

Adjuvant Systemic Therapy in Early Stage Breast Cancer

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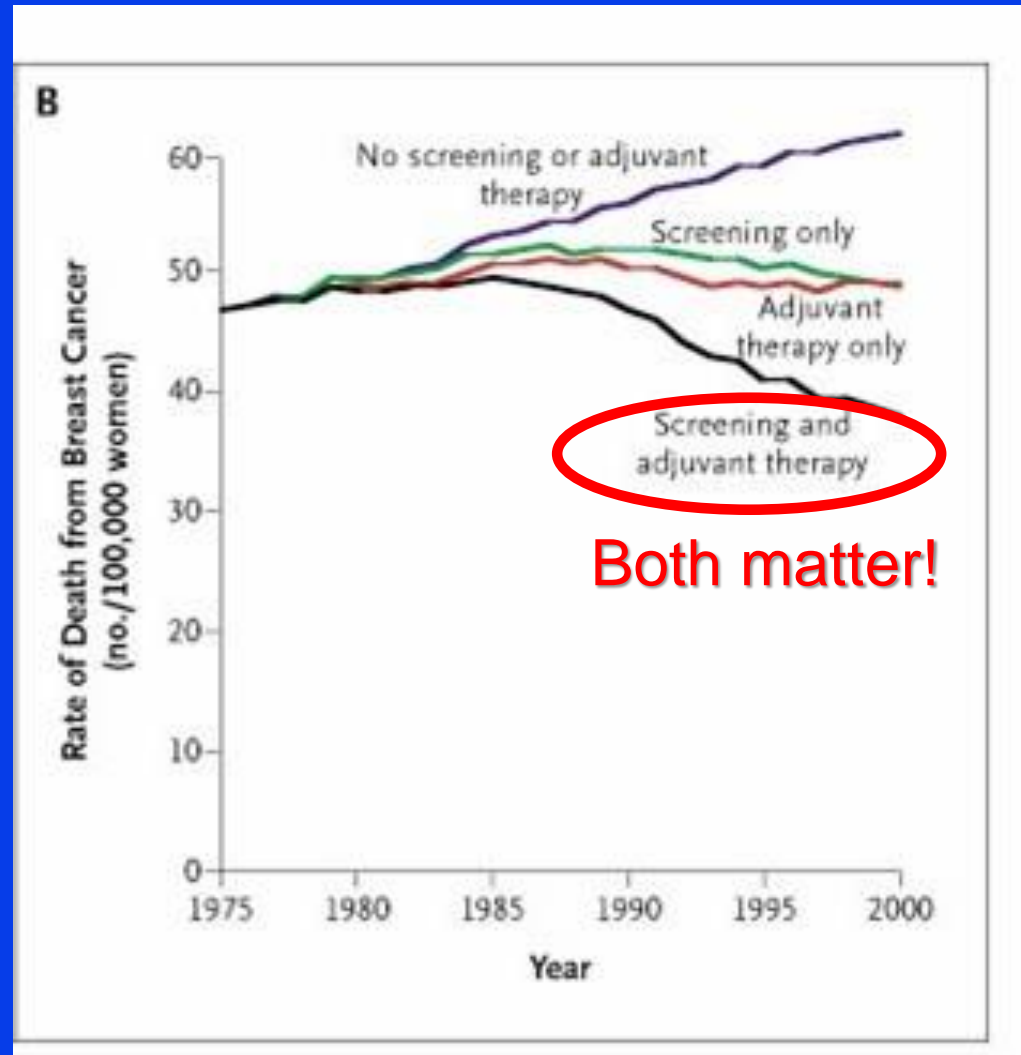
Seattle Cancer Care Alliance

Treatment of Early Stage Breast Cancer (Adjuvant Therapy)

- **Breast cancer is most curable when detected early**
 - **Micrometastases (undetectable) can exist at time of diagnosis in many patients, leading to eventual recurrence**
- **Multidisciplinary care is critical for best outcomes**
 - **Surgery**
 - **Radiation therapy**
 - **Adjuvant systemic (drug) therapy reduces risk of recurrence and death**
 - » **Should be tailored to the patient and tumor**

Is Screening or Adjuvant Systemic Therapy More Important in Breast Cancer Survival?

U.S. Breast Cancer Death Rates



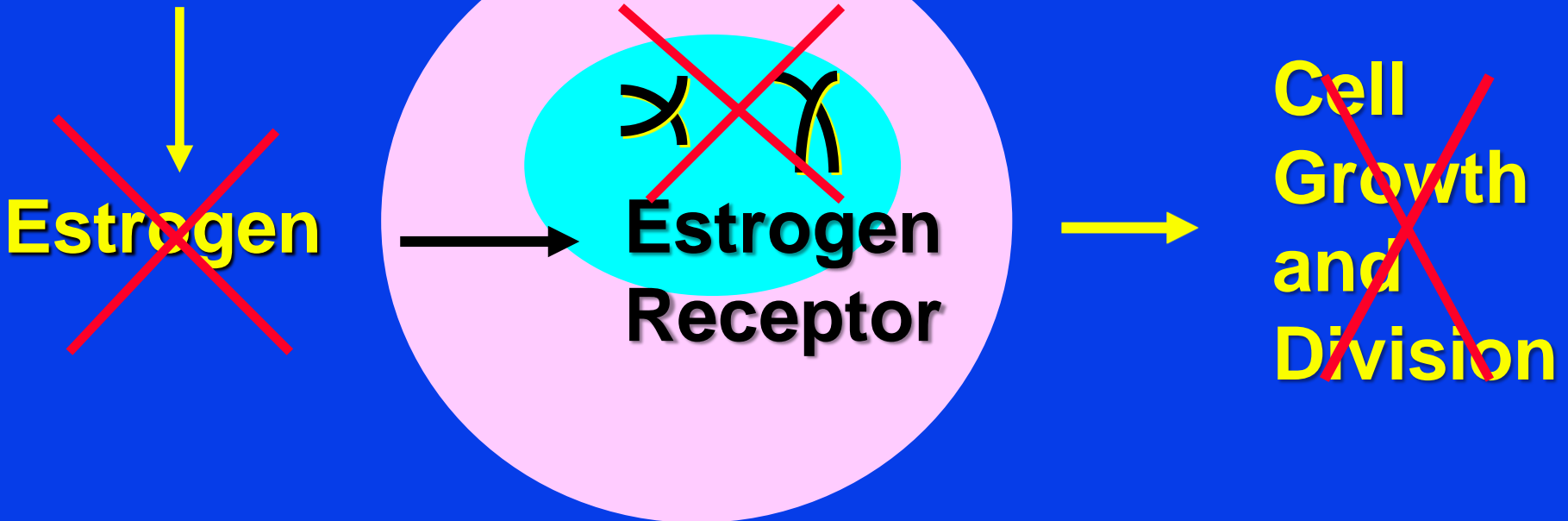
Systemic Therapy for Early Stage Breast Cancer

- **Endocrine therapy**
- **Chemotherapy**
- **Targeted Therapies**

Endocrine Therapy in Breast Cancer

Aromatase inhibitors
(anastrozole, letrozole, exemestane), **ovarian suppression** (leuprolide, goserelin)

SERMS (tamoxifen, toremifene), **SERDS** (fulvestrant)



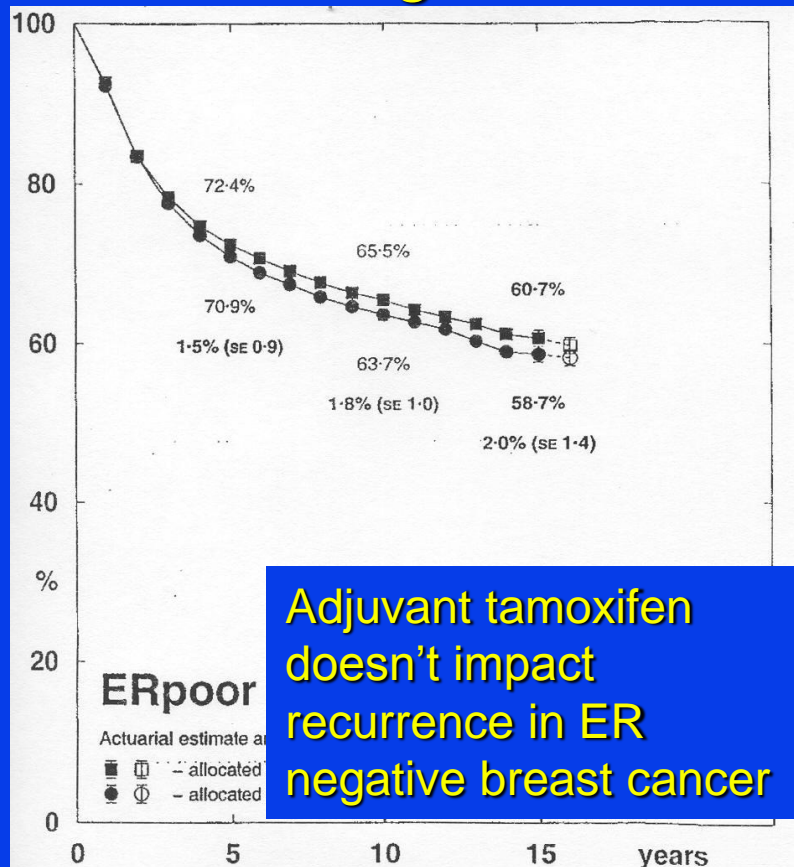
WHO Model List of Essential Medicines 19th Edition (April 2015)

Antineoplastic drugs relevant to breast cancer

- Endocrine therapy:
 - Tamoxifen
 - Anastrozole (Arimidex)
 - Leuprolide (Lupron)

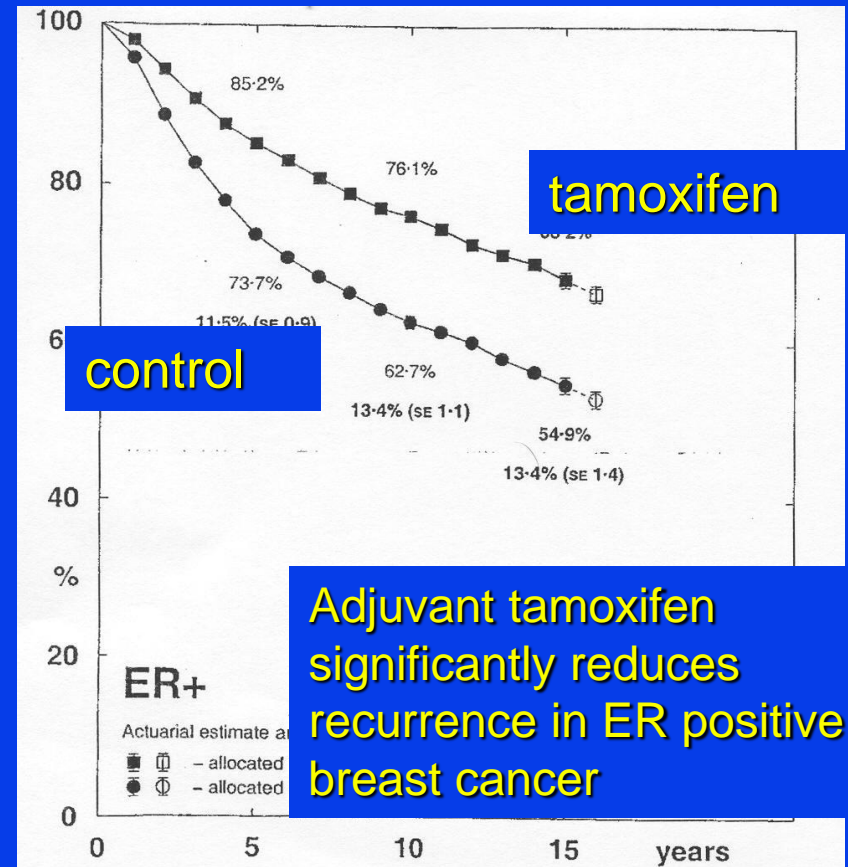
Early Breast Cancer Trialists' Collaborative Group Clinical Trials of Tamoxifen in Early Stage Breast Cancer: *Disease-free Survival*

ER Negative



Adjuvant tamoxifen
doesn't impact
recurrence in ER
negative breast cancer

ER Positive

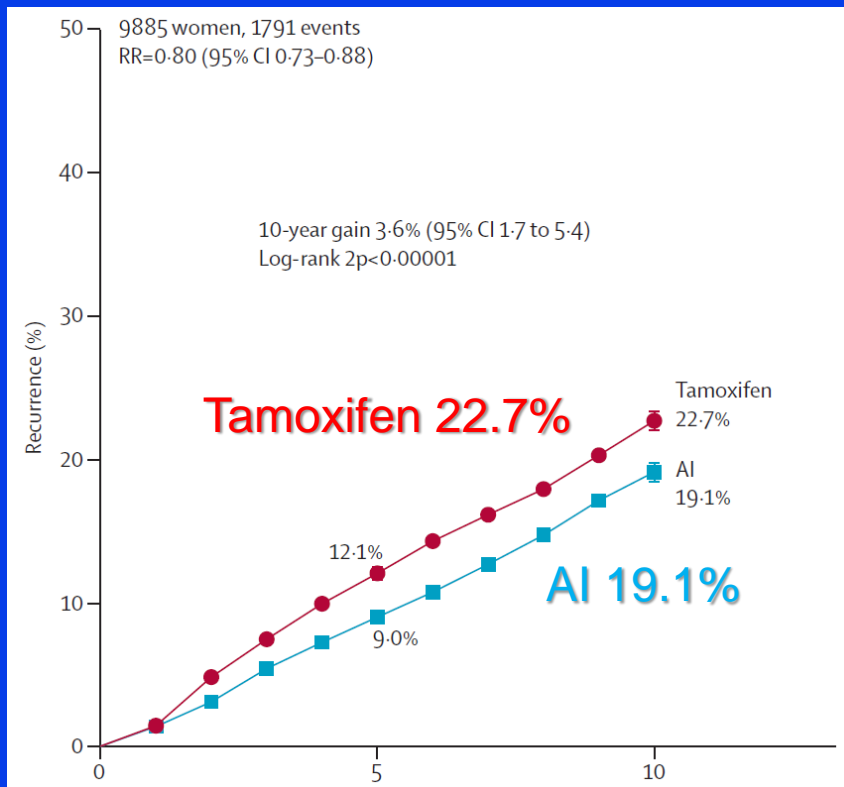


Adjuvant tamoxifen
significantly reduces
recurrence in ER positive
breast cancer

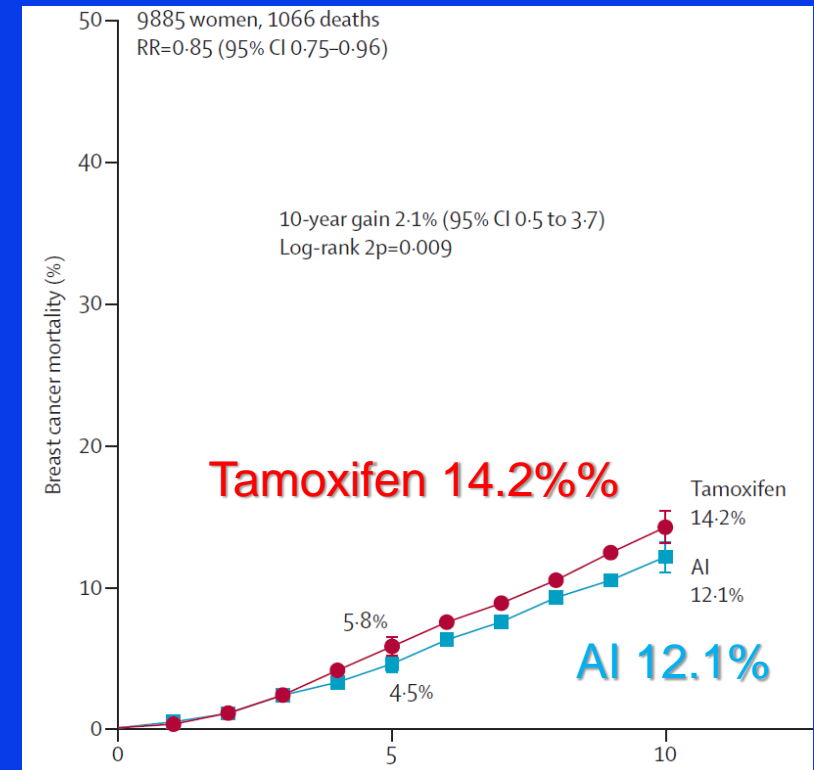
Tamoxifen effective in both pre- and postmenopausal women

Aromatase Inhibitors versus Tamoxifen in Early Breast Cancer: Meta-analysis of the Randomised Trials

EBCTCG Lancet 386:1341-52, 2015



Recurrence



Breast Cancer Mortality

Under study: Extended duration Aromatase Inhibitors (up to 10 years)

Adjuvant Endocrine Therapy in Early Stage Breast Cancer

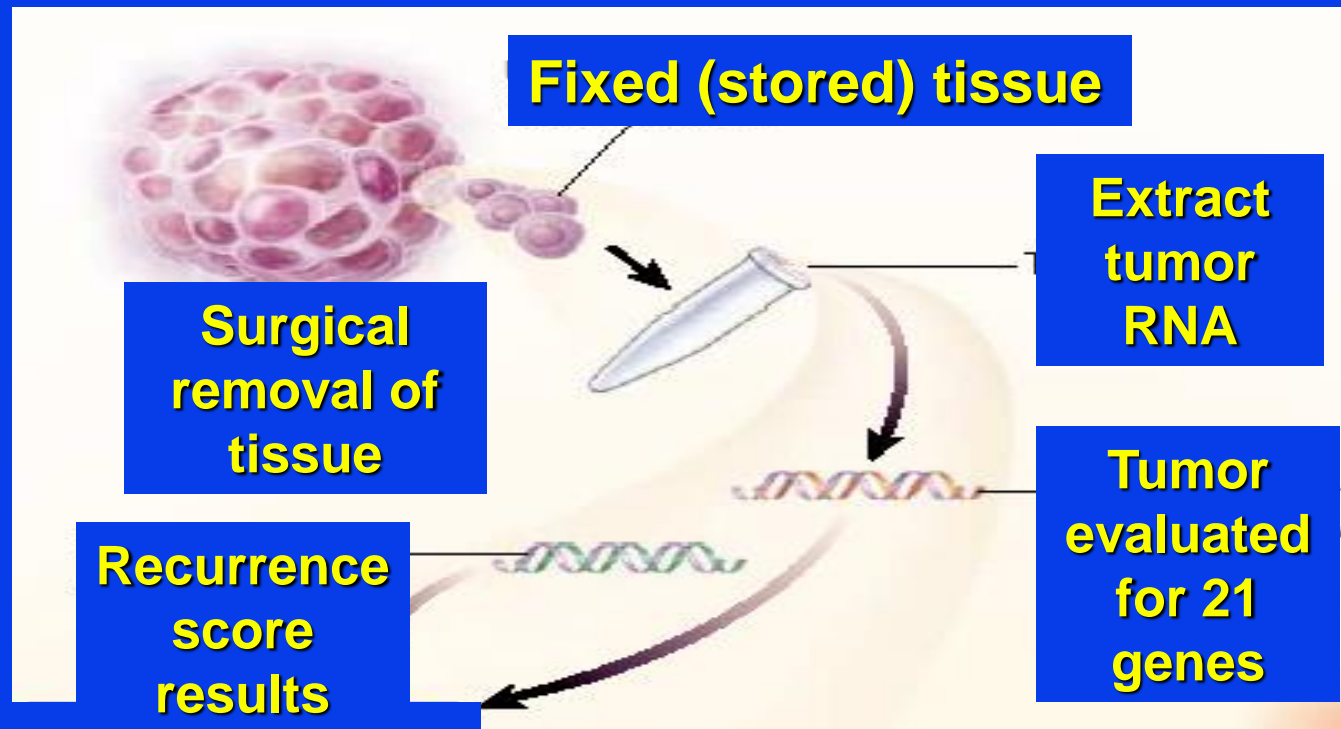
- Tamoxifen: substantial clinical efficacy, low cost, and several decades of use throughout world
 - Still the standard for premenopausal women
 - Reasonable for many postmenopausal women
 - Longer duration (> 5 years) may benefit some patients
- Aromatase inhibitors: additional small reduction in breast cancer recurrences (and deaths) compared to tamoxifen
 - Only effective in postmenopausal women
 - Side effects different (?better)
- Ovarian suppression
 - Only effective in premenopausal women
 - Addition to tamoxifen (or aromatase inhibitors) may add benefit in subset of young women (< age 35)

Chemotherapy for 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*

Genomic Profiling in Early Stage Cancer

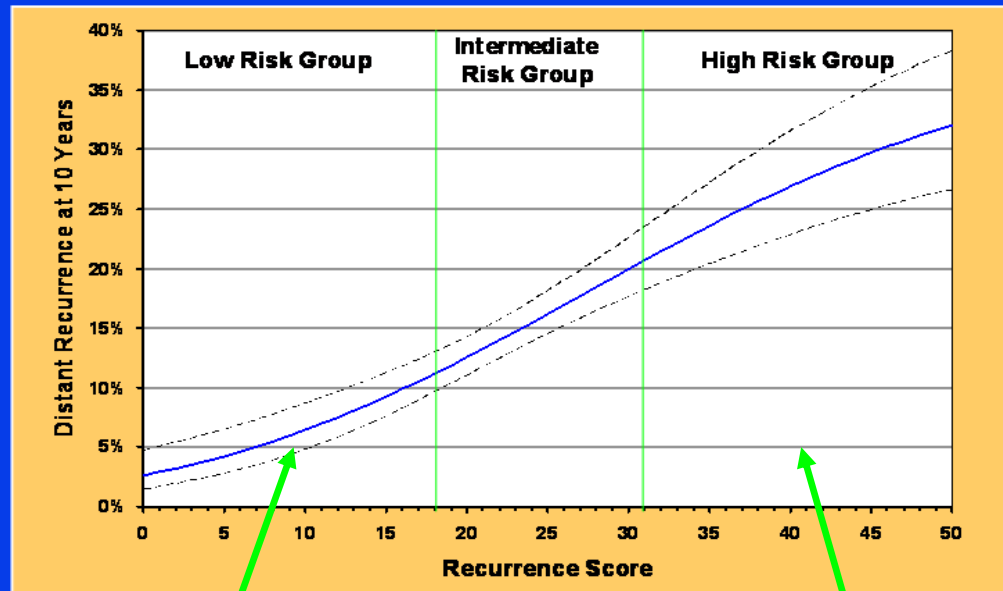
Oncotype Dx 21-Gene Recurrence Score Assay



Developed to help define which “low risk” ER+, lymph node negative patients do not need chemotherapy, and which may benefit

Genomic Profiling in Early Stage Breast Cancer: 21-Gene Recurrence Score Assay

Recurrence Score in LN-, ER+ if given only 5 Years Tamoxifen



Lower RS

- Less likelihood of recurrence
 - Greater tamoxifen benefit
- Minimal chemotherapy benefit

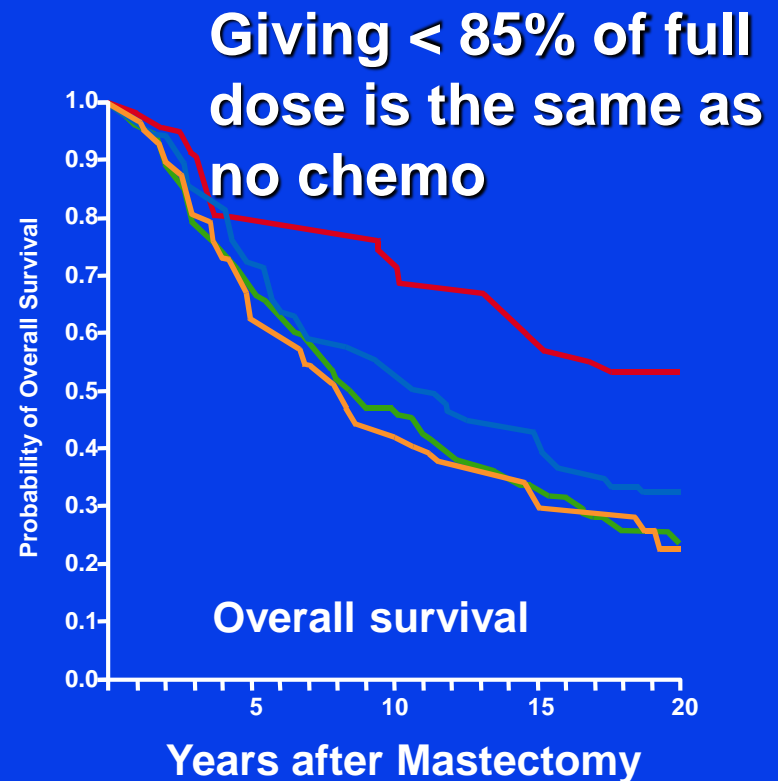
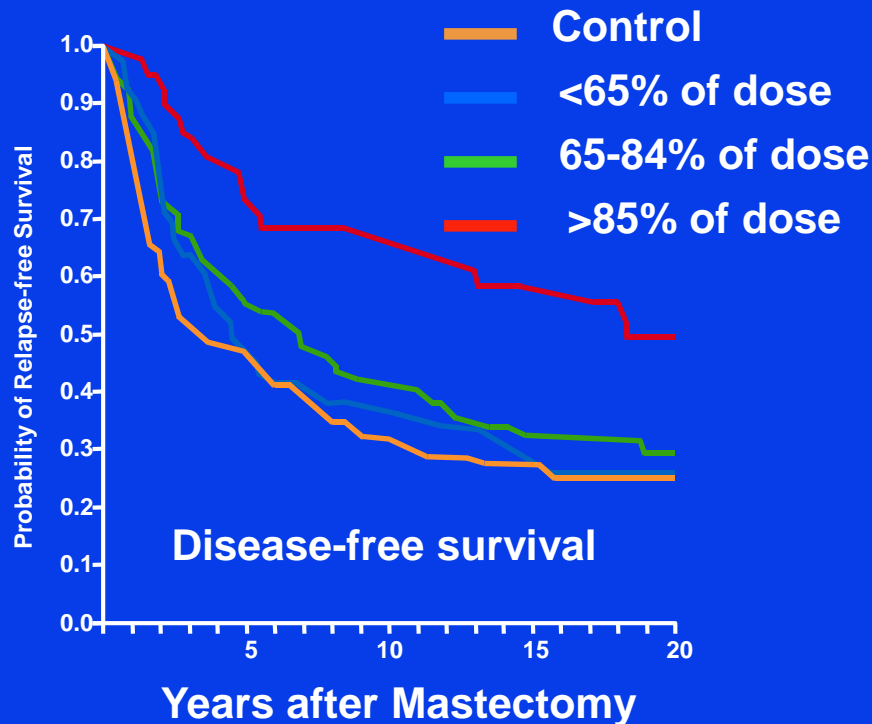
Higher RS

- Greater likelihood of recurrence
 - Less tamoxifen benefit
- Clear chemotherapy benefit

Chemotherapy Dose Matters

Adjuvant Chemotherapy - 20 Year Follow-up Milan Study

Bonadonna G et al, N Engl J Med 332: 901-6,1995



If chemotherapy is given, it should be given at full dose

WHO Model List of Essential Medicines 19th Edition (April 2015)

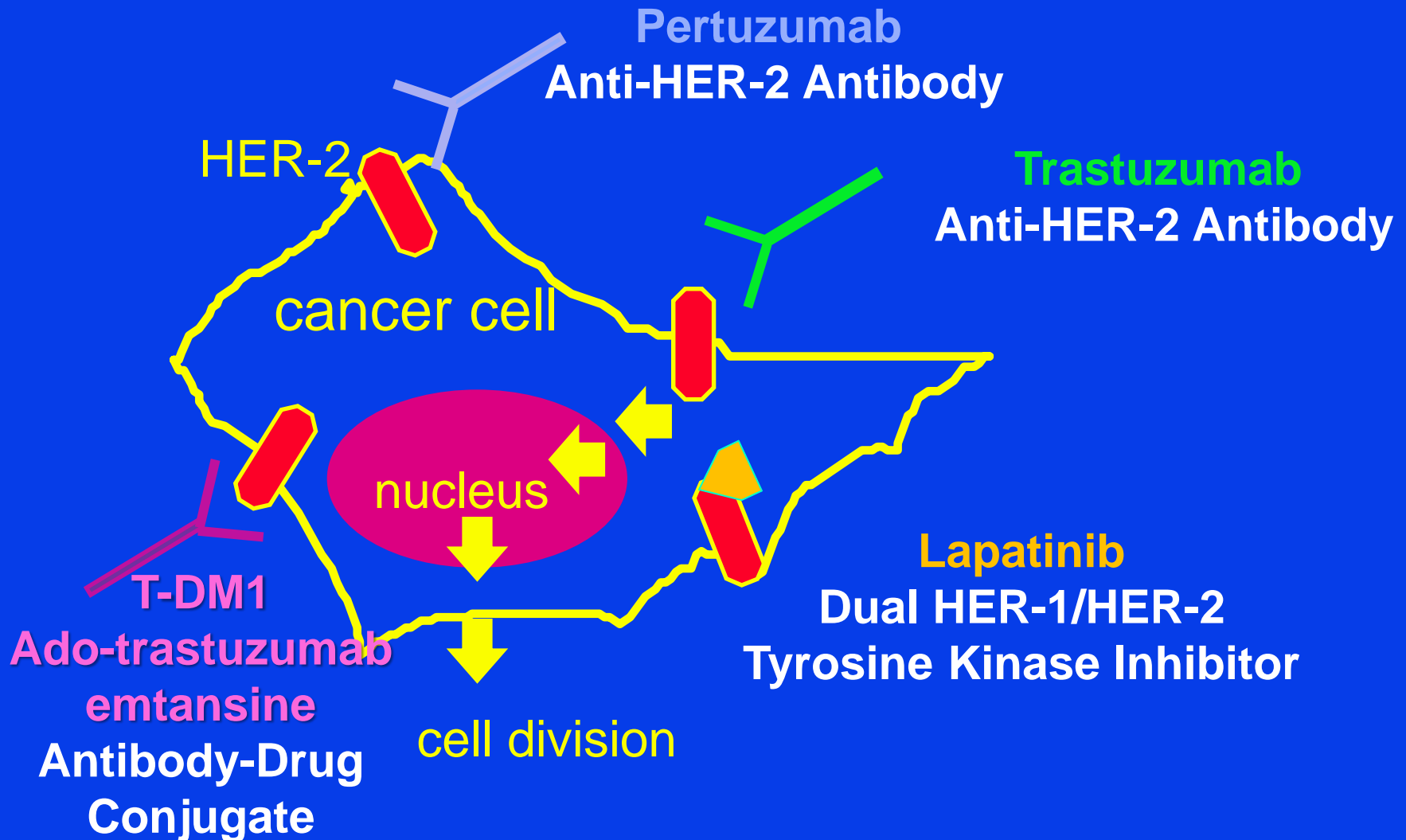
Antineoplastic drugs relevant to breast cancer

- **Chemotherapy:**
 - Doxorubicin (Adriamycin)
 - Cyclophosphamide (Cytosan)
 - Paclitaxel (Taxol)
 - Docetaxel (Taxotere)
 - Fluorouracil (5-FU)
 - Methotrexate
- **Chemotherapy (cont):**
 - Carboplatin
 - Gemcitabine (Gemzar)
 - Capecitabine (Xeloda)
 - Vinorelbine (Navelbine)

Adjuvant Chemotherapy in Early Stage Breast Cancer

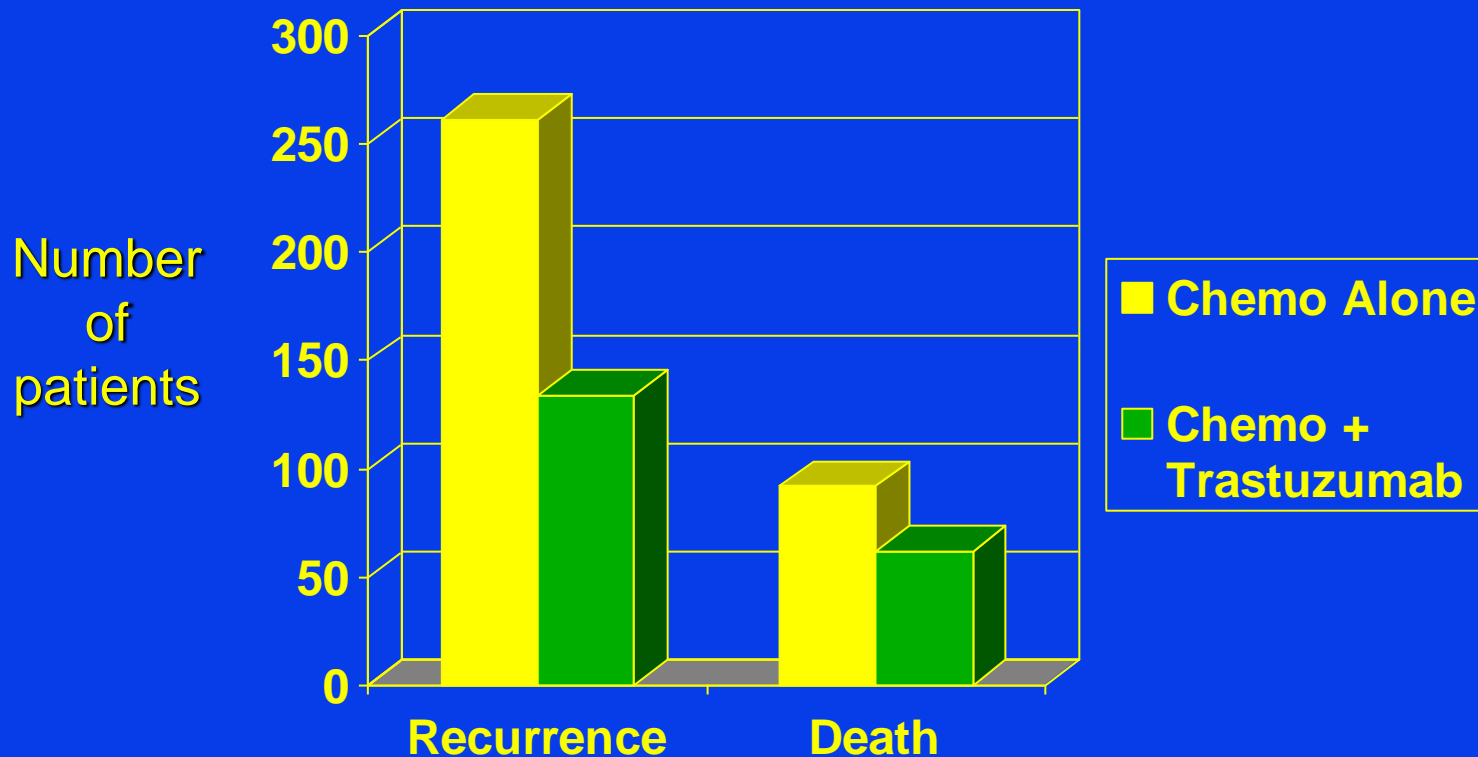
- Adjuvant chemotherapy reduces recurrences and deaths
 - Reducing dose from that proven to be effective in clinical trials reduces benefit
 - Chemotherapy drugs have significant side effects
- For **unselected patients/tumors**:
 - Anthracyclines (doxorubicin, epirubicin) better than CMF regimens
 - Taxanes (paclitaxel, docetaxel) add to anthracyclines
- Not all patients/tumors benefit from chemotherapy!
 - ER-negative, high grade, and HER-2+ tumors get most benefit from chemotherapy

Four US FDA-Approved Drugs with HER2 as a Target



Adjuvant Trastuzumab: Combined Analysis of NSABP B-31 and N9831

Romond E et al, N Engl J Med 353, 2005



- Risk of breast cancer recurrence reduced by 52% at 3 yrs
- Risk of death decreased by 33% at 2 yrs

WHO Model List of Essential Medicines 19th Edition (April 2015)

Antineoplastic drugs relevant to breast cancer

- Targeted Therapy
 - Trastuzumab (Herceptin)

ASCO Guideline: HER2 Targeted Therapy for Early Stage Breast Cancer

Giordano S et al, J Clin Oncol 2014

- **Anti-HER2 monoclonal antibody trastuzumab for 1 year is standard**
 - **Reduces recurrence by 1/2 & deaths by 1/3 when added to chemo in early stage breast cancer**
- **All regimens include chemotherapy in addition to HER2-targeted therapy**

Systemic Treatment of Early Stage Breast Cancer: Summary

- Main principles of modern oncology
 - Multidisciplinary treatment
 - Evidence-based medicine
 - Individualized (tailored) therapy
- Primary goals of therapy
 - Adjuvant: curative intent

