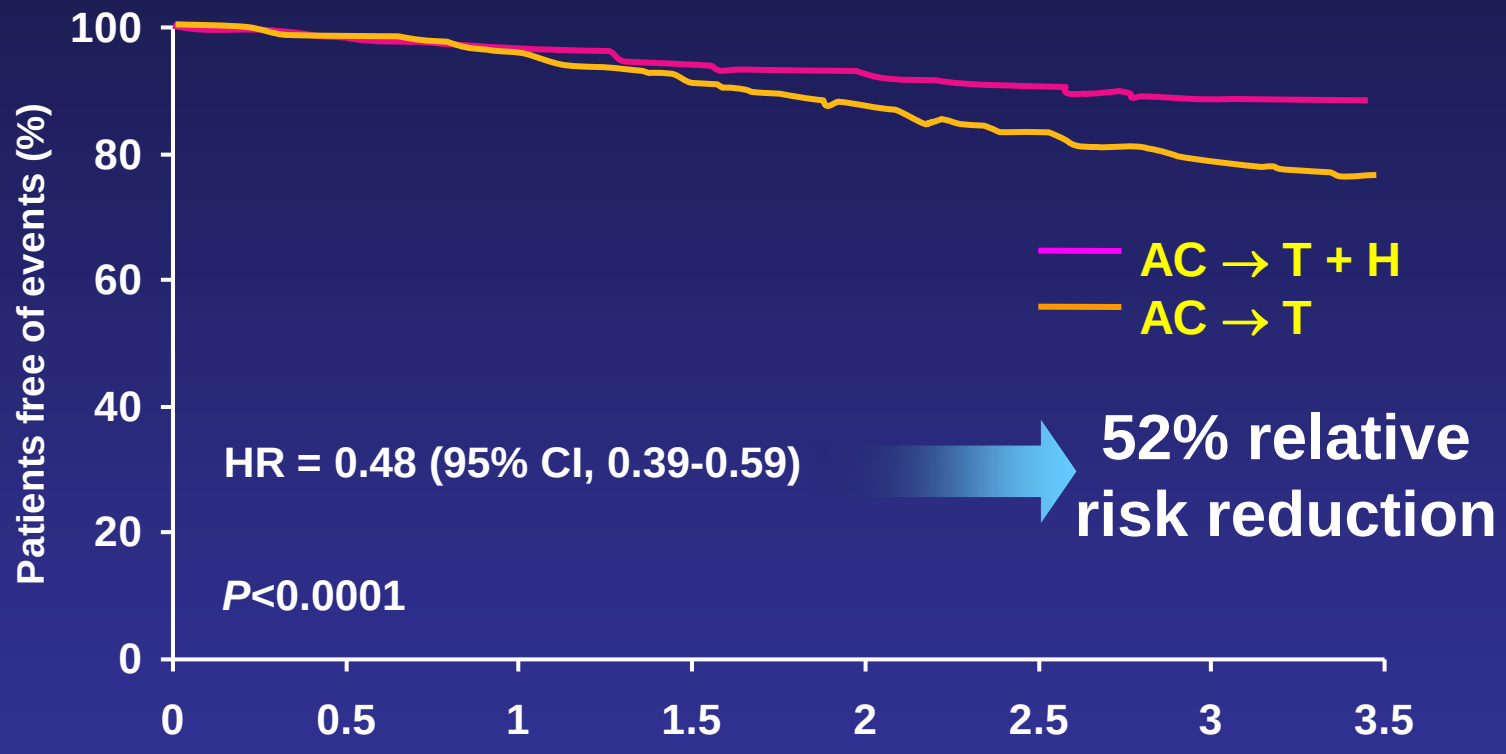
Trastuzumab (Herceptin™) Combination Pivotal Trial in First-line MBC: Overall Survival



CT = chemotherapy (either doxorubicin or epirubicin + cyclophosphamide, or paclitaxel).

Slamon et al. *N Engl J Med.* 2001;344:783.

B-31/N9831 Combined Analysis: DFS (Median f/u: 2.5 years)



Number at risk								
AC → T + H	1872	1529	1240	997	764	575	426	239
AC → T	1880	1490	1159	926	689	534	375	195

Herceptin® (trastuzumab) PI. November 2006.

Why target HER2 using agents other than Trastuzumab in Breast Cancer?

- Efficacy
- Primary resistance
- Secondary resistance
- Cardiac safety
- HER2 + molecular subtypes

Proposed mechanisms of trastuzmab resistance

PTEN loss	Trastuzumab disrupts Src binding to HER2, allowing PTEN to inhibit Akt and induce growth arrest.
Activation of alternative pathways	Insulin-like growth factor-I receptor promotes proliferation and metastases. Trastuzumab is completely unable to block proliferation in cell lines expressing IGF-IR/HER2 heterodimers
Expression of ligands of the EGFR family	Excess EGFR family ligands (particularly TGFα) drive cells towards proliferation and inhibition of apoptosis.
Receptor masking or epitope inaccessibility	MUC4 levels are higher in trastuzumab resistant clones

Lapatinib

Drug Profile

Lapatinib is the first-in-class oral small-molecule inhibitor *HER2* tyrosine kinase:

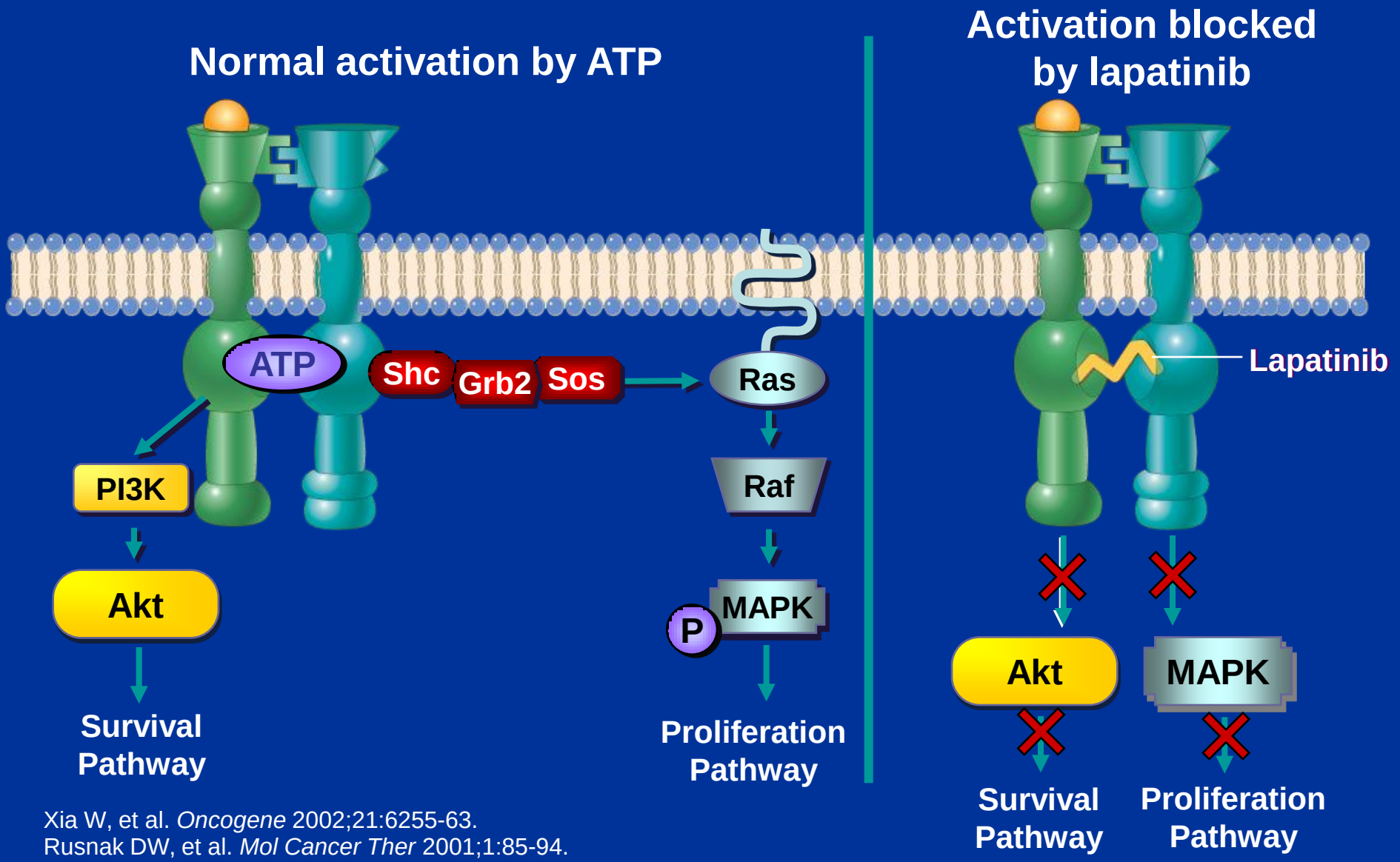
- Belongs to the 4-anilinoquinazoline class of tyrosine kinase inhibitors
- Binds reversibly to the cytoplasmic ATP-binding site of the kinase, thereby preventing receptor phosphorylation and activation
- Works intracellularly

N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2(methylsulfonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine

Xia W, et al. *Oncogene*. 2002;21:6255-6263.

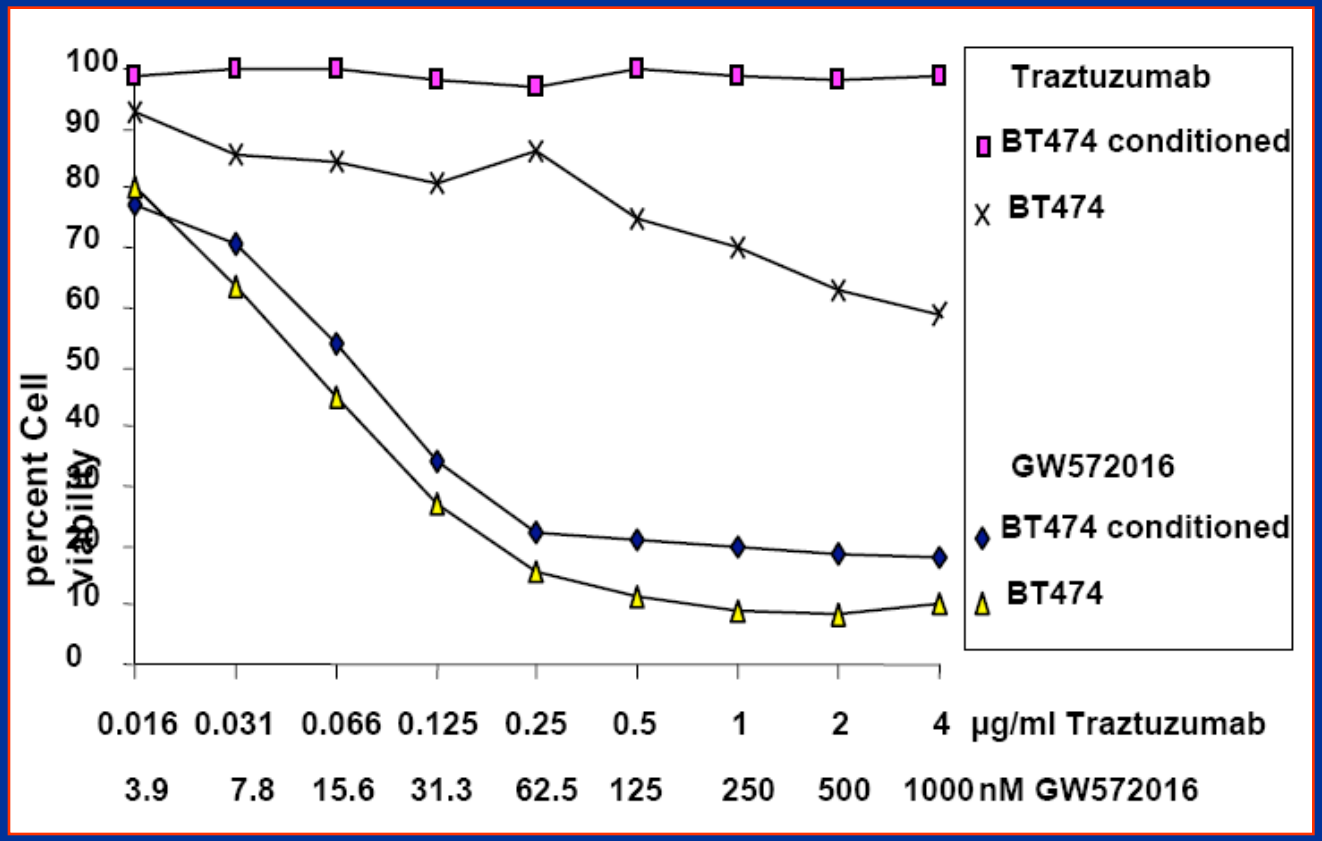
Lapatinib

Mechanism of Action



Xia W, et al. *Oncogene* 2002;21:6255-63.
Rusnak DW, et al. *Mol Cancer Ther* 2001;1:85-94.

Non cross-resistance of lapatinib and trastuzumab *in vitro*

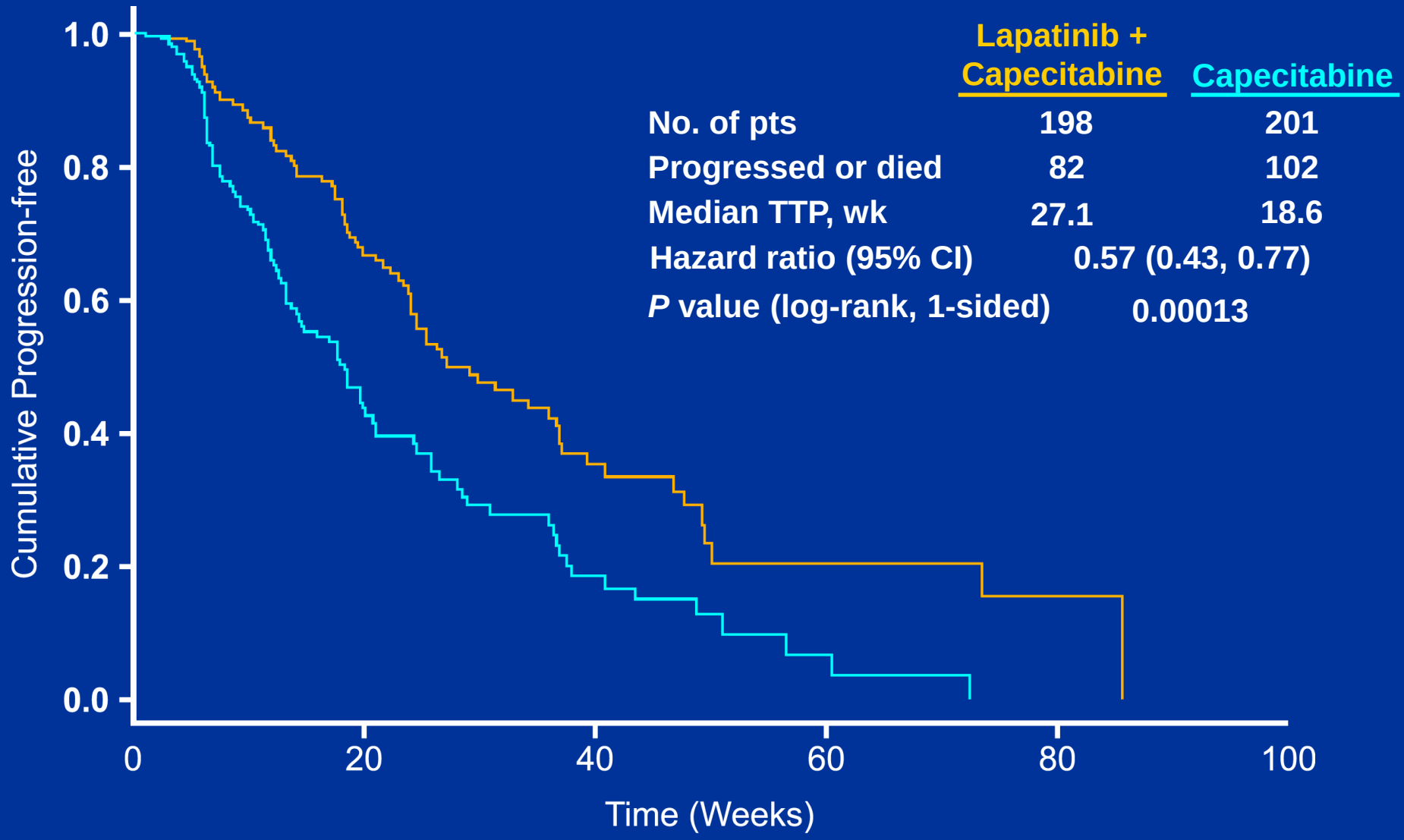


Activity of GW570216 (lapatinib) in HER2 over-expressing cells selected for long-term outgrowth in 100 µg/mL trastuzumab

Konecny, Pegram et al. *Cancer Res* 2006;66:1630-9.

Time to Progression: *Intent-to-Treat Population*

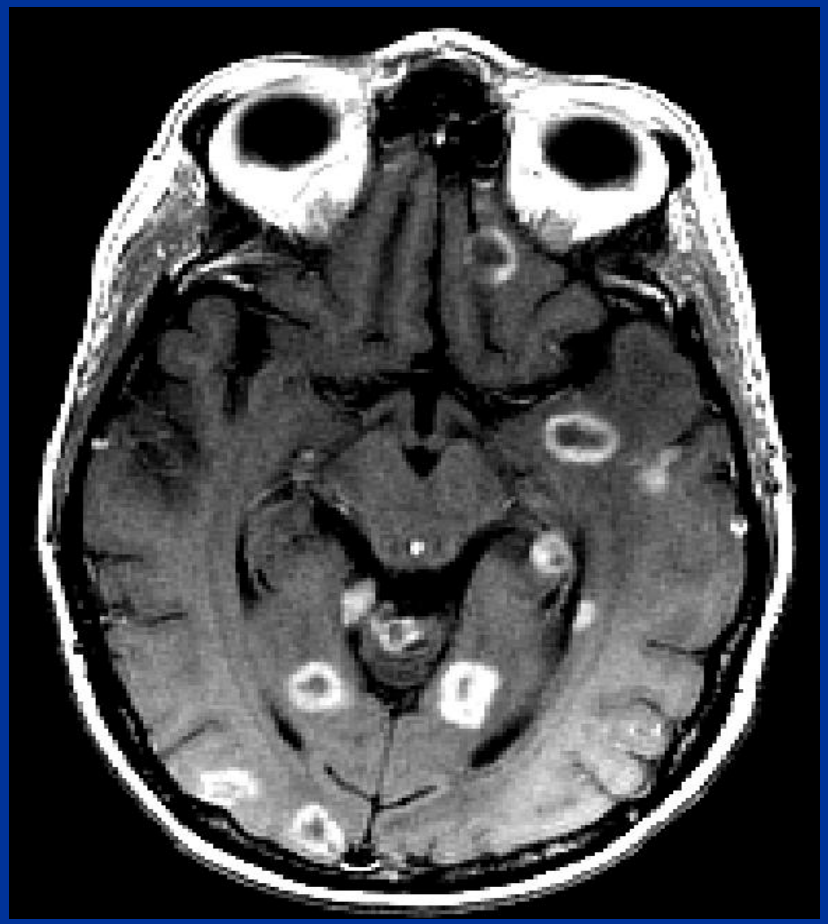
Independent Assessment



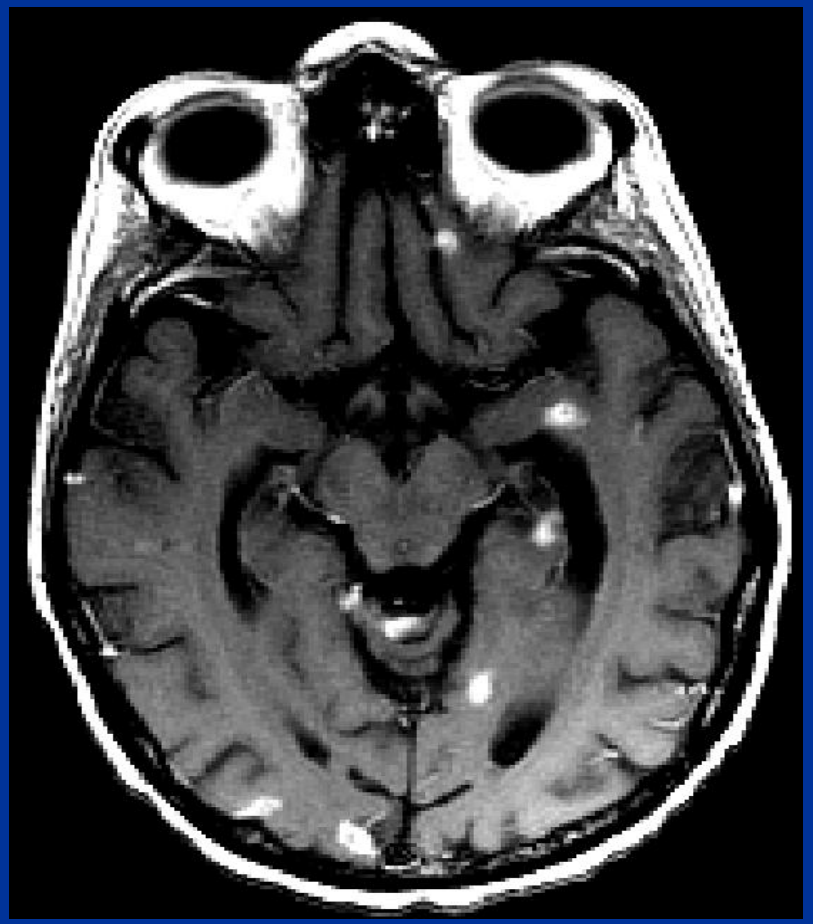
	Lapatinib + Capecitabine	Capecitabine
No. of pts	198	201
Progressed or died	82	102
Median TTP, wk	27.1	18.6
Hazard ratio (95% CI)	0.57 (0.43, 0.77)	
P value (log-rank, 1-sided)	0.00013	

CNS activity of lapatinib?

Baseline



Week 8



The Hormone Receptor-Positive subset of Breast Cancers

Estrogen as a risk factor for breast cancer

Hormone-Dependent Indicators of Breast Cancer Risk (1)

Indicator	Risk group		Relative Risk
	Low	High	
Gender	Male	Female	150
Age (y)	30 - 34	70 - 74	17.0
Age at menarche	>14 years	<12 years	1.5
Oral contraceptive use	No	Yes	1.04 – 1.2
Age at first child birth (y)	<20 years	>30 years	1.9 – 3.5
Breast feeding (mo)	>16 months	0	1.37
Parity	>5	0	1.4
Age at menopause (y)	<45 years	>55 years	2.0

Clemons and Goss. N Engl J Med. 2001;344:276.

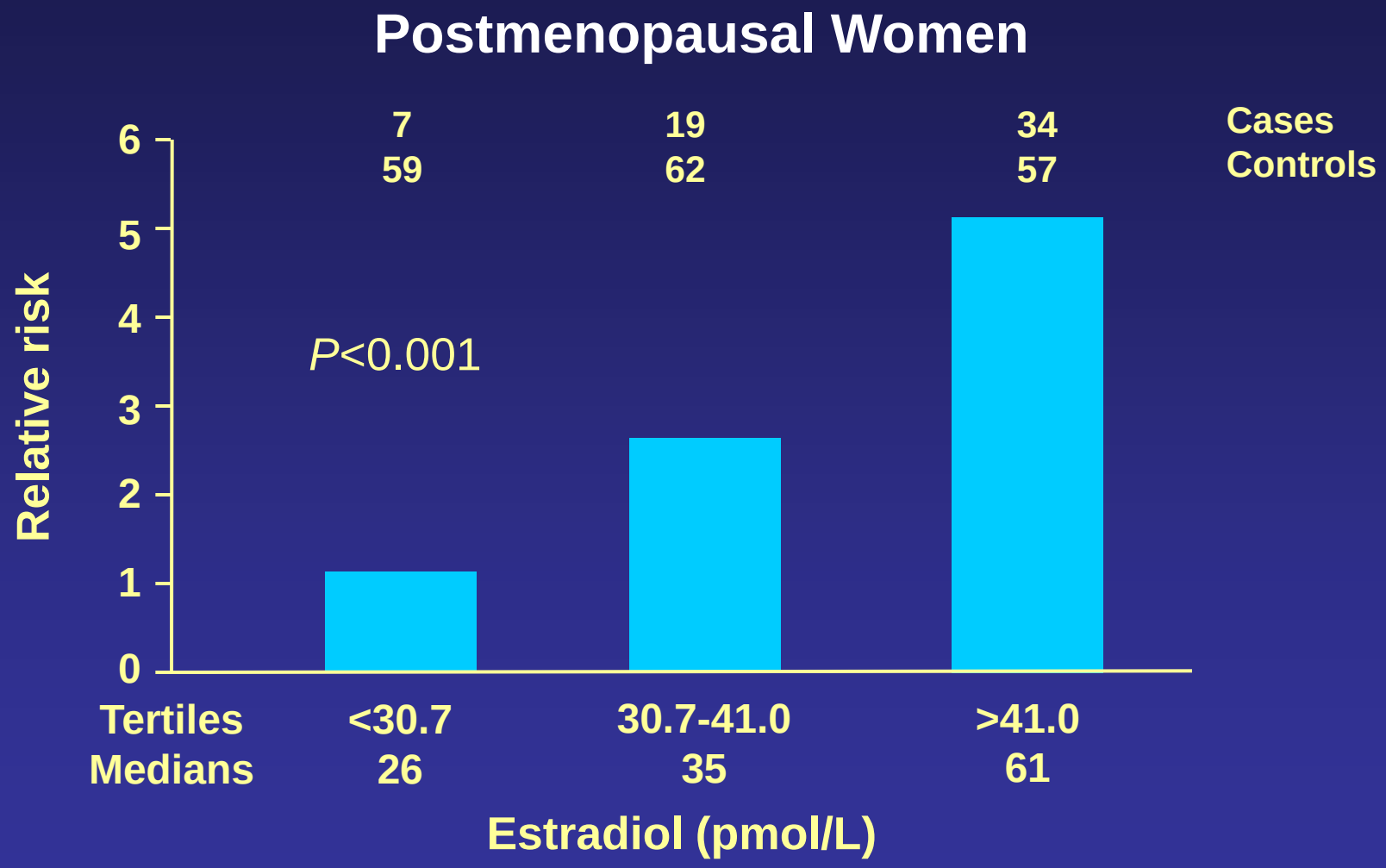
Hormone-Dependent Indicators of Breast Cancer Risk (2)

Indicator	Risk group		Relative Risk
	Low	High	
Age at oophorectomy	<35	Never	3.0
Estrogen therapy	Never	Current	1.2 – 1.4
Estrogen/progestin therapy	Never	Current	1.4
Postmenopausal BMI	<22.9	>30.7	1.6
Family history	No	Yes	2.6
Serum estradiol levels	Low quartile	High quartile	1.8 – 5.0
Breast density (%)*	0	≥75	6.0
Bone density	Low quartile	High quartile	2.7 – 3.5

***by mammography**

Clemons and Goss. N Engl J Med. 2001;344:276.

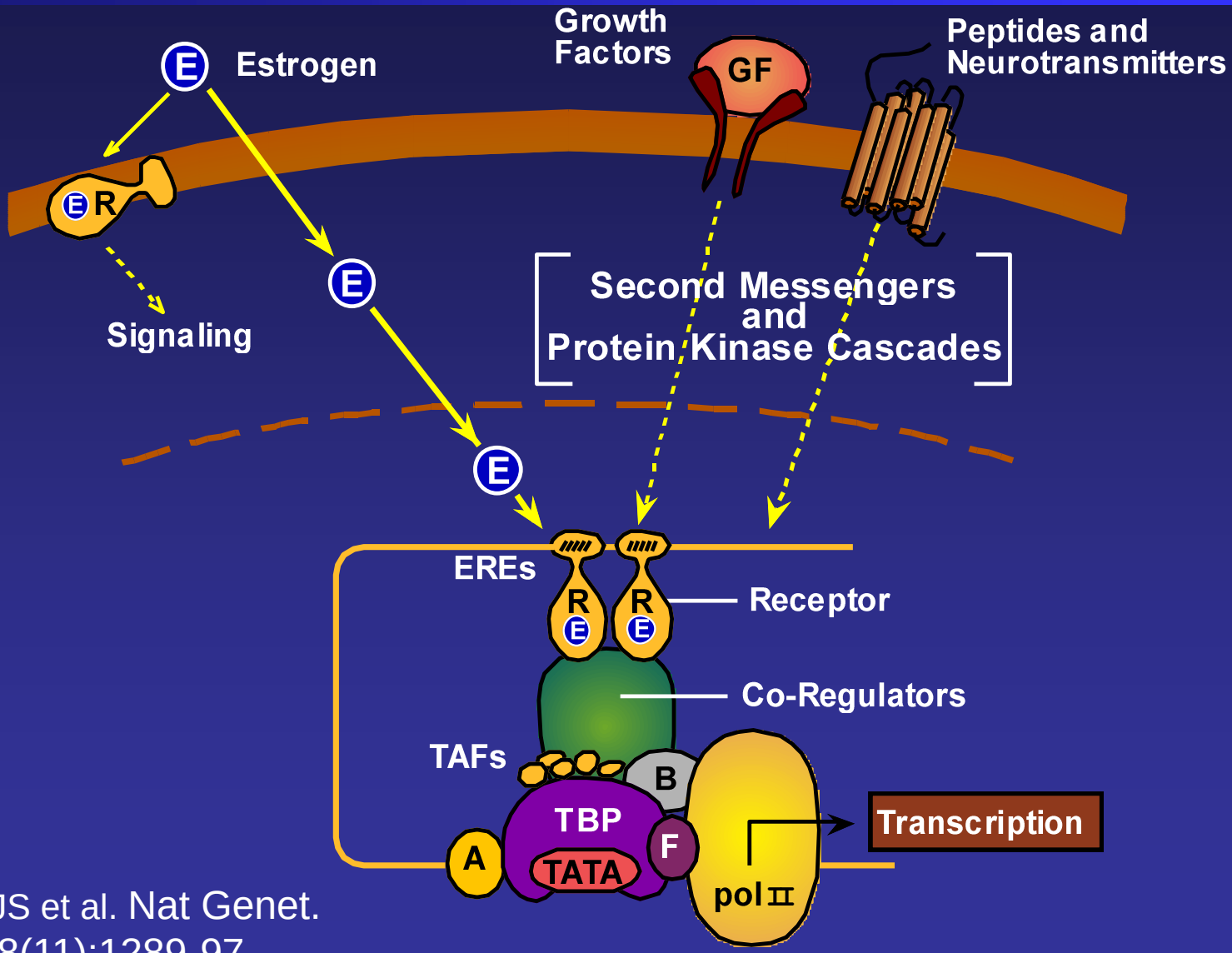
Odds Ratios of Developing Breast Cancer in Relation to Plasma Estradiol



Thomas et al. Br J Cancer. 1997;76:401.

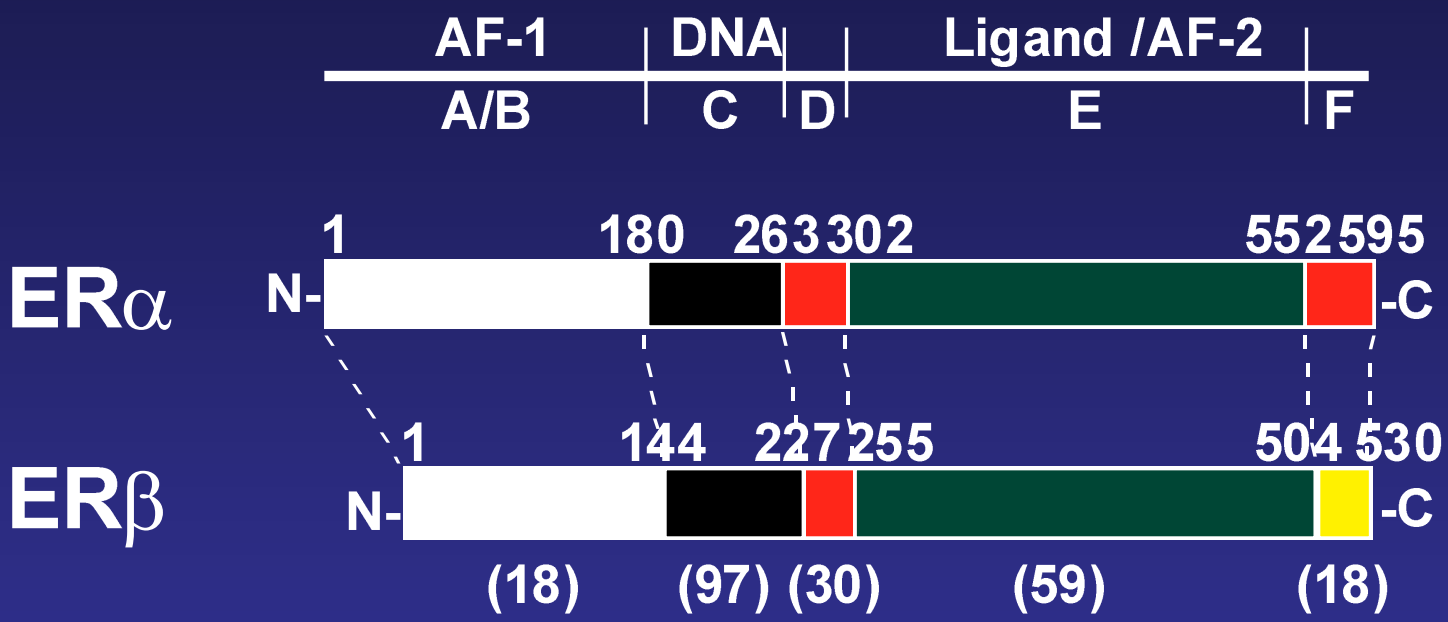
Estrogen and Carcinogenesis in the Breast

Estrogen receptor:
A Genome-Wide Transcription Regulator



Carroll JS et al. Nat Genet. 2006;38(11):1289-97

Human Estrogen Receptors α and β



- Different tissue/cell distributions
- Different affinity for ligands
- Different gene activations

Exquisite Precision in Receptor Regulation

Small Changes In Ligand Structure

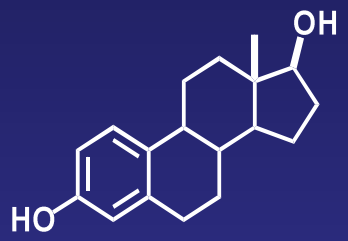
Major Changes In Biological Character

ERα, ERβ Different Ligands

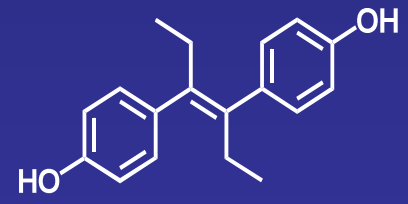
Different Pharmacology At Different Target Genes

Ligands for Estrogen Receptors

Estrogens

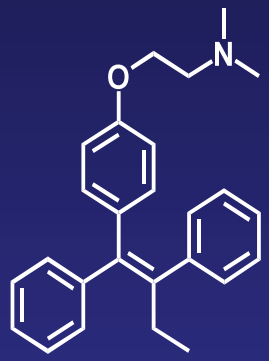


Estradiol

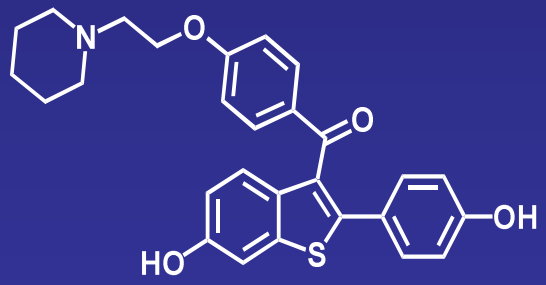


Diethylstilbestrol

Known SERMs



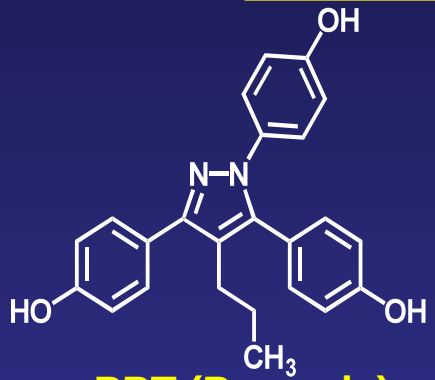
Tamoxifen



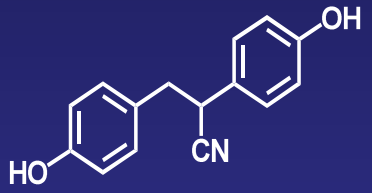
Raloxifene

Droloxifene, Idoxifene, Toremifene, GW5638, EM652, Cp-336156, others

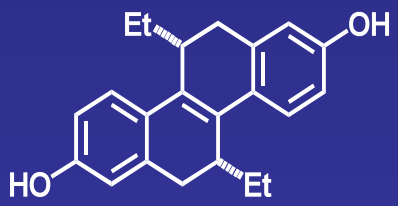
Novel ERα/ERβ Selective Ligands



PPT (Pyrazole)
ERα Agonist



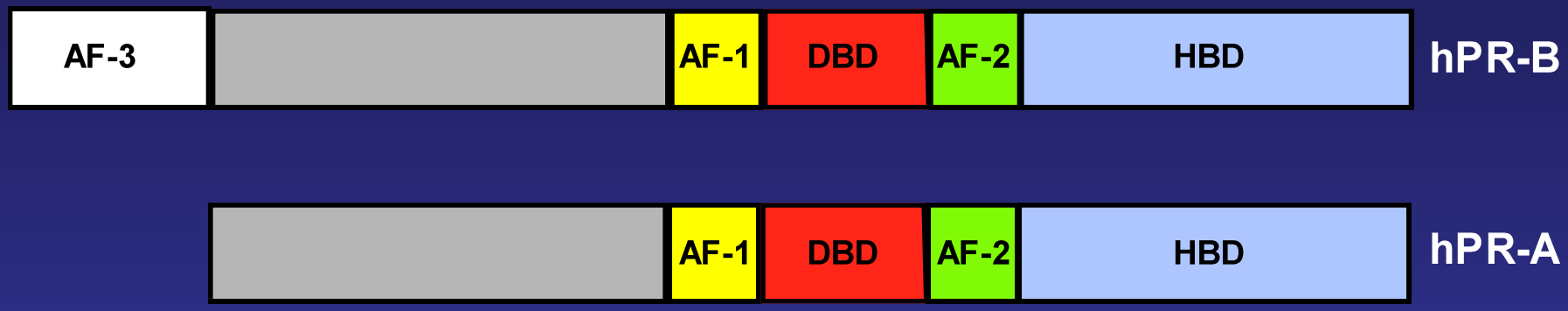
DPN (Nitrile)
ERβ Agonist



R,R-THC
ERα Agonist &
ERβ Antagonist

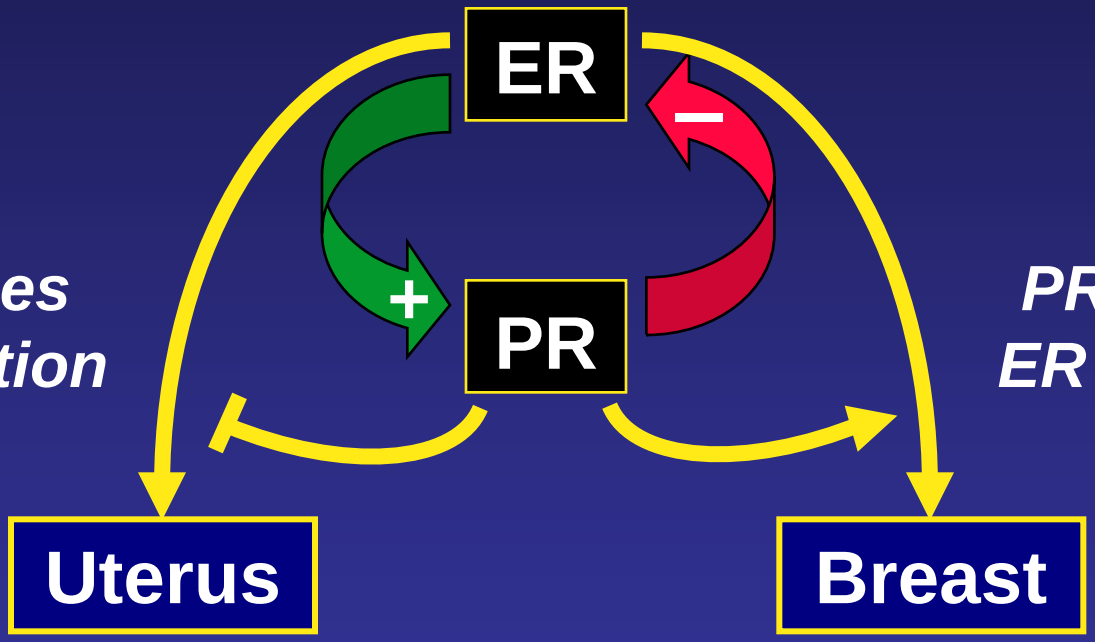
MPP
ERα Antagonist

Human Progesterone Receptor: A and B Forms



- From single gene by alternate transcription initiation (different promoters)
- Different activities

Inter-relationships Between Estrogen and Progestin Receptor Signaling Pathways



PR Opposes ER Stimulation

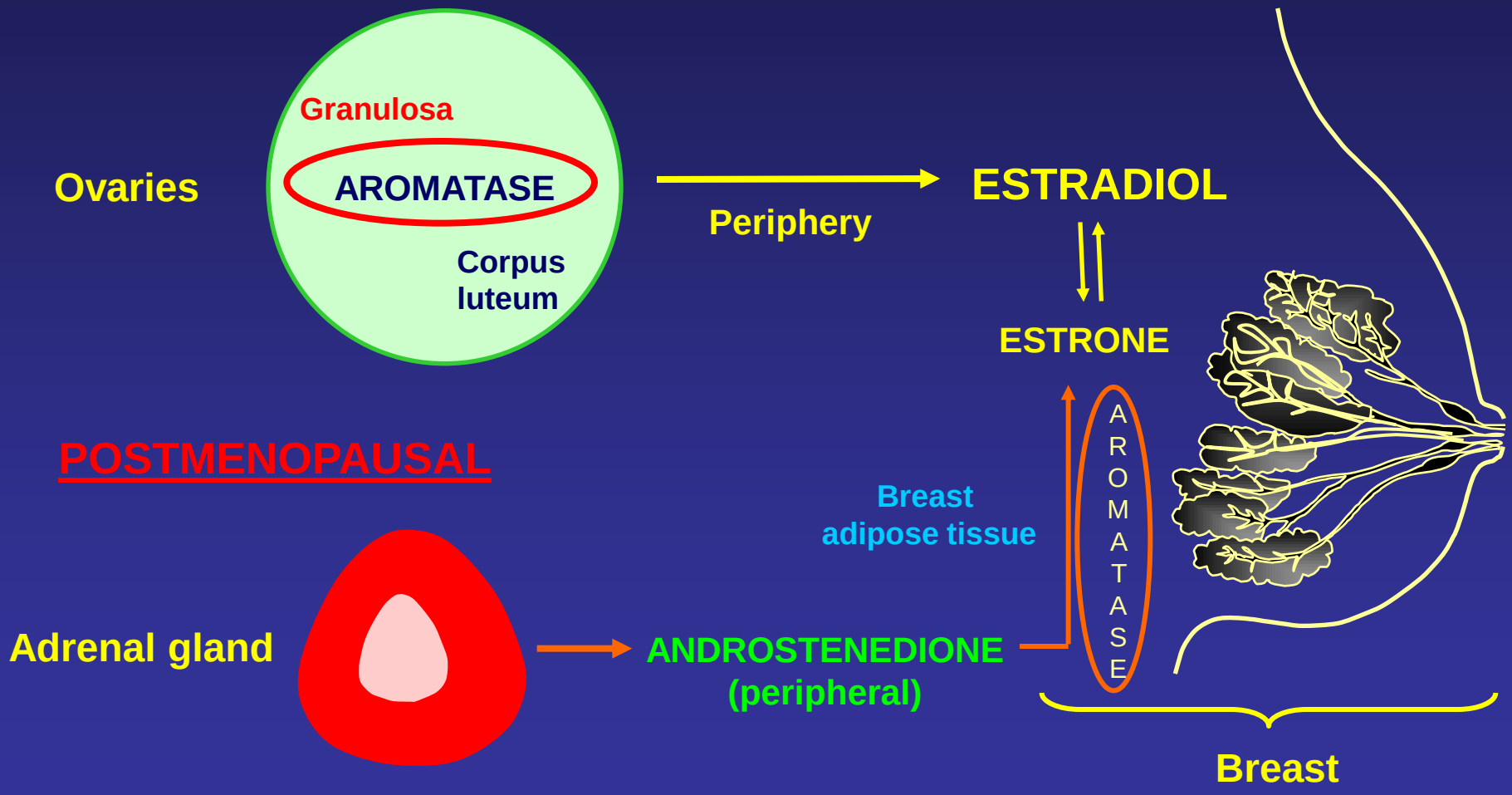
PR Enhances ER Stimulation

Other Tissues?

Biology of Estrogens and Progestins are Determined By:

- Ligand structure
- ER subtype (α or β) and PR isoform (A or B)
- Gene promoter responsive unit
- Character and balance of co-activators and co-repressors

Estrogen Stimulation of Target Tissues in Pre- and Post-menopausal Women



Mechanisms of Estrogen-Induced Carcinogenesis

- Estrogen promotes mammary cancer in rodents
- Direct proliferative effects of estrogens
  - Induction of enzymes involved in DNA synthesis
  - Activation of oncogenes
- Indirect proliferative effects of estrogens
  - Prolactin secretion
  - Production of growth factors
    - eg, TGF-α, EGF, plasminogen activators
- Genotoxic reactive metabolites

Clemons and Goss. N Engl J Med. 2001;344:276

Common Characteristics of Hormone-Dependent Breast Cancer

- Presence of estrogen and/or progesterone receptor
- Histologic differentiation
- Low S phase, diploid
- Long disease-free interval
- Indolent clinical course
- More prevalent in older patients
- Respond to endocrine therapy(ies)

Evaluating Hormone Receptor Status

Estrogen Receptor Status

- Evaluation of ER and PgR status in the tumor is ESSENTIAL for adequate management of breast cancer patients

- Treatment decisions are often made according to arbitrarily set cut-off values of receptor positivity

ER and PgR are NOT standardized tests

- Quantitative biochemistry
  - Ligand binding DCC assay requires radioactive tracer & fresh tissue
- Semi-quantitative immunohistochemistry
  - Use of different antibodies
  - Multiple ways of scoring, different cut-off points
  - Cannot distinguish low levels of hypersensitive receptors

Hormone receptor testing: KNOW YOUR LAB!!!

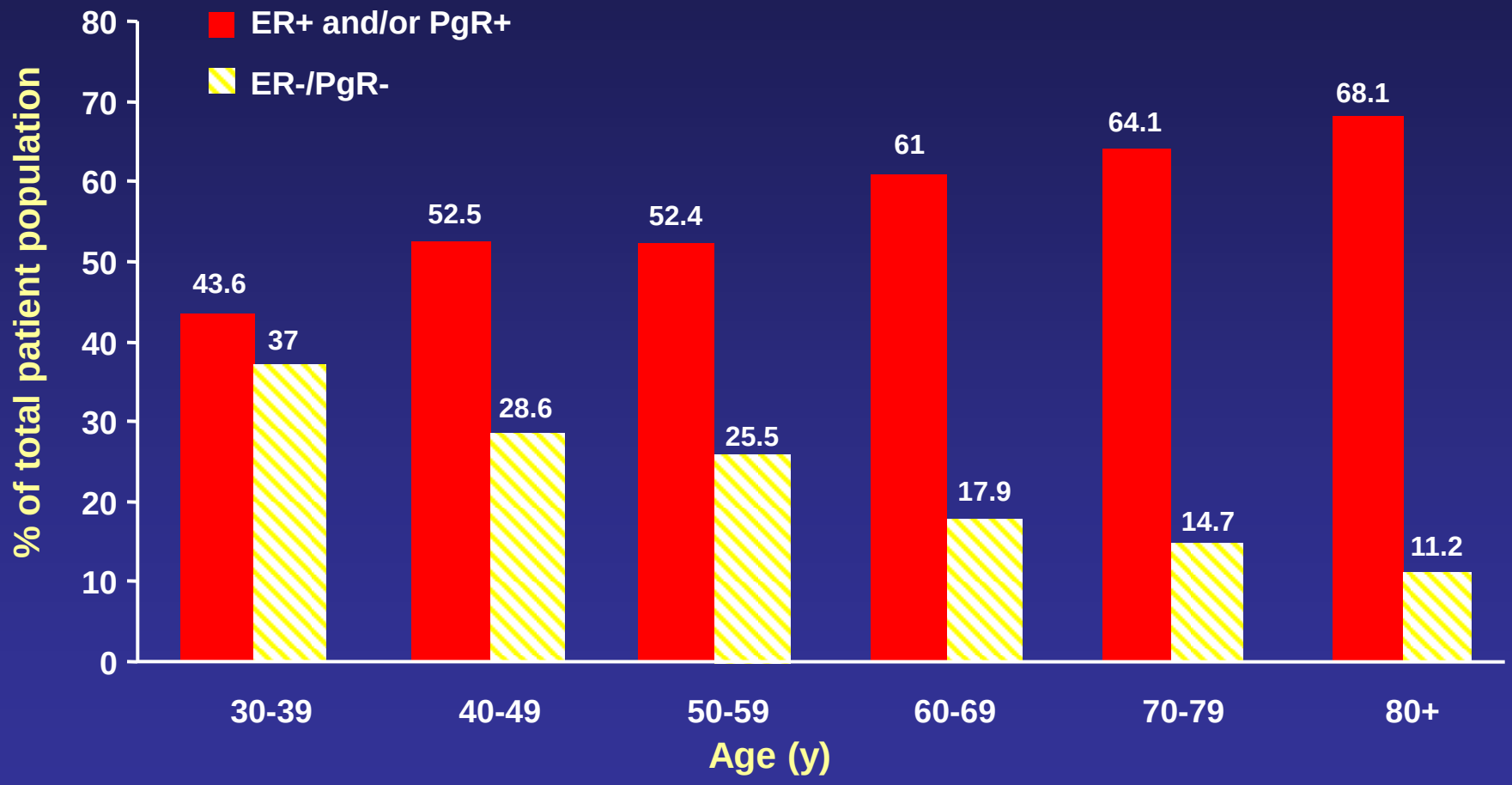
NSABP B-24 *(TAM vs. placebo for DCIS)*:

- Local lab: **30% ER negative**
- Central review: **20% ER negative**

Allred et al. SABCS 2002, abst 30.

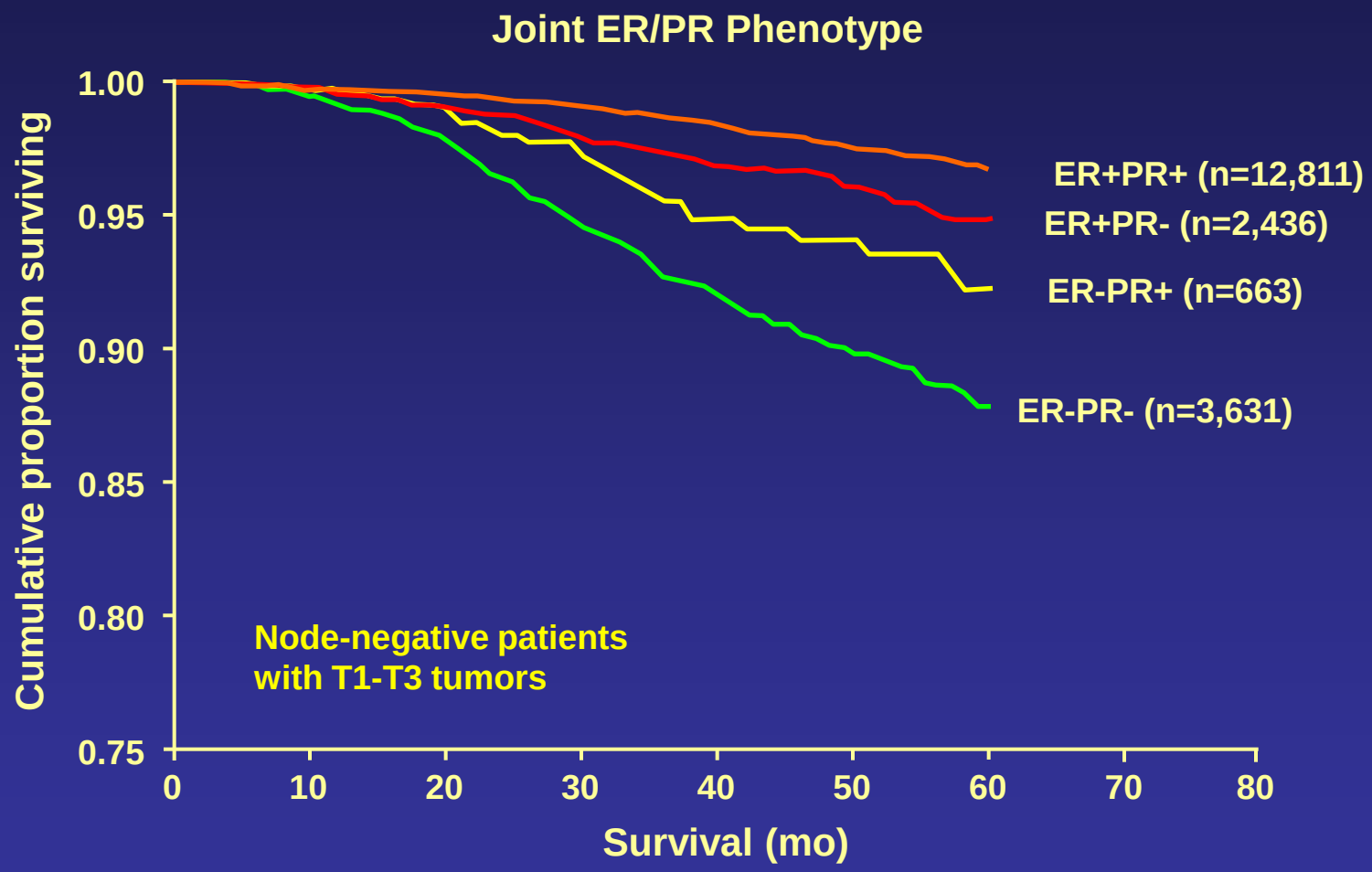
Estrogen receptor status: Incidence and Survival

Sex Hormone Receptor Status as a Function of Age



Wittliff et al. Steroid and peptide hormone receptors: methods, quality control, and clinical use. In: Bland, Copeland, eds. *The Breast.* 2nd ed. 1998:470.

Breast Cancer–Specific Survival by Joint Hormone Receptor Expression (SEER Data)



Anderson et al. Tumor variants by hormone receptor expression in white patients with node-negative breast cancer from the surveillance, epidemiology and end results database. *J Clin Oncol.* 2001;19:18. Reprinted with permission from the American Society of Clinical Oncology.

Endocrine-Based Breast Cancer Therapies

Endocrine therapy options for breast cancer (1)

- Selective Estrogen Receptor Modulators
  - Tamoxifen, toremifene
- Aromatase Inhibitors (post-menopausal)
  - Anastrozole, letrozole, or exemestane
- Selective Estrogen Receptor Downregulators
  - Fulvestrant
- Progestins
  - megace 40 mg po 4 x daily
- Ovarian suppression (pre-menopausal)
  - luteinizing hormone releasing analog
  - oophorectomy

Endocrine therapy options for breast cancer (2)

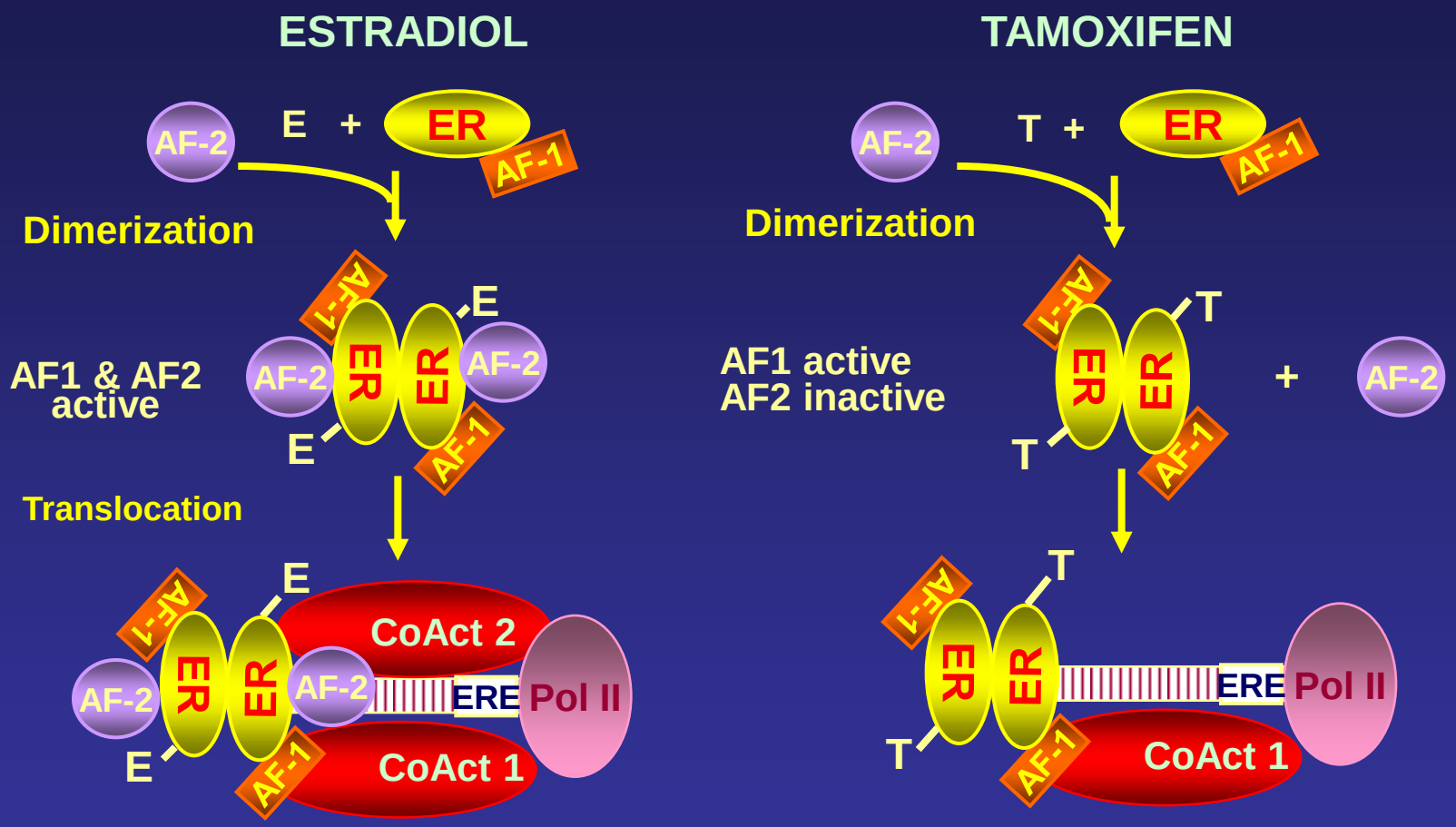
- High dose estrogen
  - Diethystilbesterol 5 mg PO tid
  - Permarin 2.5 mg PO tid

  - Breast tenderness
  - Vaginal discharge
  - Thromboembolism
  - CHF

- Androgens
  - Testosterone
  - Fluoxymesterone 10 mg PO bid
  - Testolactone

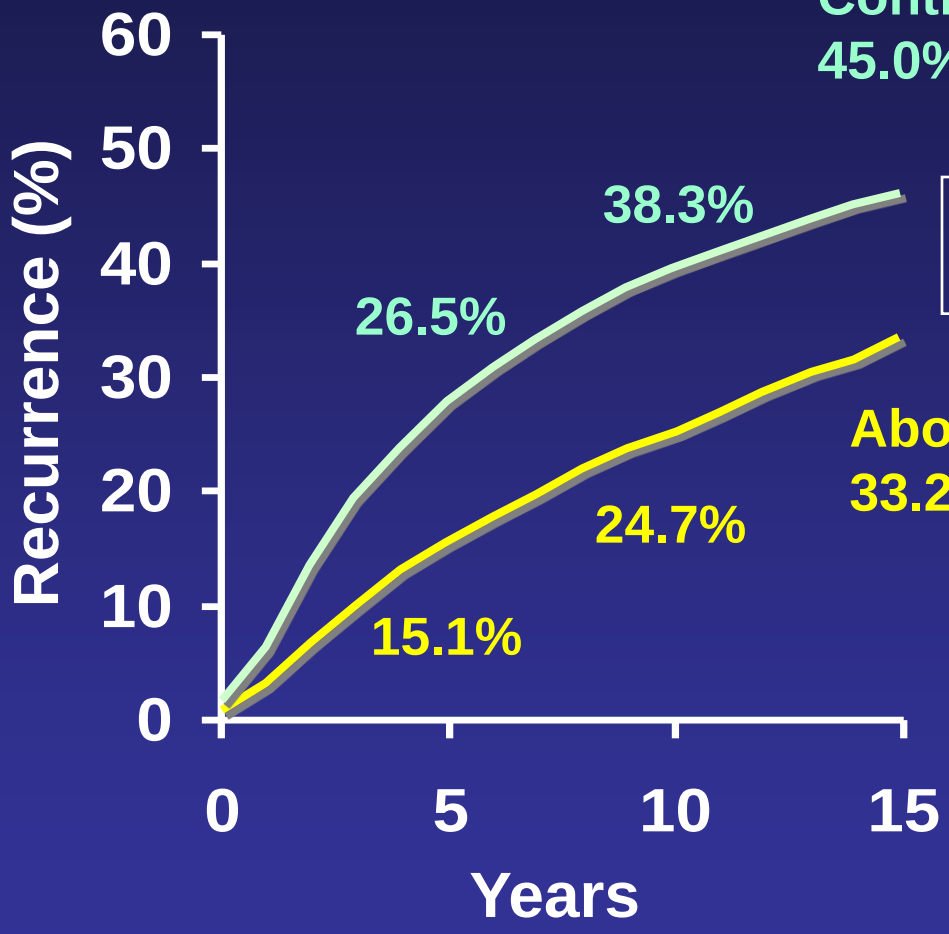
  - Virilizing; RR ~20%
  - Rarely used; inferior to high-dose estrogens

Comparative Mechanisms of Action: Estradiol and Tamoxifen



Adapted from Howell et al. *Cancer*. 2000;89:817.

Tamoxifen (for ~5 yrs) in HR+ Early Breast Cancer: Oxford Overview Meta-Analysis (N = 10,385)



Control:
45.0% recurrence @ 15 years

Hazard Ratio for Recurrence (Control/Tamoxifen) ~1.69

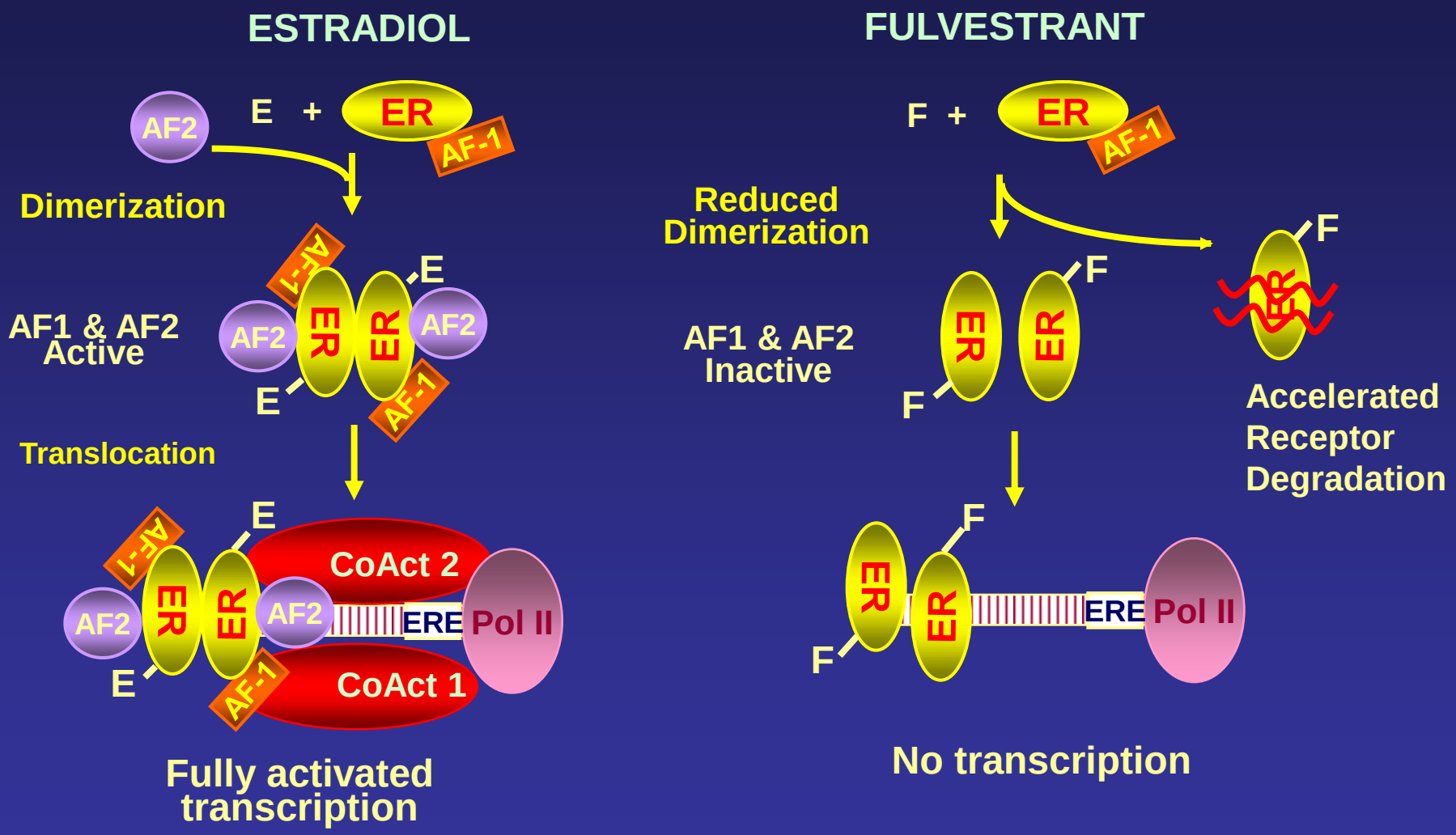
About 5 years of tamoxifen:
33.2% recurrence @ 15 years

Early Breast Cancer Trialists' Collaborative Group Lancet 2005; 365: 1687

Selective Estrogen Receptor Modulators

- Tamoxifen was the first selective estrogen receptor modulator to be developed
- Rationale for development of new SERMs
  - Optimize antagonistic/agonistic profile
  - Reduce toxicity and increase efficacy
- Current status: advantage over tamoxifen not shown, limited benefit in tamoxifen-resistant patients

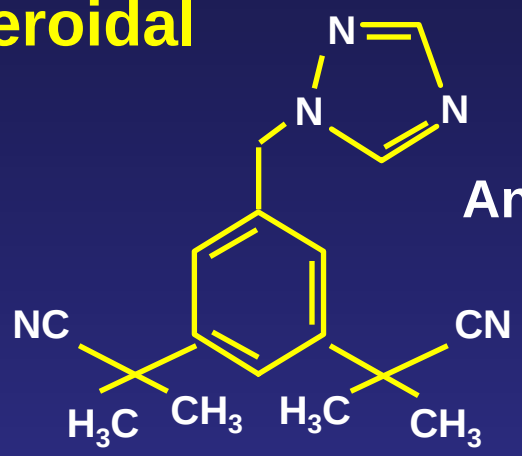
Comparative Mechanisms of Action: Estradiol and Fulvestrant



Adapted from Howell et al. *Cancer*. 2000;89:817

Aromatase Inhibitors

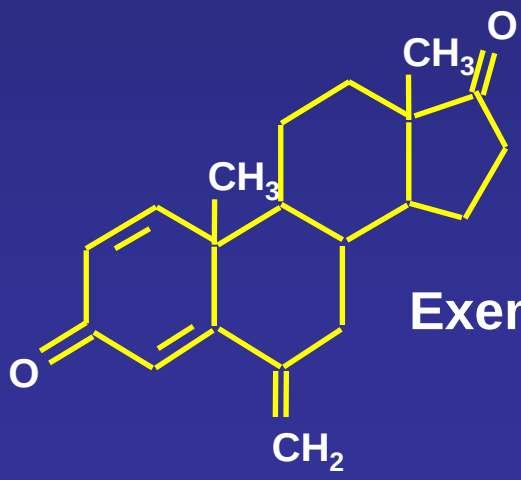
Non-steroidal



Anastrozole

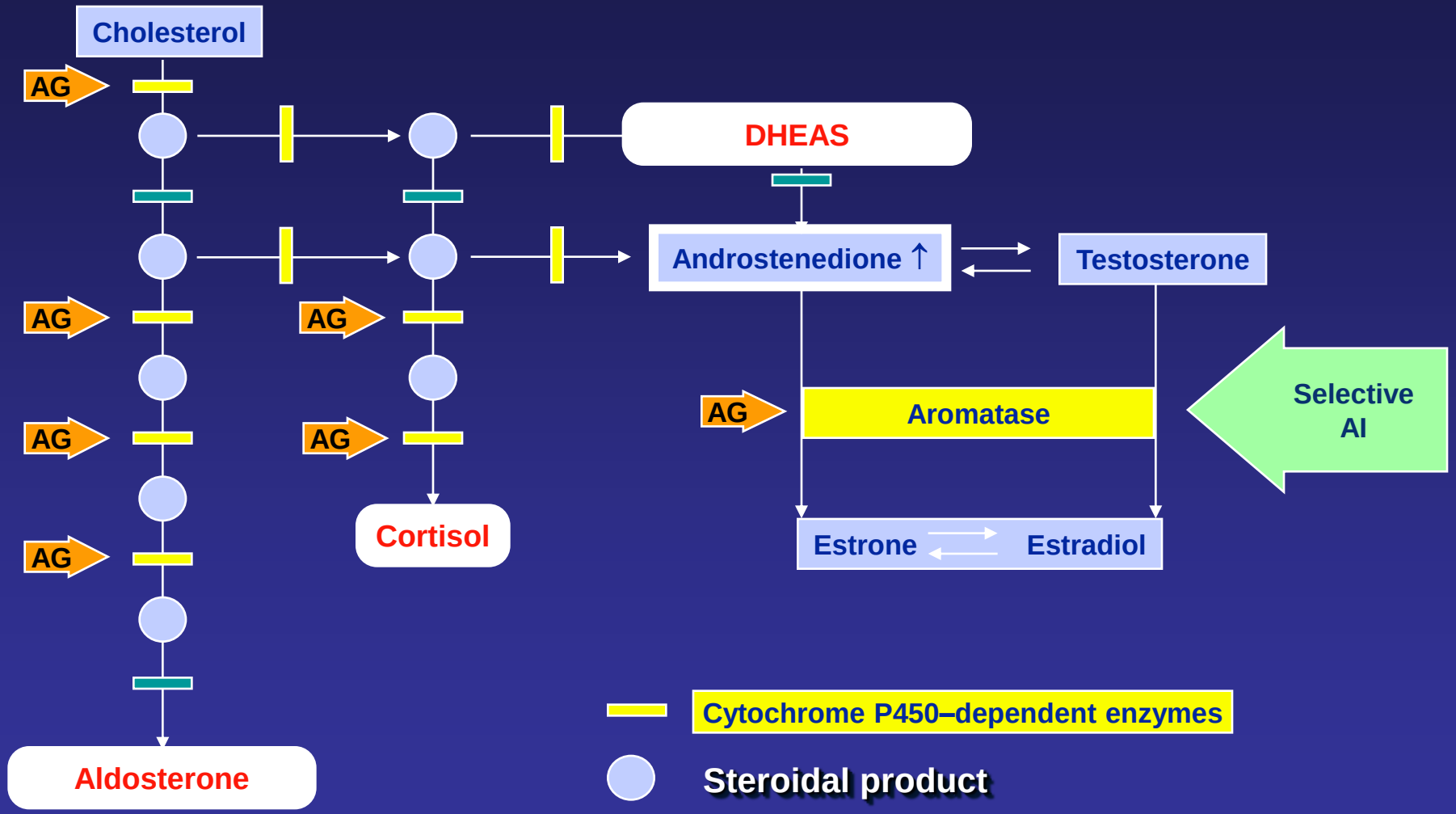
Letrozole

Steroidal



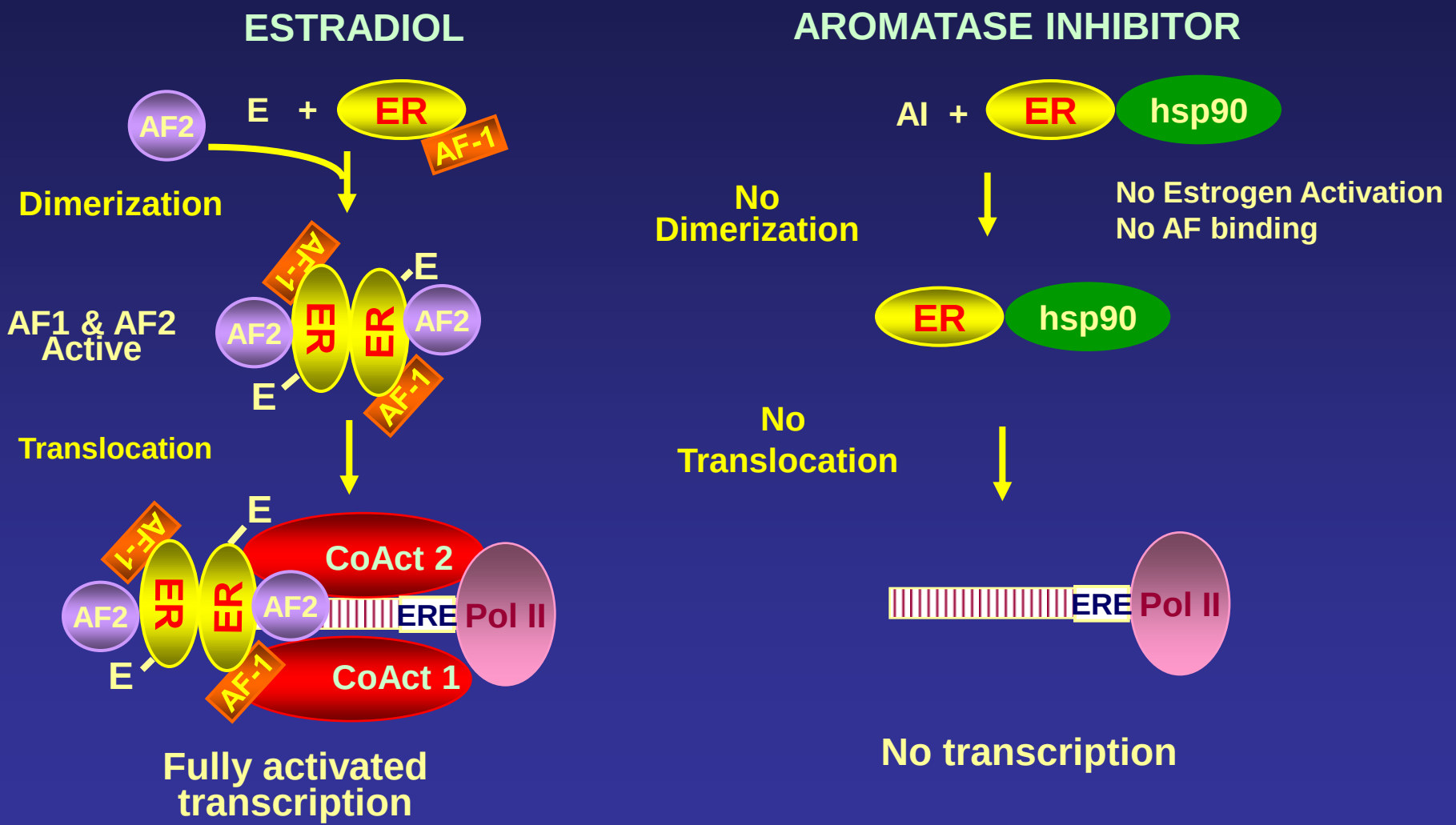
Exemestane

Main Pathways of Steroidogenesis



DHEAS = dehydroepiandrosterone sulfate.

Comparative Mechanisms of Action: Estradiol and Aromatase Inhibitor



Adapted from Howell et al. *Cancer*. 2000;89:817.

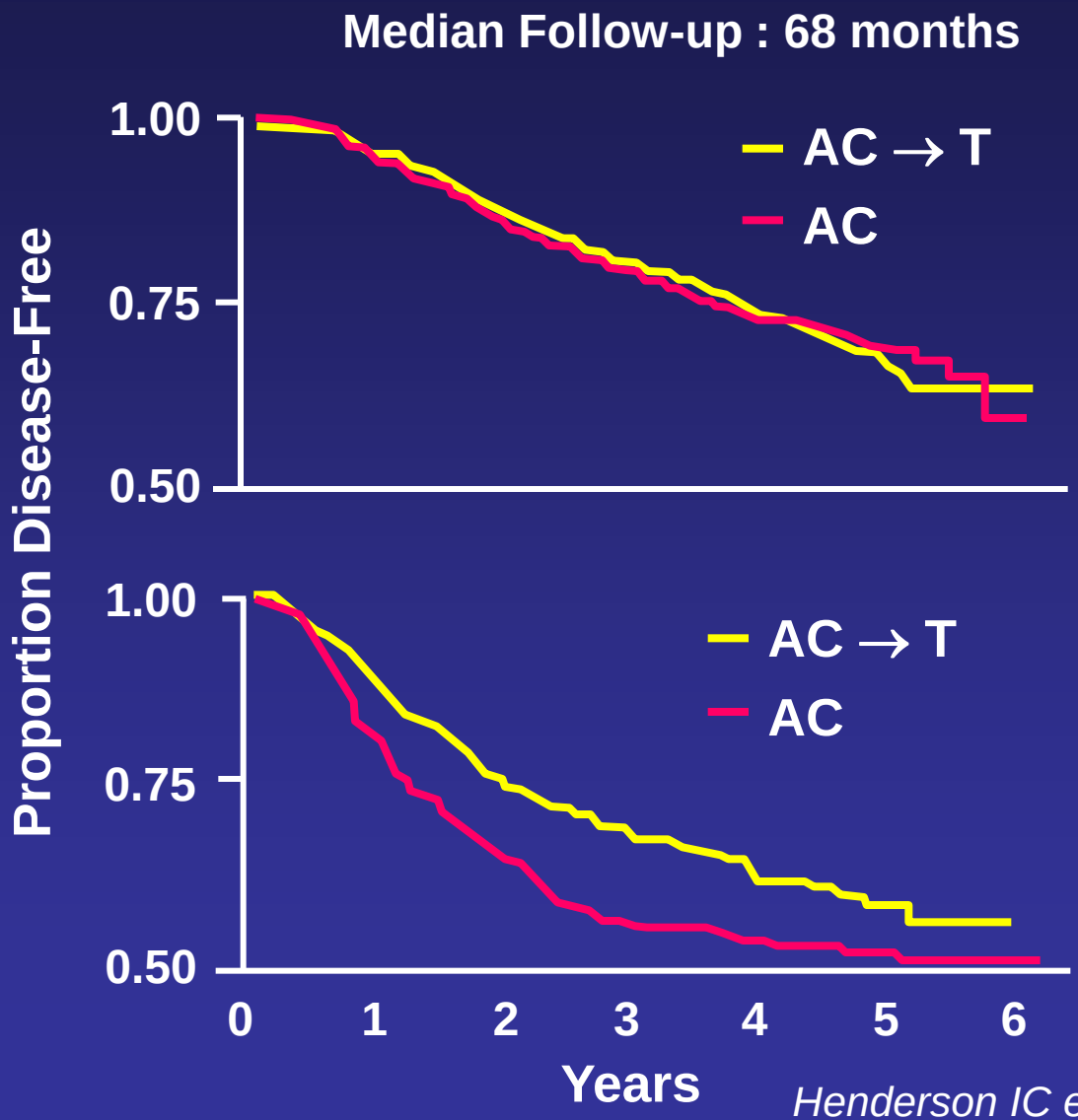
AI improves DFS compared to TAM in postmenopausal HR+ early breast cancer

For hormone receptor-positive breast tumors, the MAJORITY of benefit comes from ADJUVANT ENDOCRINE THERAPY!

She MUST receive endocrine therapy!!!!

Does hormone receptor status predict response to chemotherapy?

CALGB 9344: DFS by receptor status



Hormone Receptor Status Positive
***p* = 0.25**

Hormone Receptor Status Negative / Unknown
***p* = 0.0006**

Henderson IC et al. J Clin Oncol 2003;21:967.

HR status and likelihood of pathologic complete response to pre-operative chemo

Study	N	Regimen	PathCR in HR neg	PathCR in HR pos
MDACC	1018	Pooled data	**20.6%**	**5.6%**
GEPARDUO	913	ddAD/AC-D	**22.8%**	**6.2%**
ECTO	438	AP-CMF	**42.2%**	**11.6%**
NSABP B27	2411	AC vs AC-D	**16.7%**	**8.3%**
GEPARTRIO	286	DAC/DAC-NX	**36.6%**	**10.1%**
GEPARDO	250	ddAD+/TAM	**15.4%**	**1.1%**

Improved PathCR rates for pre-op chemo in HR neg does not translate into OS benefit

	ER neg	ER pos
pathCR	24%	8%
5 yr OS	84%	96%

Guairi JCO 2006

Cytotoxic chemotherapy has less relative benefit in estrogen receptor-positive early breast cancers

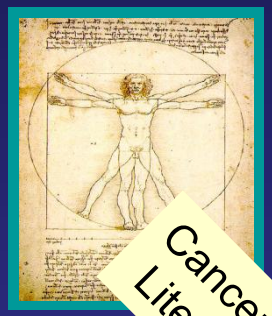
Which brings us to……

The Oncotype Dx™ 21-gene recurrence score

Can we predict which HR+ tumors will benefit from cytotoxic chemotherapy, and which HR+ tumors will not?

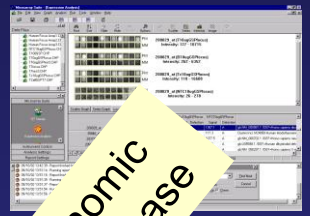
Oncotype DX™ Technology: Candidate Gene Selection

From ~25,000 genes:

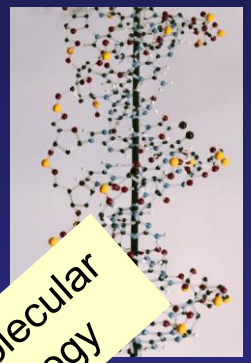


Cancer Literature

Microarray Data*



Genomic Databases



Molecular Biology

250 cancer-related candidate genes

***Sources include: van't Veer et al, *Nature* 2002;415:530-6.**
Sorlie et al, *PNAS* 2001 98:10869-74.
Ramaswamy et al, *Nat Genet* 2003;33:49-54.
Gruvberger et al, *Cancer Res* 2001;61:5979-84.

Oncotype DX 21 Gene Recurrence Score (RS) Assay

16 Cancer and 5 Reference Genes

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN
ER
PR
Bcl2
SCUBE2

GSTM1

BAG1

CD68

INVASION
Stromolysin 3
Cathepsin L2

HER2
GRB7
HER2

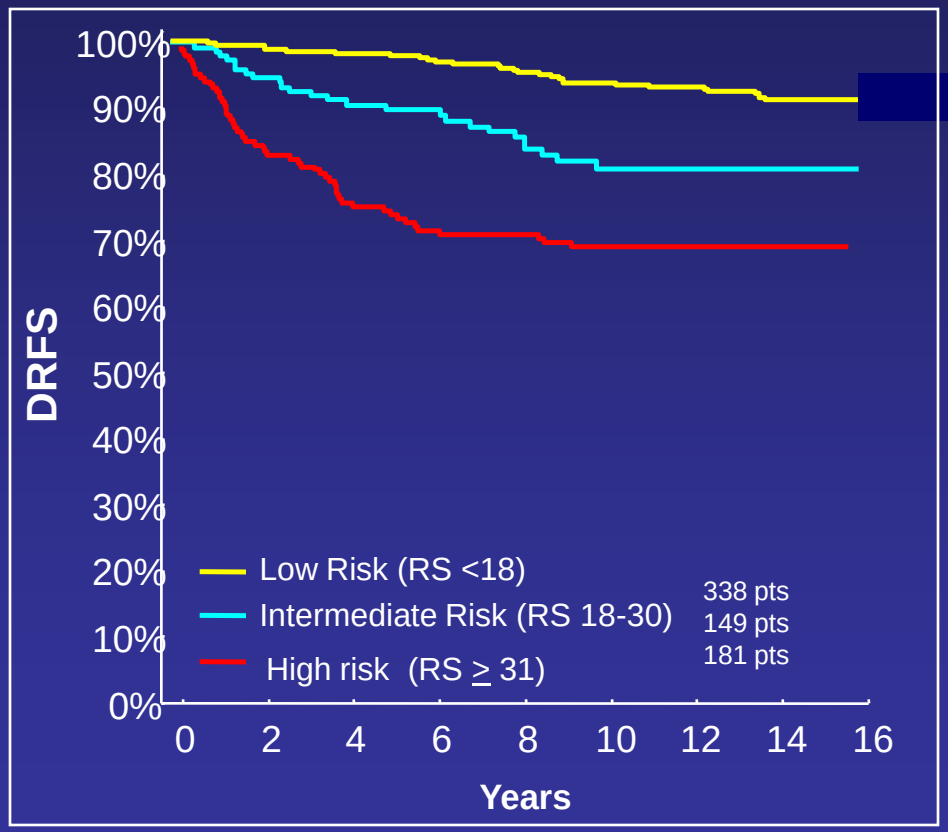
REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

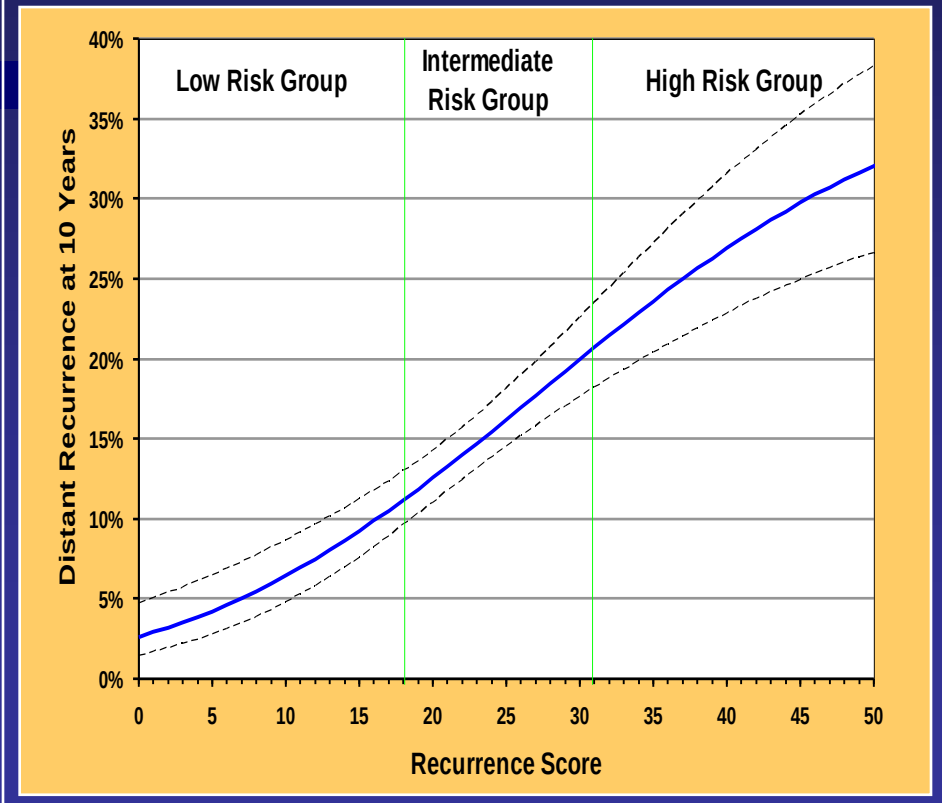
RS = + 0.47 x HER2 Group Score
- 0.34 x ER Group Score
+ 1.04 x Proliferation Group Score
+ 0.10 x Invasion Group Score
+ 0.05 x CD68
- 0.08 x GSTM1
- 0.07 x BAG1

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

Validation Study of Oncotype DX

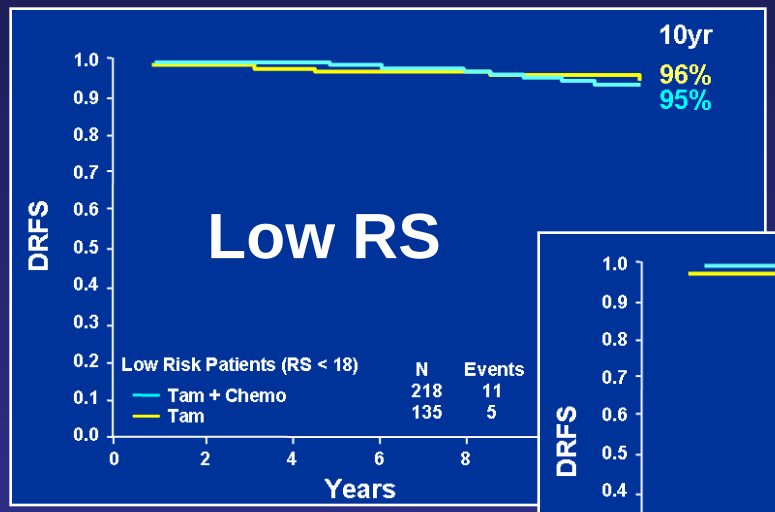
- Pts Rx w/ Tamoxifen from NSABP B-14 (N=668)
- Performance exceeds that of patient age, tumor size

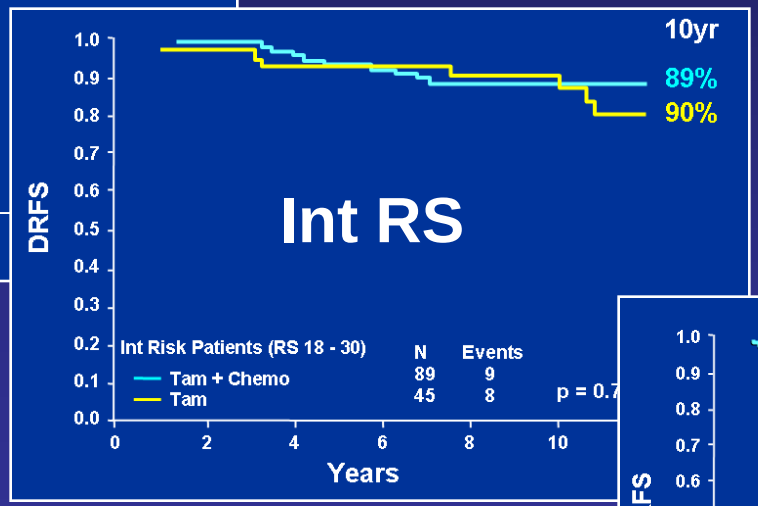


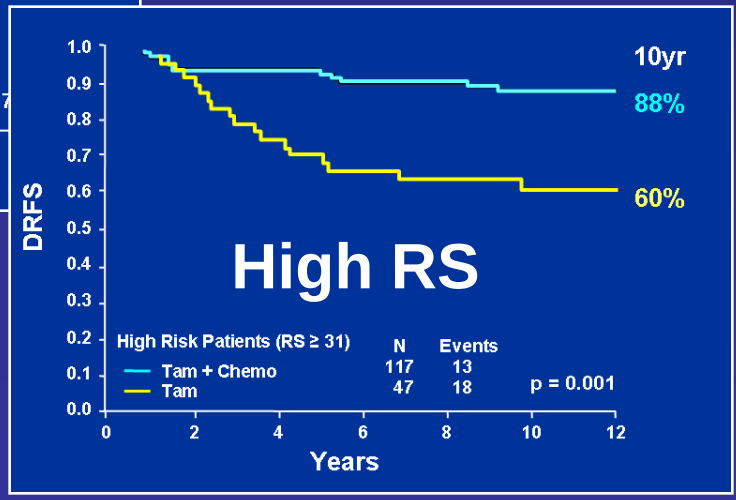


Oncotype Dx: Chemotherapy benefit according to Recurrence Score in NSABP B20 (Node neg ER+)

TAM vs TAM + Chemo







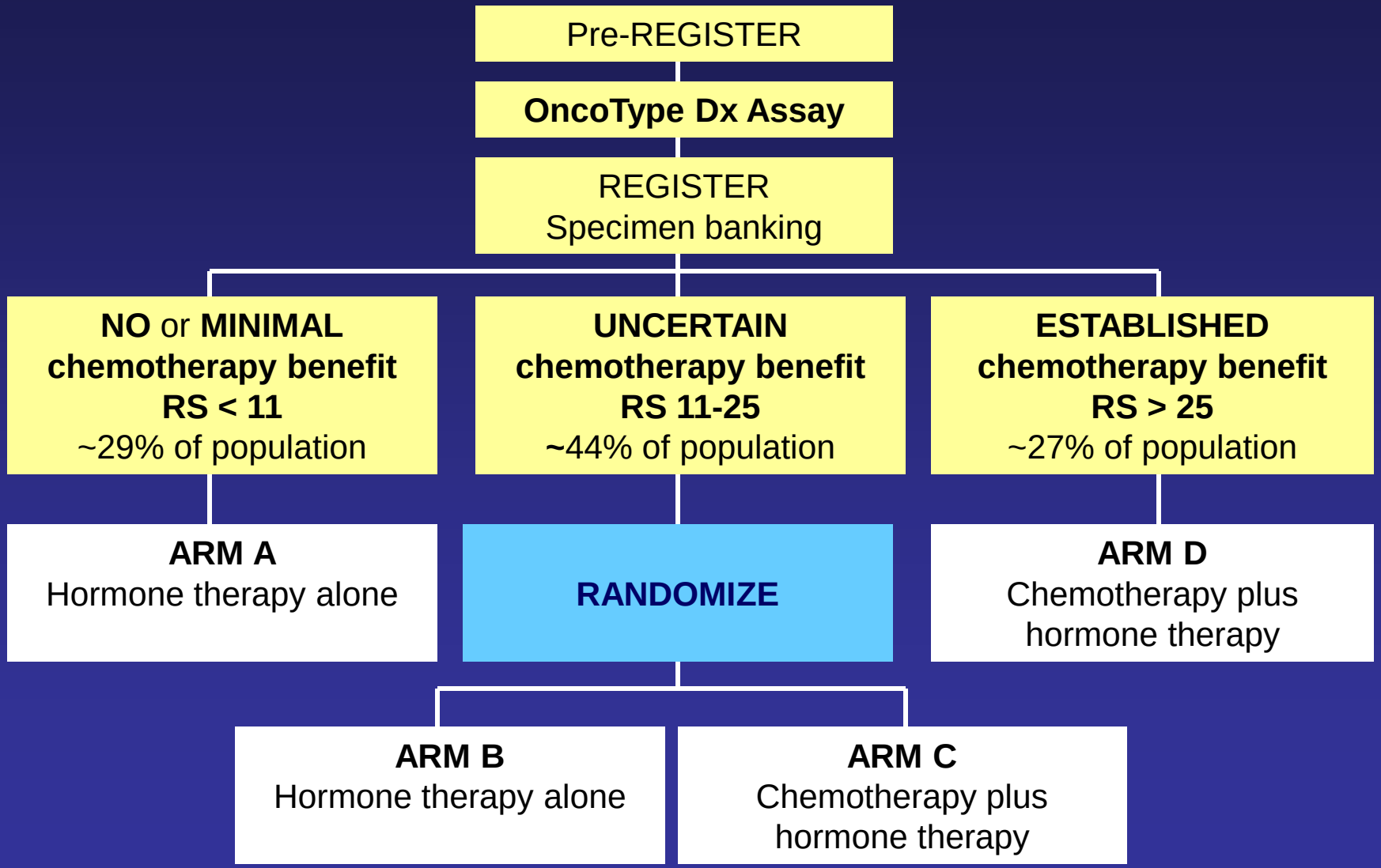
Oncotype Dx™ 21-gene Recurrence Score

- Prognostic?
- Predicts tamoxifen response?
- Predicts chemotherapy response?
- Low RS associated with no chemotherapy benefit?
- High RS associated with large chemotherapy benefit?

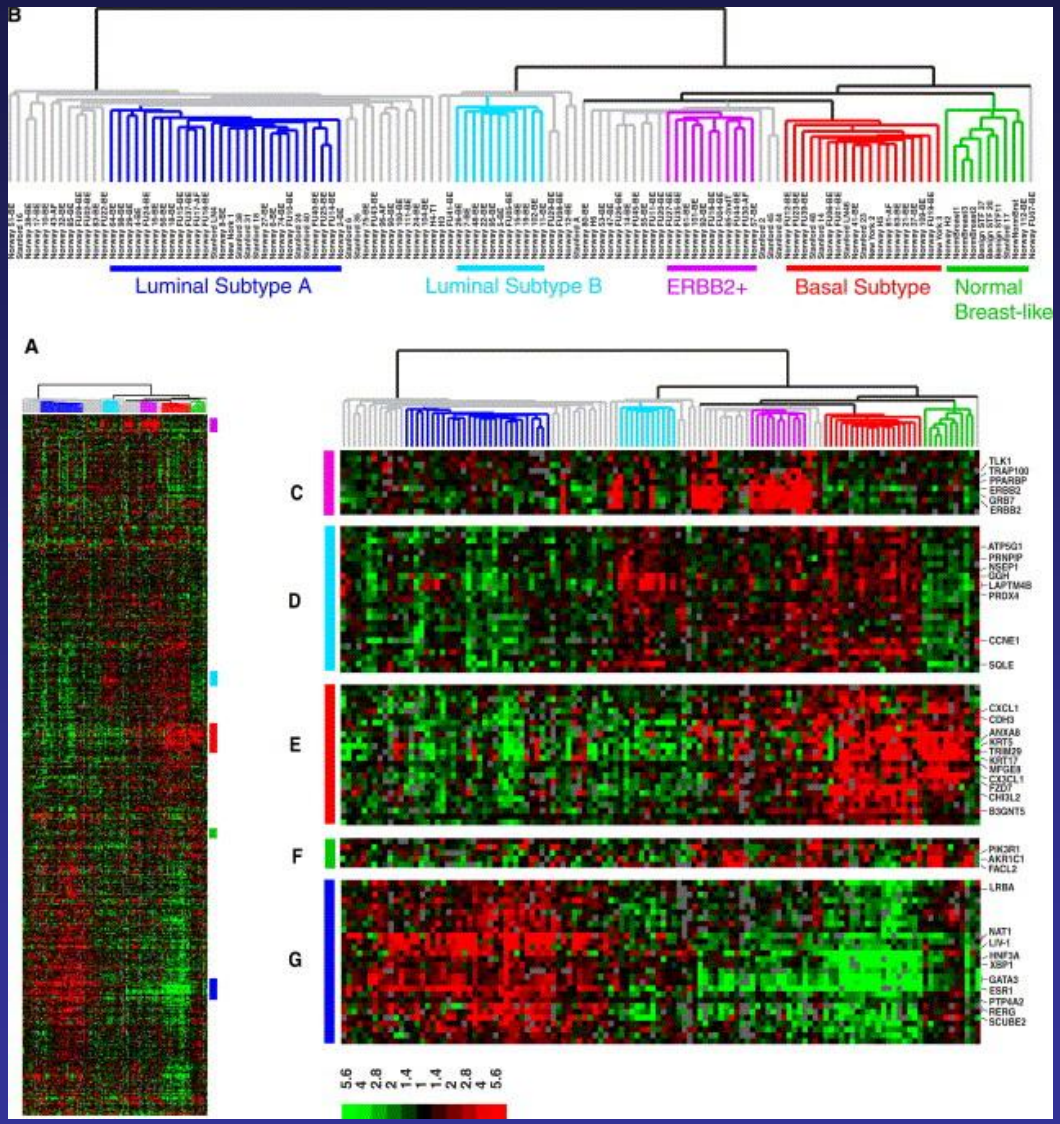
Criticisms/Comments regarding the 21-gene recurrence score

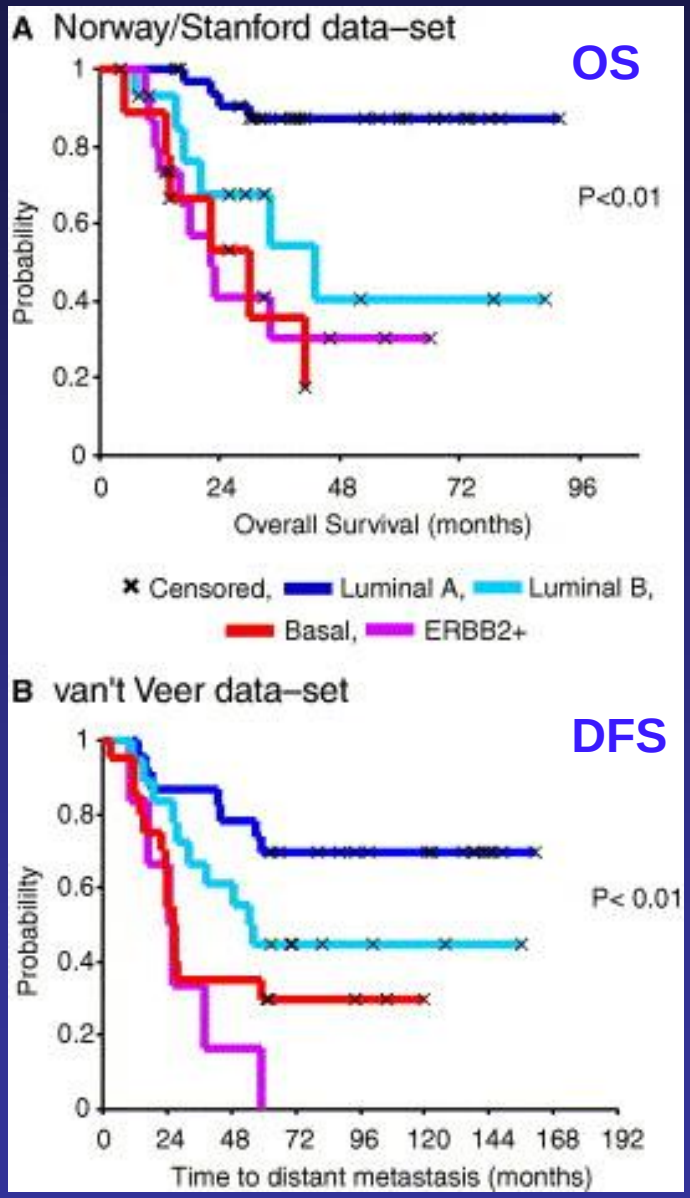
- Developed in retrospective fashion in clinical trials that utilized inferior chemotherapy and endocrine therapy
  - *Prospective validation is pending!*
- Only use for HR+, axillary node-negative, HER2-negative tumors!
- DO NOT use Oncotype as a tool to decide if you will or will not give endocrine therapy for a HR+ tumor!

PACCT-1 TAILORx Trial (Trial Assigning Individualized Options for Treatment)



Breast Cancers are a Heterogeneous Group of Diseases





Sorlie, T et al: PNAS 2001; 98:10869-10874