Choices in the Treatment of Metastatic Breast Cancer

- Choice of treatment is based on many factors:
  - *Patient age, menopausal status, general health and functional status*
  - *Tumor ER status, HER-2 status*
  - *Previous treatments*
  - *Extent and sites of disease*
  - *Available therapies in the patient's country*

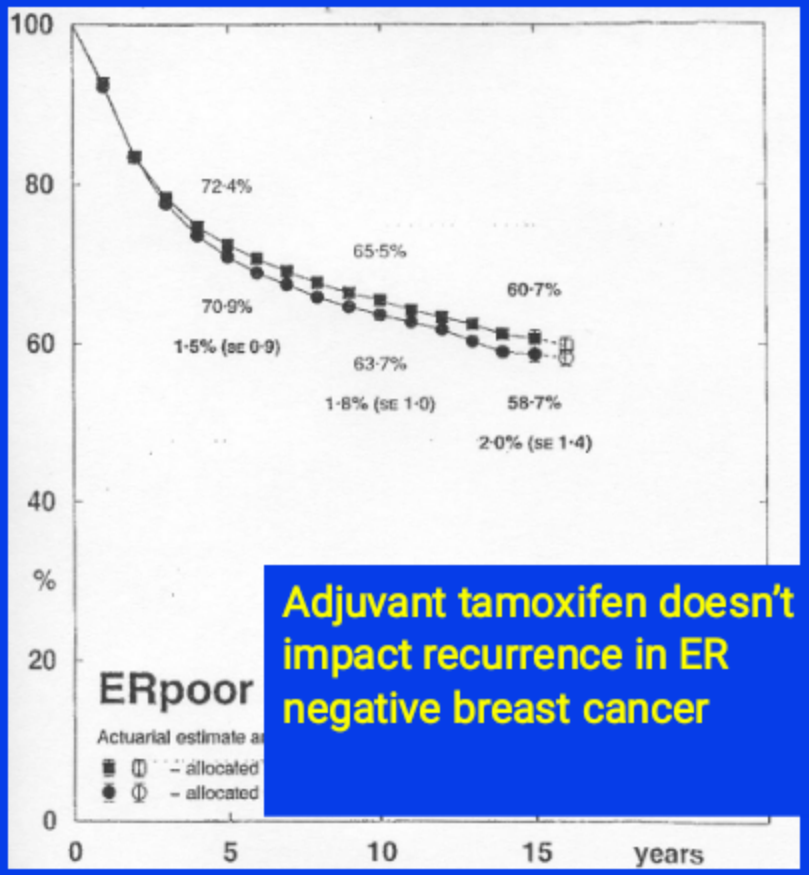
Adjuvant (Early Stage) Endocrine Therapy in Breast Cancer

- Tamoxifen has substantial clinical efficacy, less cost, and several decades of use throughout world
  - Still the standard for premenopausal
  - Reasonable for many postmenopausal
  - Longer duration (> 5 years) may benefit many patients
- Adjuvant aromatase inhibitors: small differences in recurrences (and in some trials deaths)
  - Side effects different
- Ovarian suppression effective as a sole treatment
  - Still unclear whether it adds to chemo/tamoxifen

Early Breast Cancer Trialists' Collaborative Group

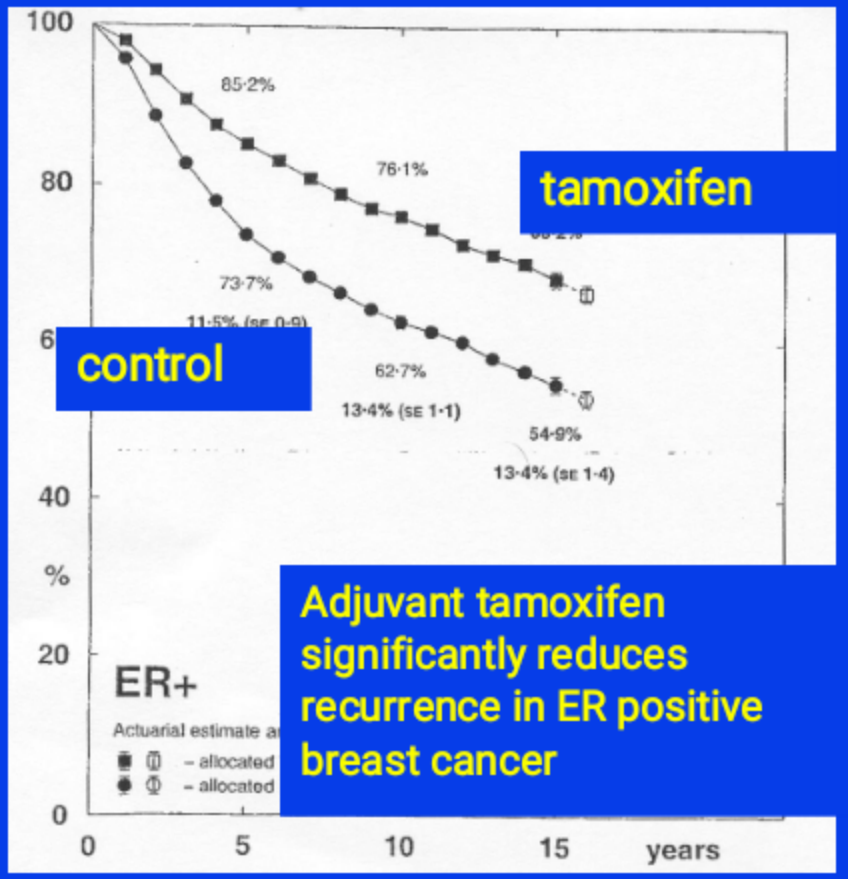
Clinical Trials of Tamoxifen in Early Stage Breast Cancer: *Disease-free Survival*

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

Tamoxifen*

- Works by blocking estrogen receptors in breast cells, inhibiting their growth
- Can be given to pre or post menopausal women
- Side effects include hot flashes, depression, increased risk of uterine cancer and blood clots
- Taken daily by mouth for 5 years

Aromatase Inhibitors*

Aromatase is the enzyme that converts androgens to estrogen

AIs are only given to postmenopausal women

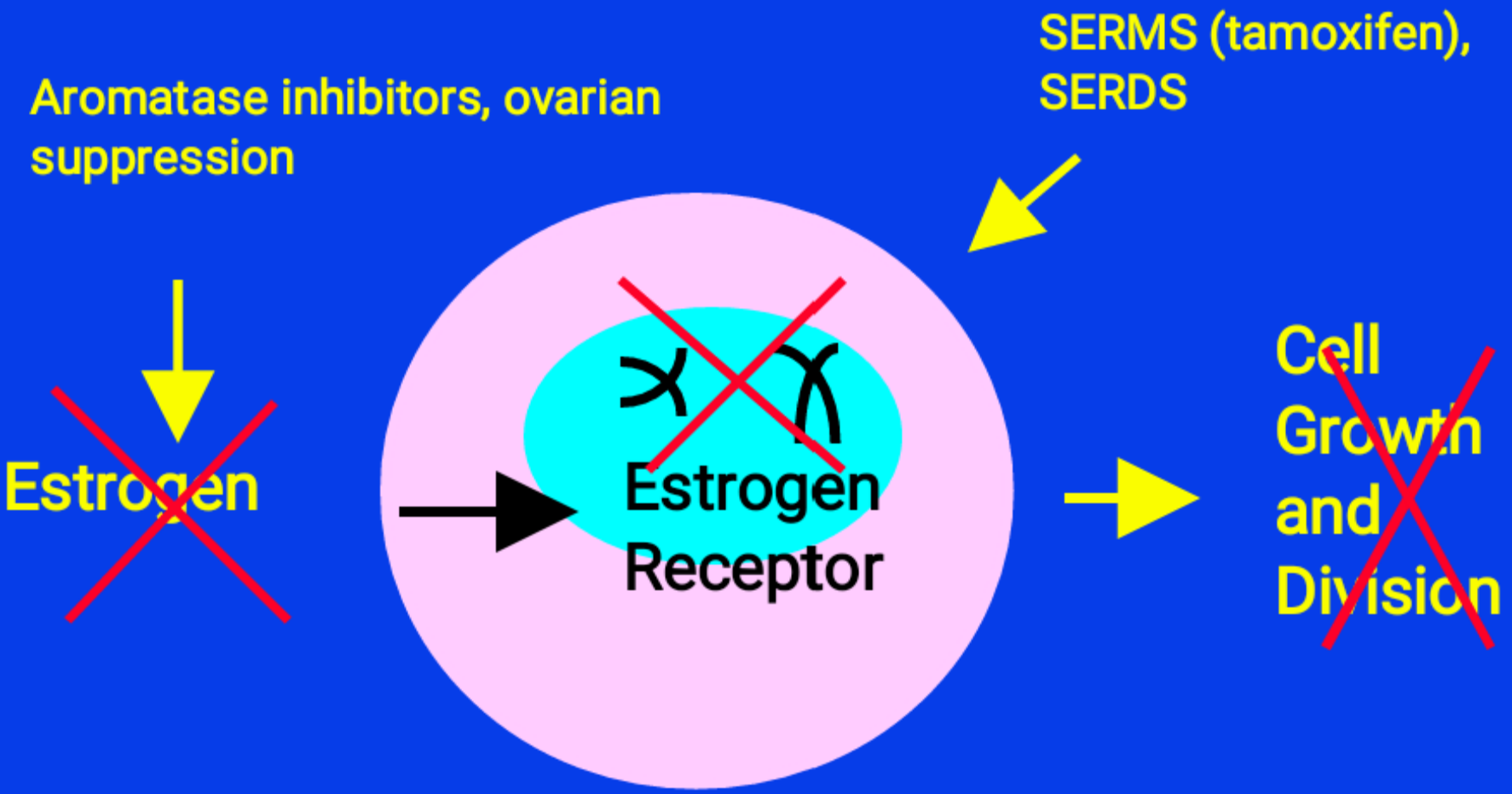
Examples: Anastrozole/Arimidex, Letrozole/Femara, Exemestane/Aromasin

- "May" be more effective than Tamoxifen
- Side effects include hot flashes, depression, osteoporosis, joint pains
- Taken daily by mouth for variable periods of tim

Endocrine Therapy for Metastatic Breast Cancer

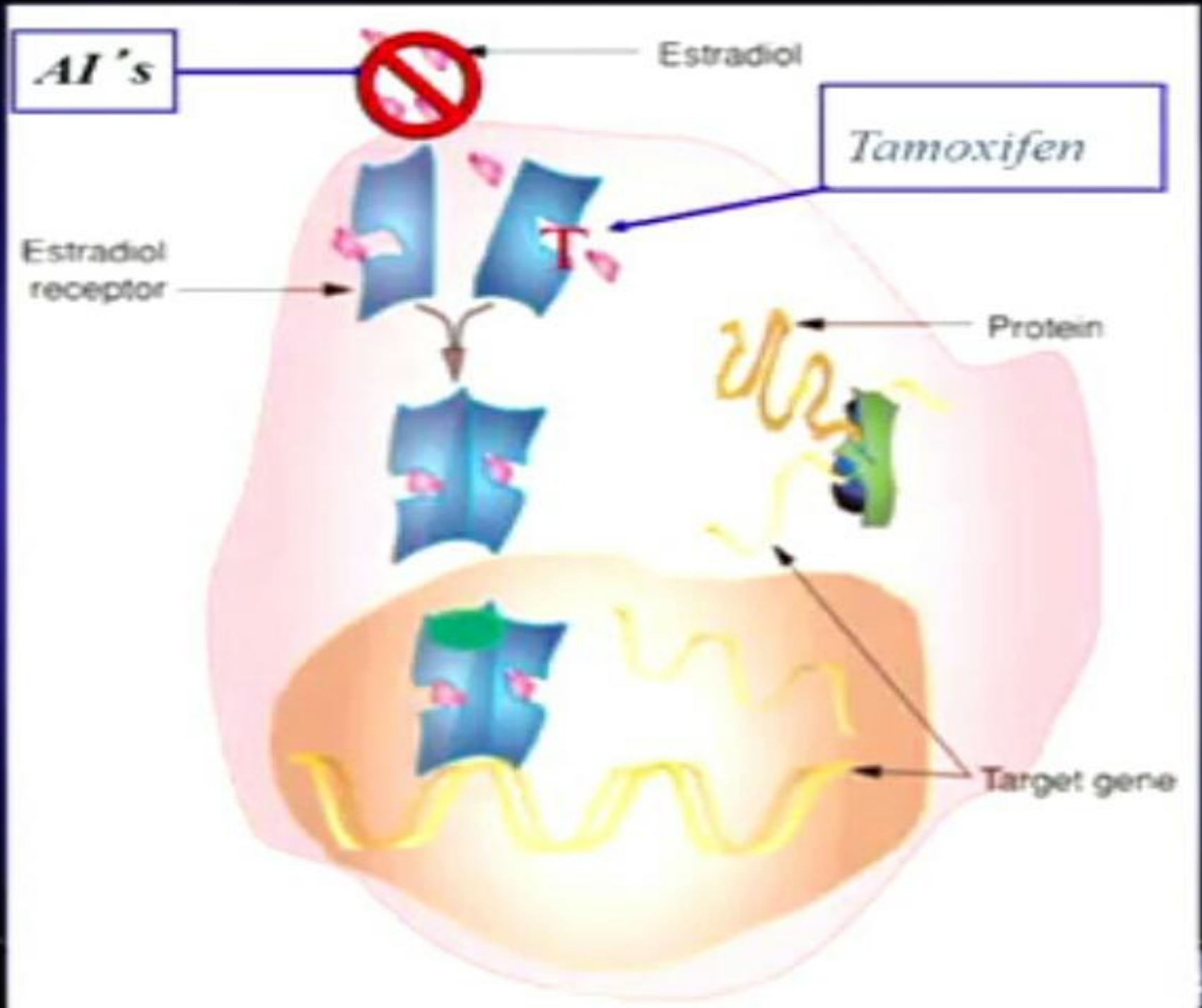
- Endocrine therapy is the preferred choice for ER+ metastatic breast cancer
  - Less side effects than chemotherapy
- Exceptions:
  - Concern or proof of endocrine resistance
  - Need for fast response (location, symptoms)

Endocrine Therapy in Breast Cancer



Endocrine therapy effective only in ER-positive breast cancer

ER/PR staining: CRITICAL IN SELECTING THERAPY!


AI 's
Estradiol
Tamoxifen
Estradiol receptor
T
Protein
Target gene

AIs versus tamoxifen: benefit/risk

↓ Osteoporosis risk

↓ Musculoskeletal syndrome

↓ Cost

Neurocognition

Sexual function

Hyperlipaemia

Cardiovascular disease

↓ DVT

↓ Stroke

↓ Endometrial cancer

↓ Hot flashes

Chemotherapy

Adjuvant (Early stage) Chemotherapy in 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 better than CMF regimens*
  - *taxanes add to anthracyclines – expensive*
- *Not all patients/tumors benefit from chemotherapy!*
  - *ER-negative, high grade, HER-2+ tumors get most benefit from chemotherapy*

European School of Oncology Guideline: Chemotherapy for Metastatic Breast Cancer
Cardosa F et al, J Natl Cancer Inst 101:1174-1181, 2009

- Sequential single agent chemotherapy generally preferred choice
  - Less toxicity than combination chemo
  - No data to support optimal sequence
- Combination chemotherapy reserved for patients with:
  - rapid clinical progression
  - life-threatening visceral metastases
  - need for rapid symptom/disease control
- Chosen regimen should be evidence-based, with proven efficacy and acceptable toxicity

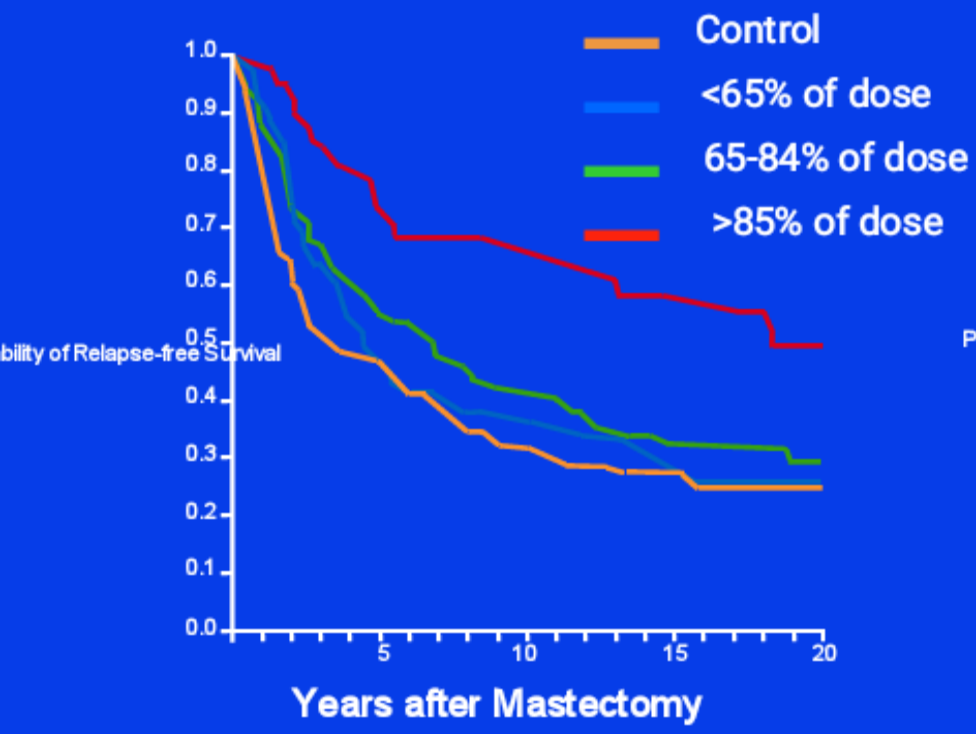
Chemotherapy Dose Matters

Adjuvant Chemotherapy - 20 Year Follow-up

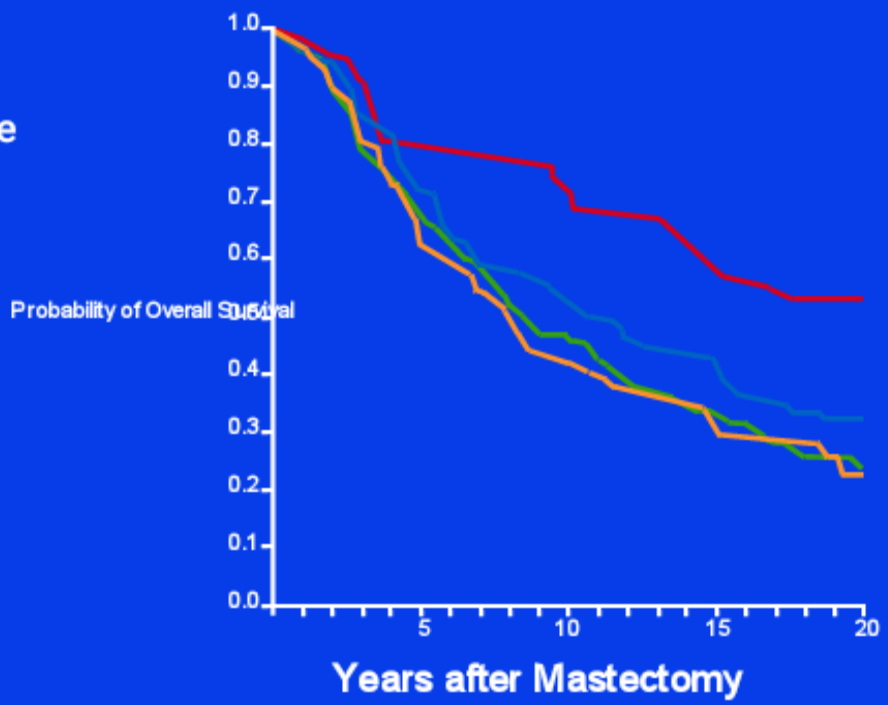
Milan Study

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

Disease-free survival



Overall survival

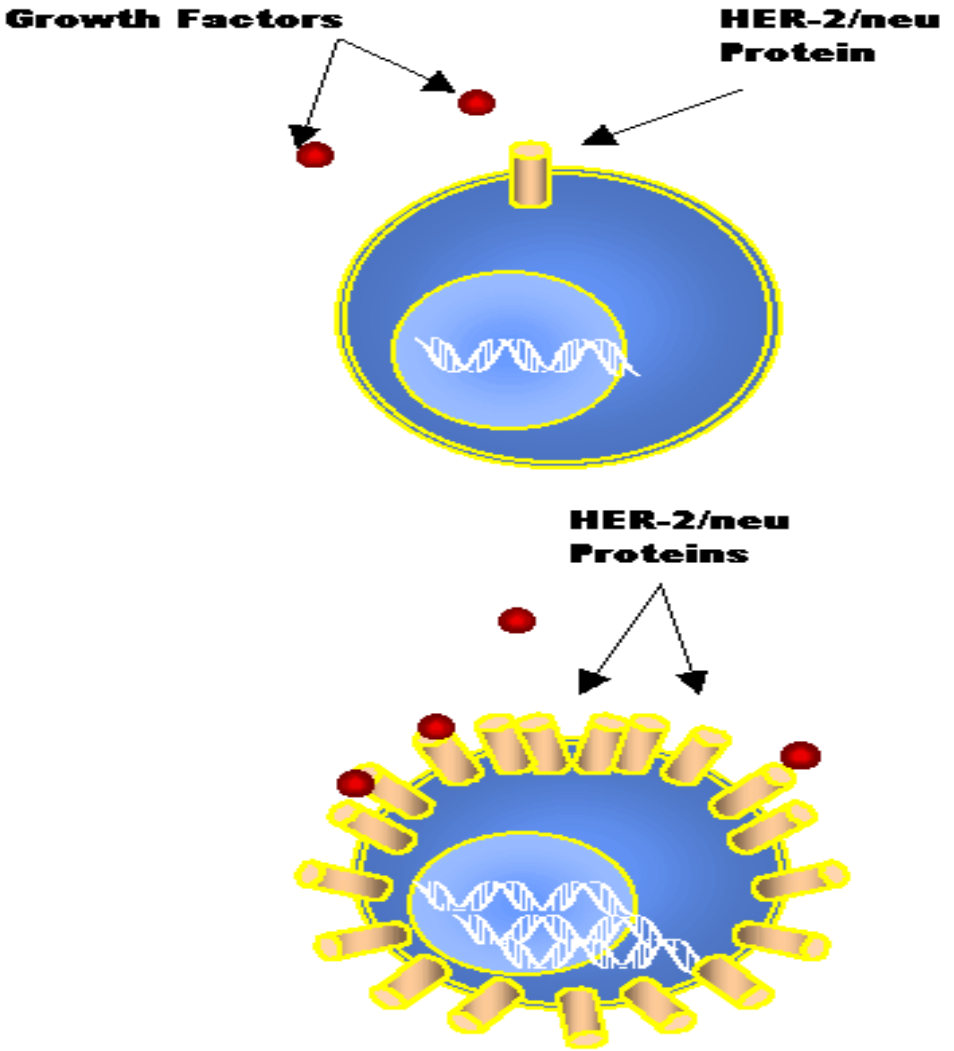


If chemotherapy is given, it should be given at full dose

Biologically-Targeted Therapy

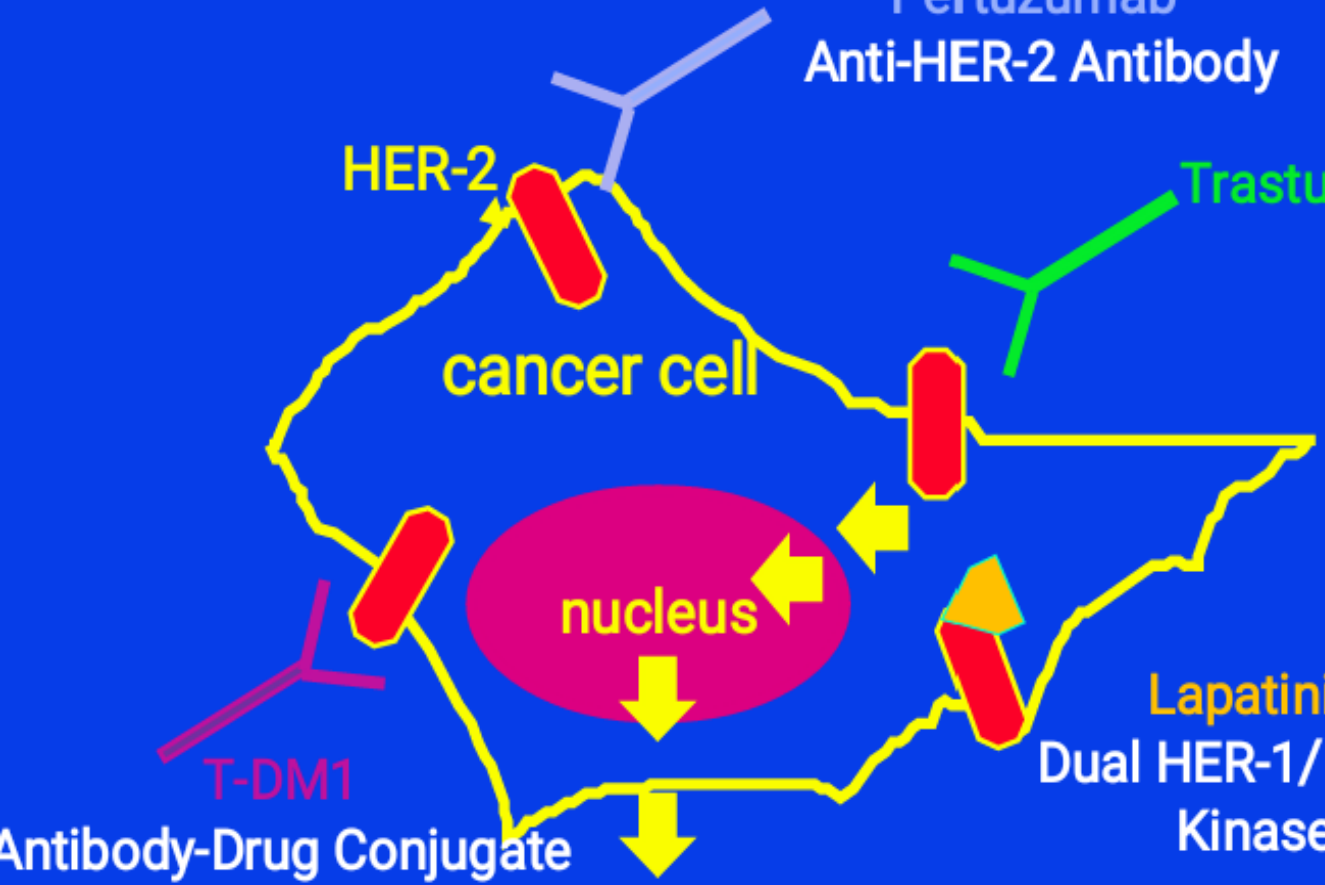
HER-2/neu

- Growth-stimulating protein
- Normal cells express a small amount on their plasma membranes
- On surface of breast cancer cells
- Sends messages from cell to "growth factors" outside cell
- Overabundant on surface of cancer cells in 30% of women with breast cancer



Four US FDA-Approved Drugs with HER-2 as a Target

20-25% of breast cancers overexpress HER2



Only effective for HER2+ breast