

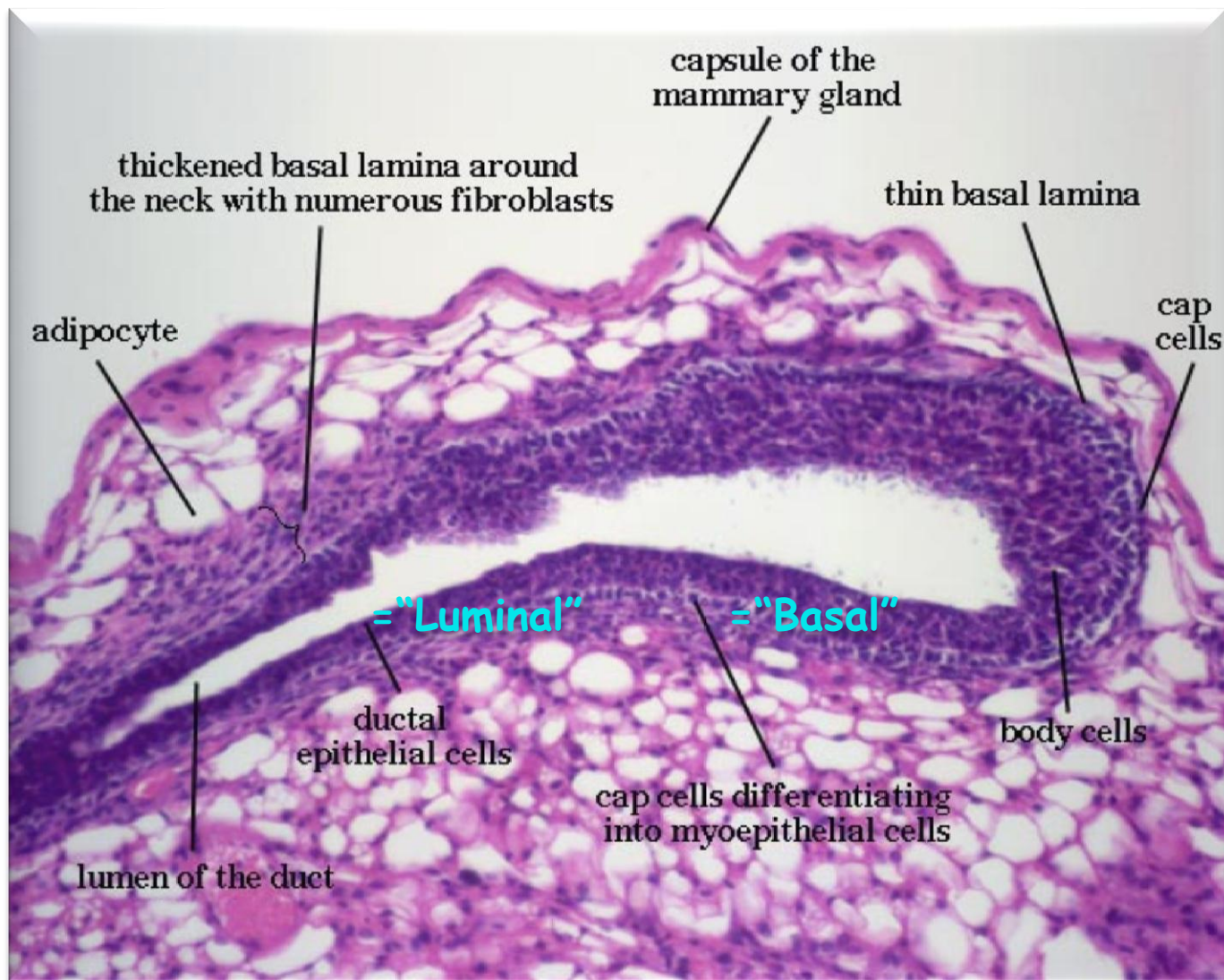
# A Researcher's Perspective: Myths and Facts About Triple Negative Breast Cancer

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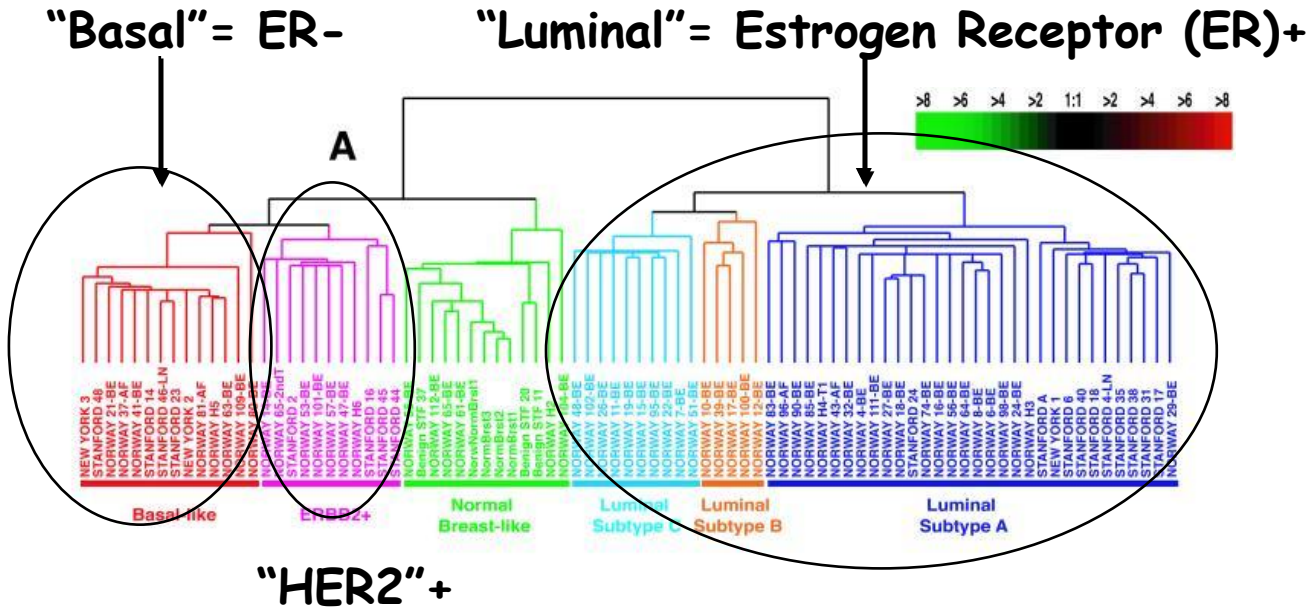


Talya C. Arbisser - Photos by Talya

# Breast Cancer Begins in Cells Within the Terminal Ducts



# Breast Tumor Molecular Subtypes



*Nature, 2000, Perou et al.*

# Molecular Subtypes

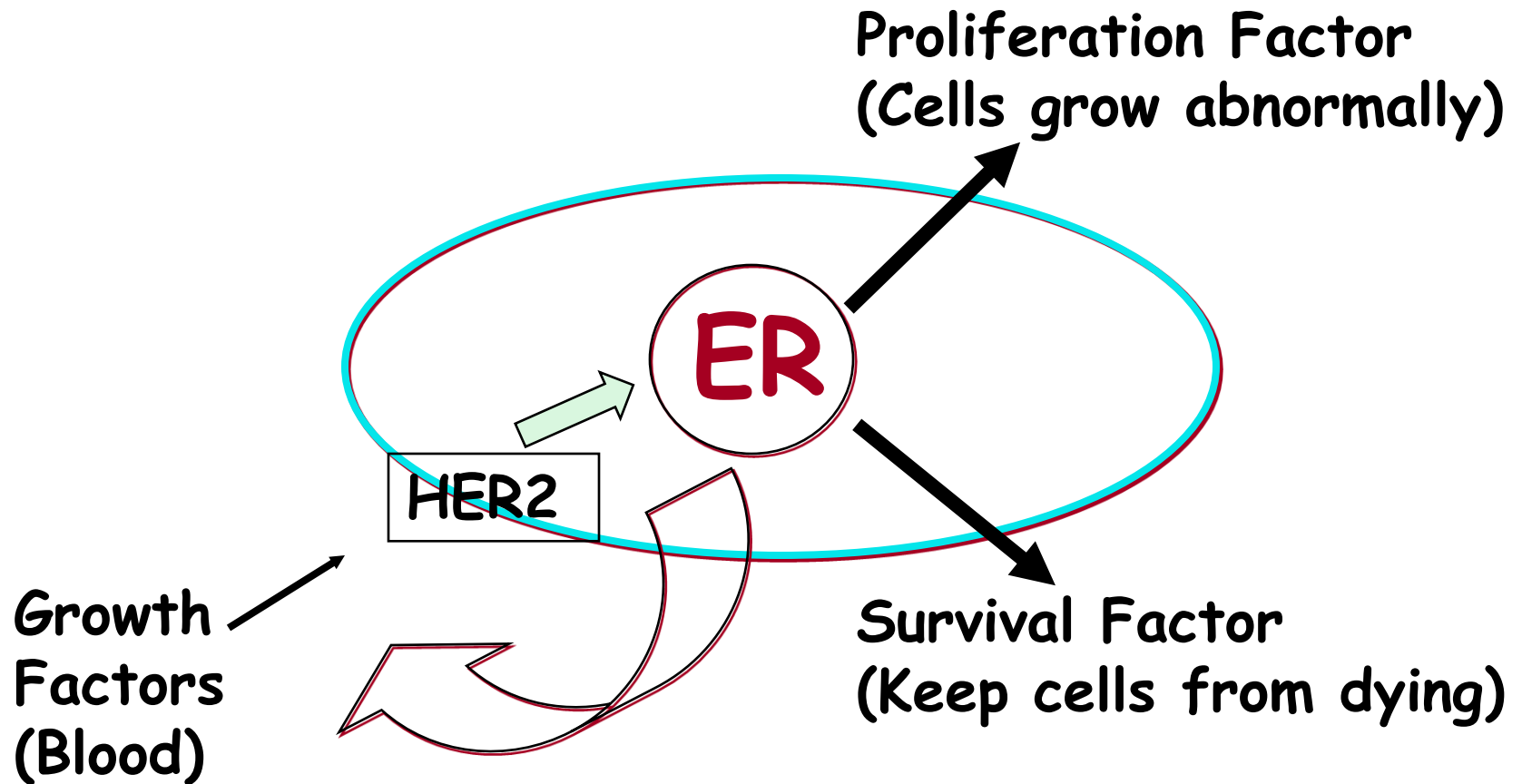
- **Luminal**: High expression of **ER**, the estrogen-regulated progesterone receptor (PR), and cytokeratins 8 and 18 (none overexpress HER2). Longest disease-free survival.
  - **HER2**: Overexpress this oncogene and other genes which are co-amplified with it. Some may also express low levels of ER.
  - **Basal**: Do not express ER or PR. Express cytokeratins 5, 6, and 17. Significantly shorter survival times.
- “*Triple negative*” is a subset of Basal (12-24% of all breast cancers) that does not express ER, PR, or HER2.

**Breast Cancer Subtype #1:**

**Luminal ER+**

# Growth Factor-ER Crosstalk is a Vicious Circle

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# Cases

Julie Nangia, MD  
Assistant Professor  
Lester & Sue Smith Breast Center  
Baylor College of Medicine

**Patient LT: ER+ Breast Cancer**

# Pt LT: Initial Presentation

- 74yo African American woman
- Medical History  
hypertension, hyperlipidemia, diabetes, heart disease
- Surgical History  
CABG, cholecystectomy
- Social History  
No tobacco or alcohol, married, retired
- Allergies  
none
- Medications  
Pravastatin, toprol-XL, zestril, glyburide, metformin,  
norvasc, aspirin, actos
- Family History  
No cancers

# Pt LT: Diagnosis

- **Screening mammogram**  
Indeterminate calcifications left breast, new LNs left axilla rec additional views/bx
- **Left diagnostic mammogram**  
Heterogeneous calcifications in the inferior left breast, rec biopsy and US
- **Breast US Left Axilla**  
Multiple enlarged LNs largest 2.7cm
- **Biopsy**  
Left Axilla LN = metastatic carcinoma, ER 8/8, PR 2/8, Her2-

# Pt LT: Examination & Staging

- Exam

Breasts

- Right: no masses, skin or nipple changes
- Left: 5 x 5cm mass in the upper outer quadrant
- Lymph nodes: 2cm left axilla LN

Otherwise exam was normal

- Staging Work-up

Bone scan

- NED

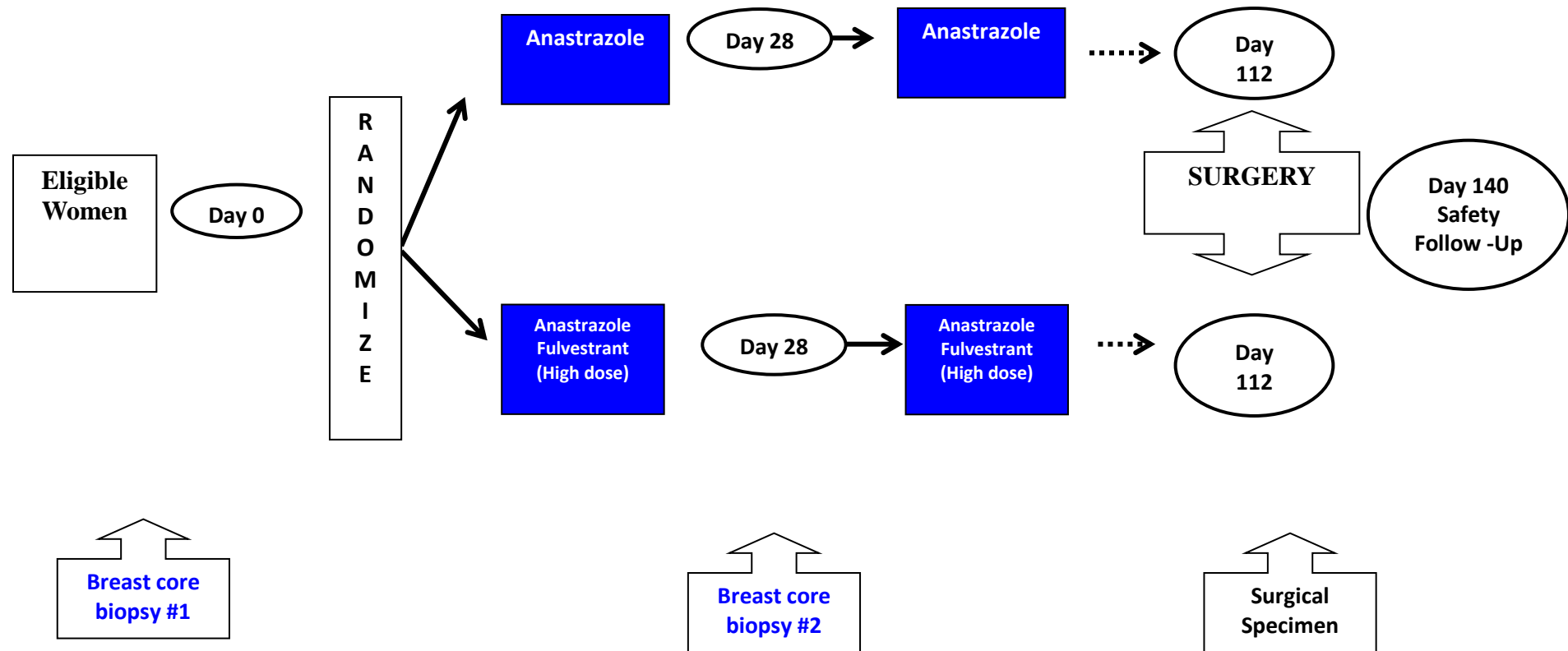
CXR

- Nodular density left lower lung

CT chest

- NED, no nodules

# Pt LT: Treatment Clinical Trial



# Pt LT: Treatment

- Randomized to **anastrozole + fulvestrant** which she received for 140 days
- Left breast mass disappeared & left axilla LN was smaller
- Left mastectomy
  - No remaining invasive carcinoma
  - 6/23 LN+
  - ER 5/8, PR 0, Her2-
- Radiation therapy
- Anastrozole (Arimidex<sup>TM</sup>) for total of 5 years

# Is ER a Useful Target? Yes

- Expression of ER predicts a better outcome
- Adjuvant therapy (treatment after surgery/radiation)
  - 40-50% reduction in recurrence.
- Metastatic disease (treatment after recurrence)
  - 30-50% clinical benefit.
- However, incomplete cross-resistance can develop which necessitates **sequential** hormonal therapies.

# Established Endocrine Therapy

## Two pharmacological strategies

- **Antiestrogens**

Tamoxifen (Nolvadex™)

Fulvestrant (Faslodex™)

- **Aromatase inhibitors**

Anastrozole (Arimidex™)

Letrozole (Femara™)

Exemestane (Aromasin™).

# Antiestrogen Therapy

- Reduces recurrence by 1/2, death by 1/3
- Benefit is continuing out to 15 years after 5 years of tamoxifen
- Tamoxifen blocks estrogen binding, but fulvestrant also causes ER loss
- Fulvestrant has not proven better than tamoxifen, maybe due to poor metabolism.
- Clinical trials now are evaluating higher doses of fulvestrant.

# Tamoxifen Saves Lives

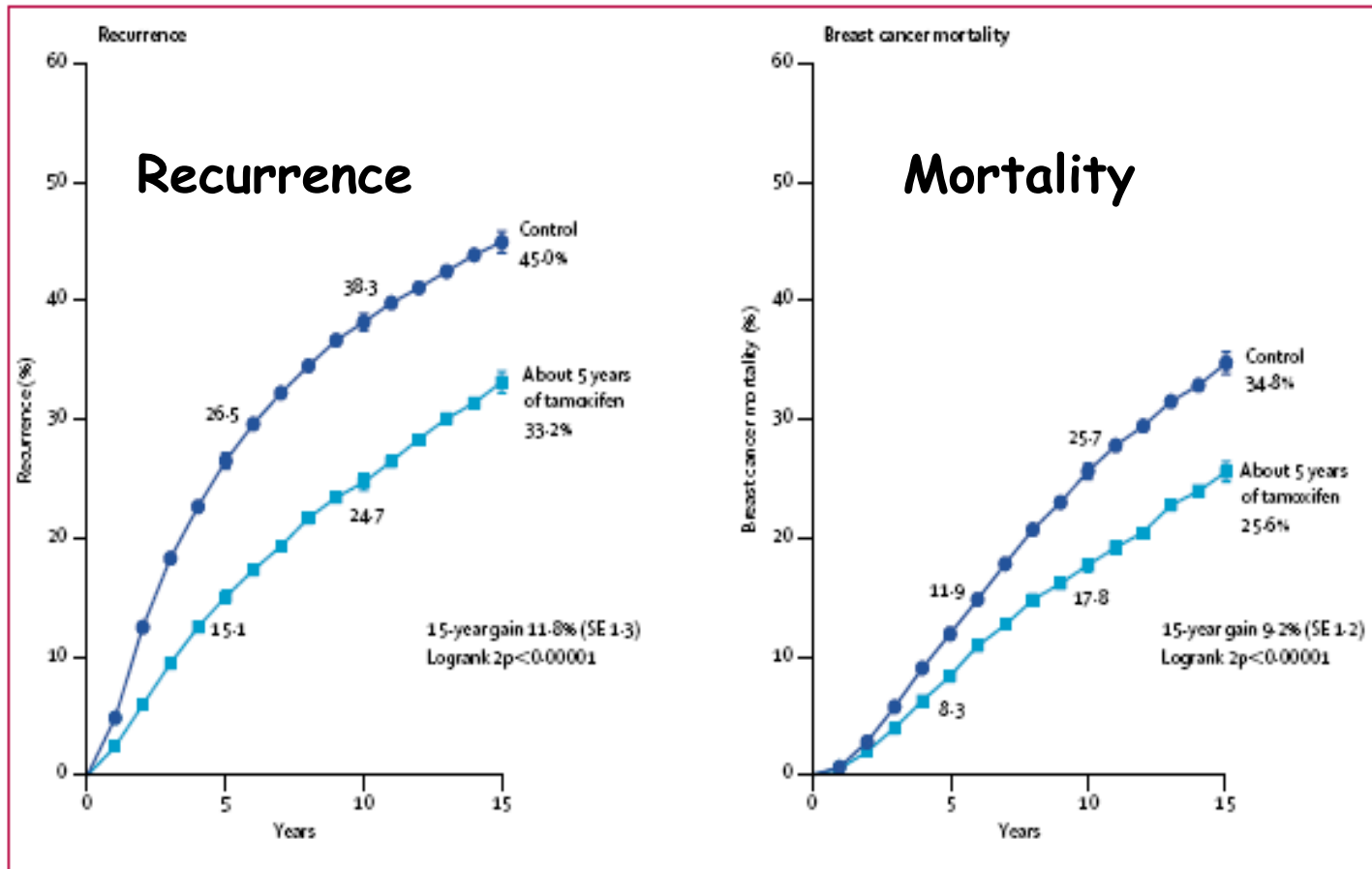
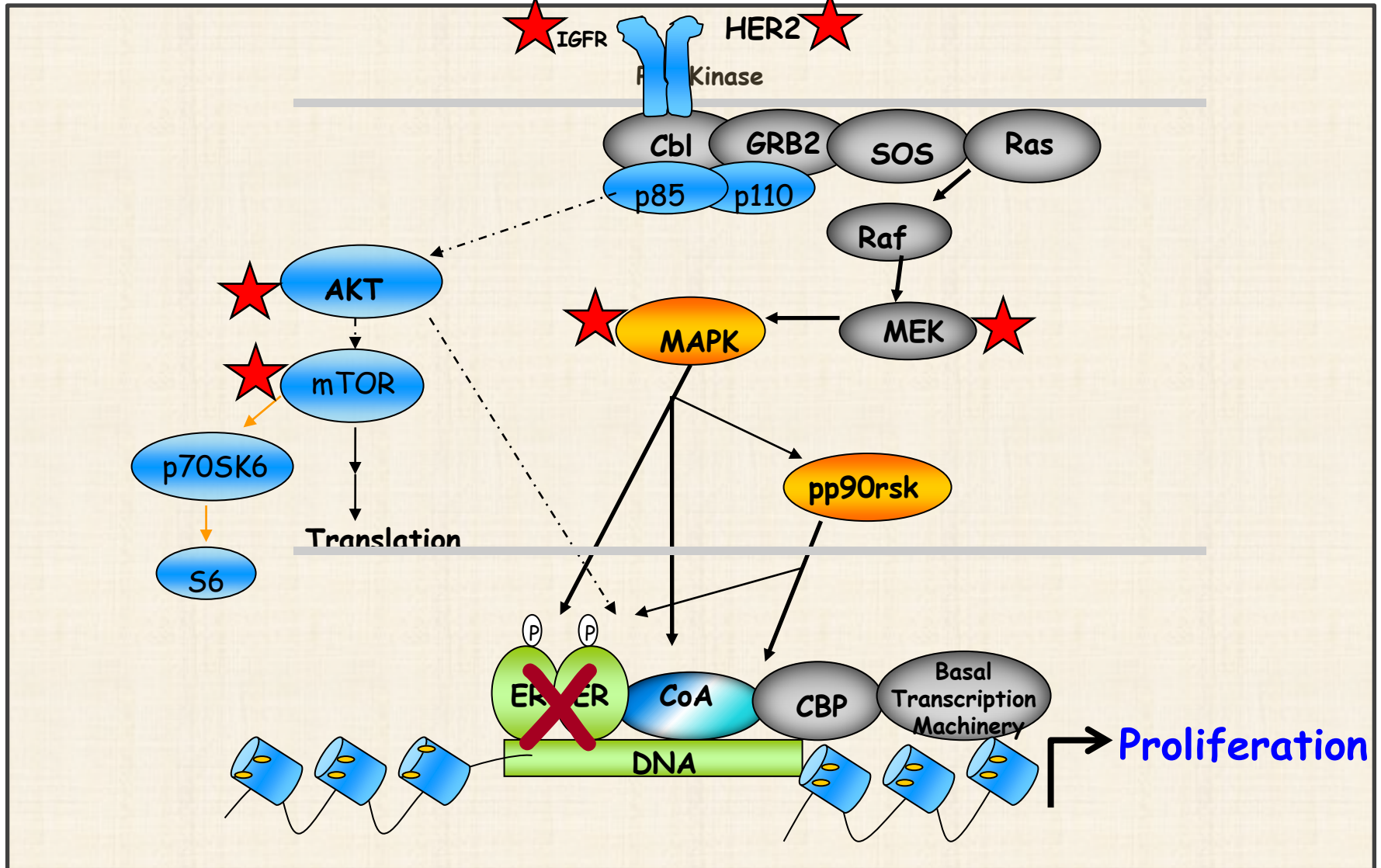


Figure 8: About 5 years of tamoxifen versus not in ER-positive (or ER-unknown) disease: 15-year probabilities of recurrence and of breast cancer mortality  
10 386 women: 20% ER-unknown, 30% node-positive. Error bars are  $\pm 1SE$ .

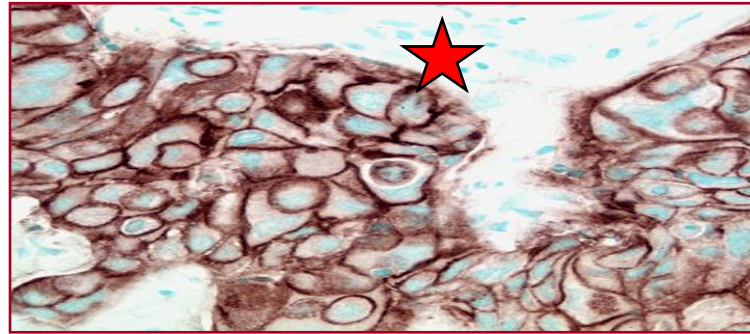
# The Future: Hormonal Therapy ~~X~~ + Targeted Therapy ★



**Breast Cancer Subtype #2:**

**HER2+**

# HER2 Targeted Therapy



- Membrane protein overexpressed in 15-20% of breast cancers.
- Before targeted therapy was associated with poor prognosis.
- Target with antibodies (trastuzumab/pertuzumab) and receptor enzyme inhibitors (lapatinib).
- Clinical trials combining these +/- chemotherapy are underway. So far dual anti-HER2 therapy appears better.

# Cases

Julie Nangia, MD

**PATIENT MB: HER2+ BREAST CANCER**

# Pt MB: Initial Presentation

- 43yo woman
- Past Medical History  
none
- Surgical History  
none
- Social History  
No alcohol or tobacco, married
- Family History  
No FH cancers
- Allergies  
none
- Medications  
none

# Pt MB: Diagnosis

- Pt felt a mass in her left breast
- Diagnostic bilateral mammogram  
3.5cm lobulated mass left breast at 12:00
- Biopsy  
Infiltrating Ductal Carcinoma  
Grade 3  
ER-, PR-, HER2+

# Pt MB: Examination & Staging

- Examination

  - Breasts

    - Right: No masses, skin or nipple changes.
    - Left: 4 x 4cm mass superior of the nipple at 12:00
    - Lymph Nodes: no axillary LN bilaterally

- Staging

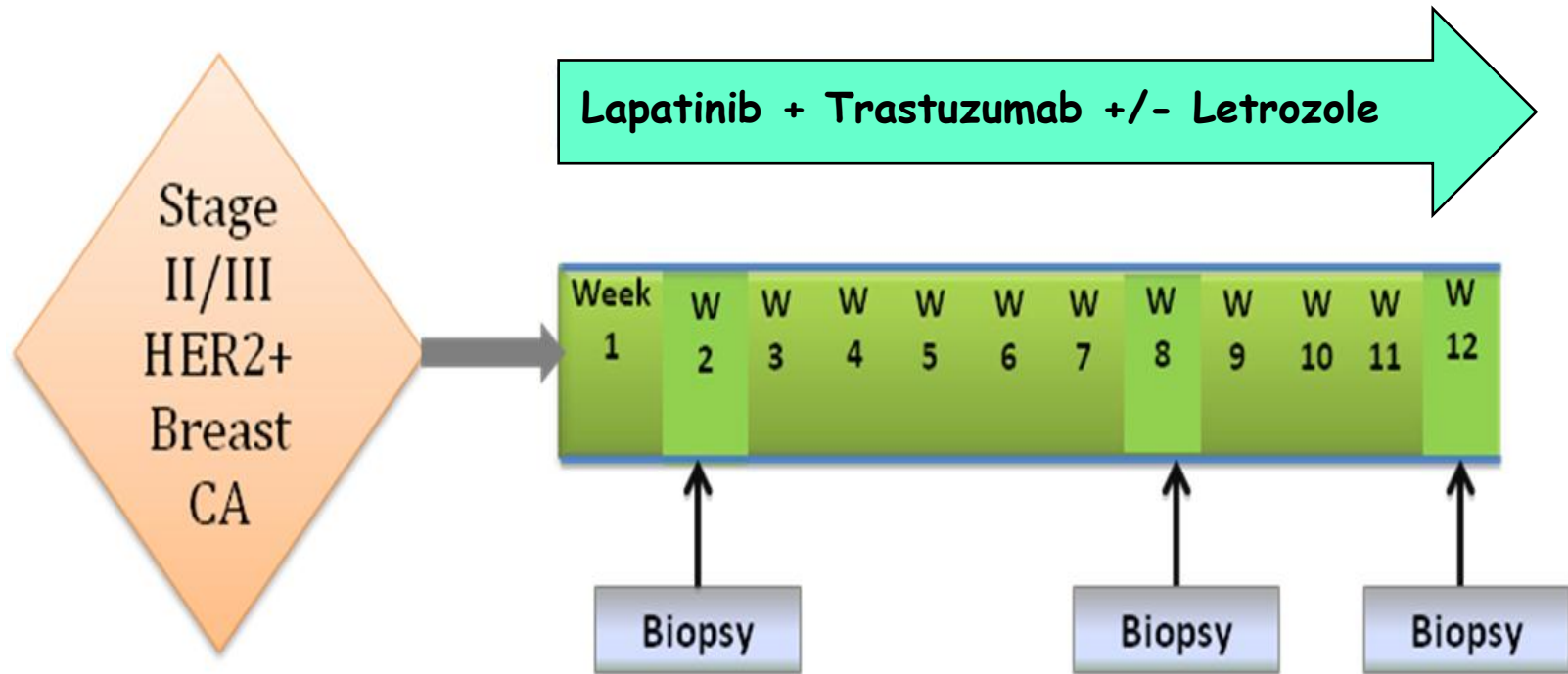
  - Bone Scan

    - NED

  - CXR

    - NED

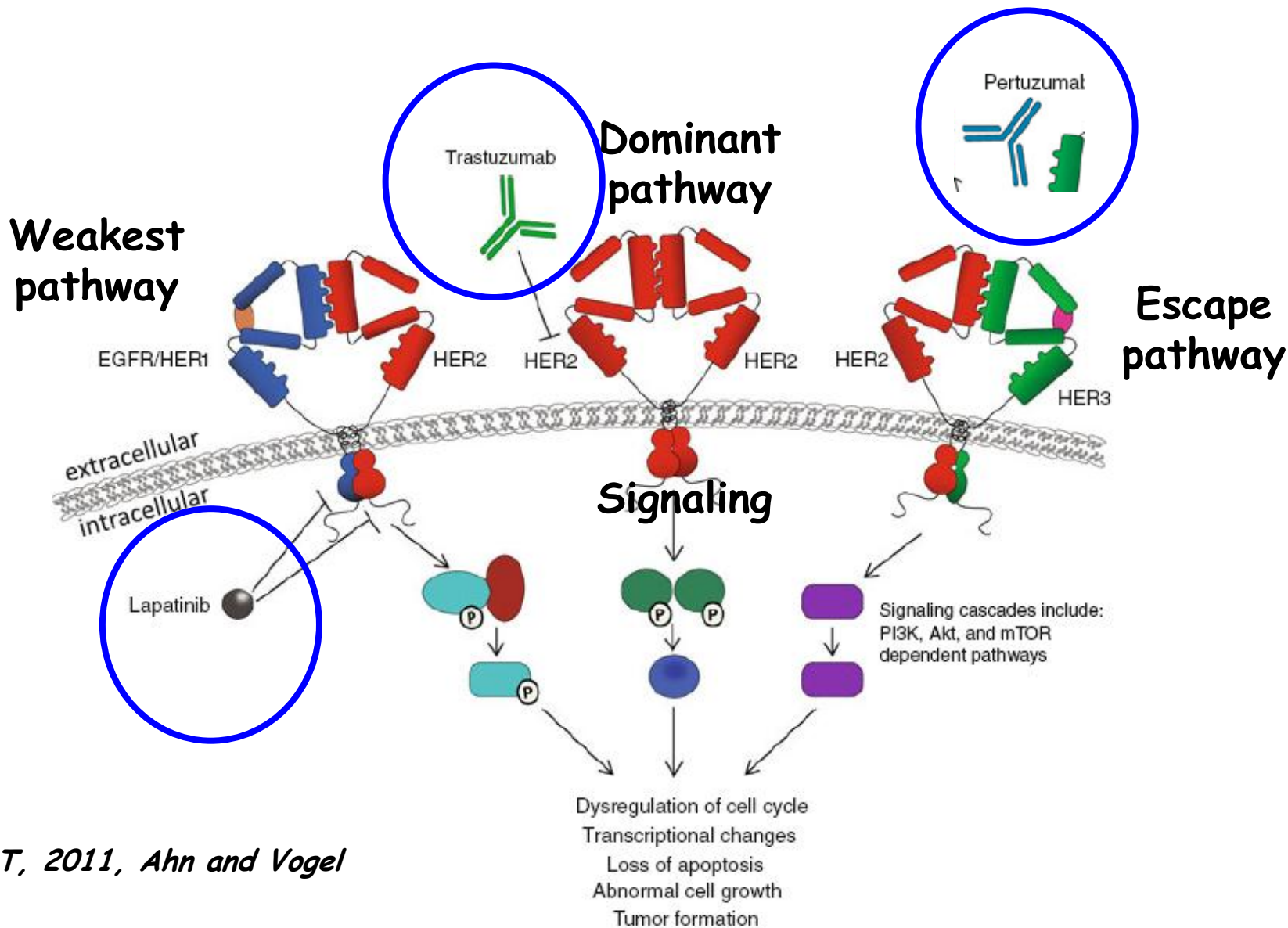
# Pt MB: Treatment



# Pt MB: Treatment

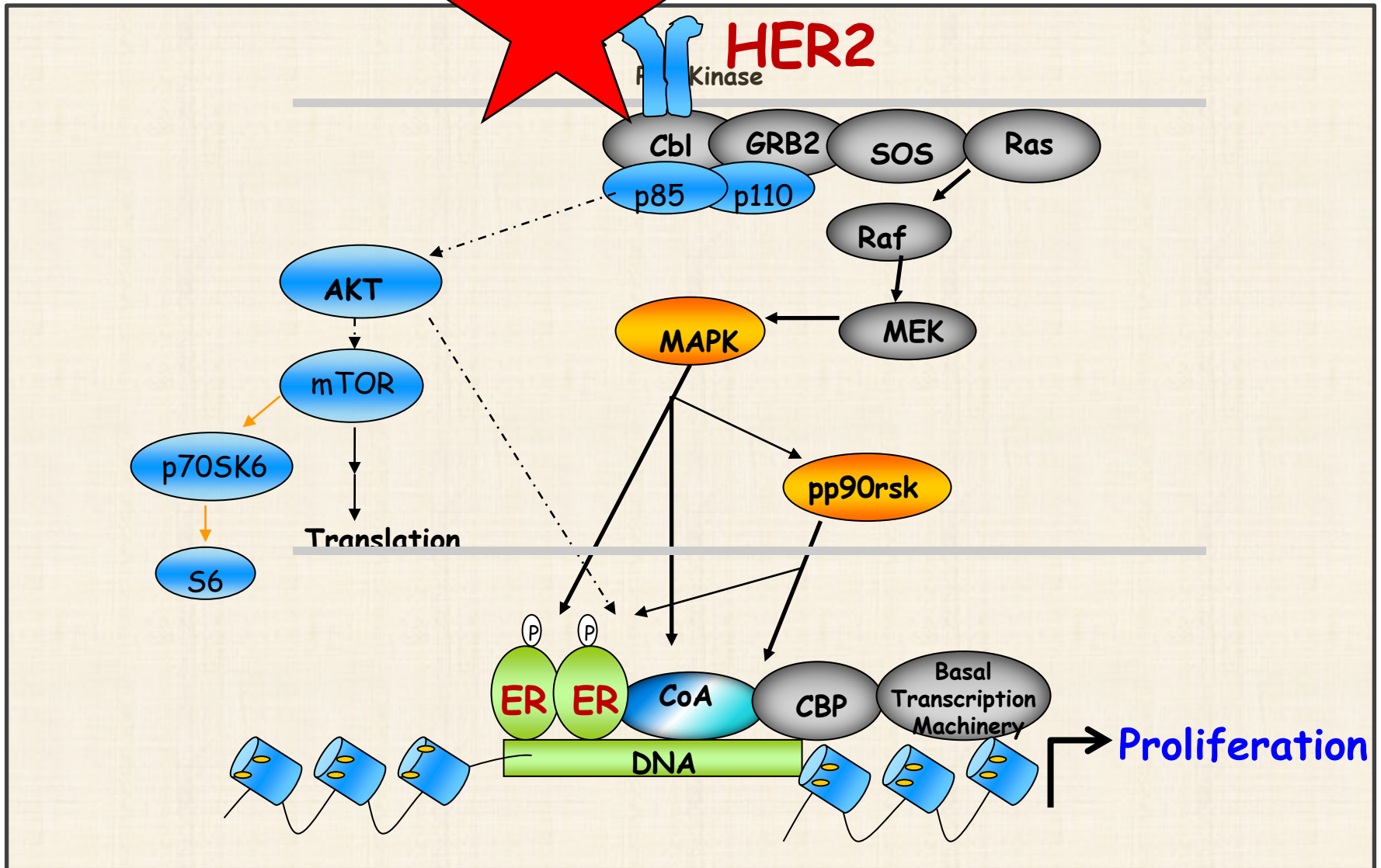
- Placed on the study and received 12 weeks of trastuzumab + lapatinib
- Left mastectomy
  - Pathologic Complete Response!!!
  - No residual cancer in the breast
  - 0/4 LN+

# Why Dual HER2 Targeted Therapy is Better: The Cancer is "Addicted" to HER2 Stimulation!



BCRT, 2011, Ahn and Vogel

# The Future: The Yin-Yang of HER-2 Targeted Therapy With ER



## Breast Cancer Subtype #3:

Triple Negative (TN) = ER-/PR-/HER2-

# Clinical Problem

- ~25% of breast cancers are ER-negative.
- Unfortunately, these patients are still being treated with chemotherapy which does not cure all patients.
- Goal is to identify molecular targets that control cancer cell growth.
- At the Lester and Sue Smith Breast Center and Ben Taub clinic, we see 1200 patient visits; 120 new cases are TN.

# Clinical Features of TN Tumors

## Patient char.

Younger age at diagnosis

African origin

BRCA1 carrier

## Tumor char.

Ductal invasive cancer

High grade

Negative for ER, PR, HER2

Elevated mitotic count

Tumor necrosis

Pushing margin of invasion

Larger tumor size

Axillary nodal involvement

## Treatment/Prognosis

Chemosensitive

Few targets

Poorer prognosis (trend to relapse first 3 yrs.)

Aggressive relapse

# Cases

Julie Nangia, MD

**PATIENT RO: METASTATIC TN  
BREAST CANCER**

# Treatment of TN BC

- No targeted therapy
- Unless <1cm give chemotherapy containing an anthracycline and taxane
- Typical treatment is 8 cycles of chemotherapy
- No markers to predict prognosis
- More likely to recur than other subtypes
- If a patient has a pathologic CR they do better!

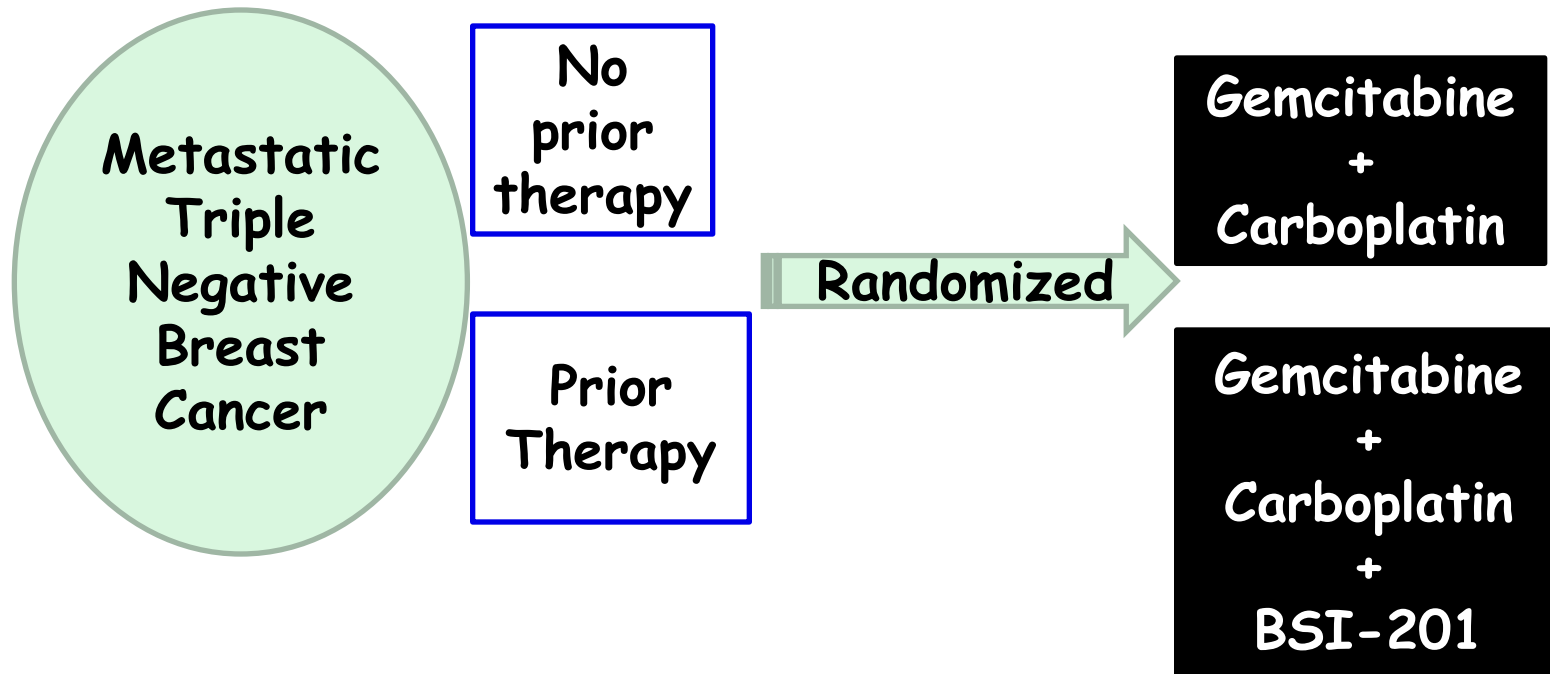
# Pt RO: Initial Presentation

- African American with a history of breast cancer
- s/p right lumpectomy
  - Infiltrating ductal carcinoma 3.5cm
  - ER-, PR-, HER2-
  - 0/8 LN+
- Received chemotherapy
  - AC x 4, Taxotere x 4
- Received Radiation
- Then 3 years later...

## Pt RO: Recurrence

- Goes to the hospital short of breath
- CT chest
  - Multiple bilateral pulmonary lung nodules
  - Mediastinal LAD
  - Right pleural effusion
- CT abdomen/pelvis
  - + bone involvement, no additional disease
- Bone Scan
  - + bone involvement diffusely
- Biopsy of lung nodule
  - Metastatic adenocarcinoma consistent with breast cancer

# Pt RO: Treatment



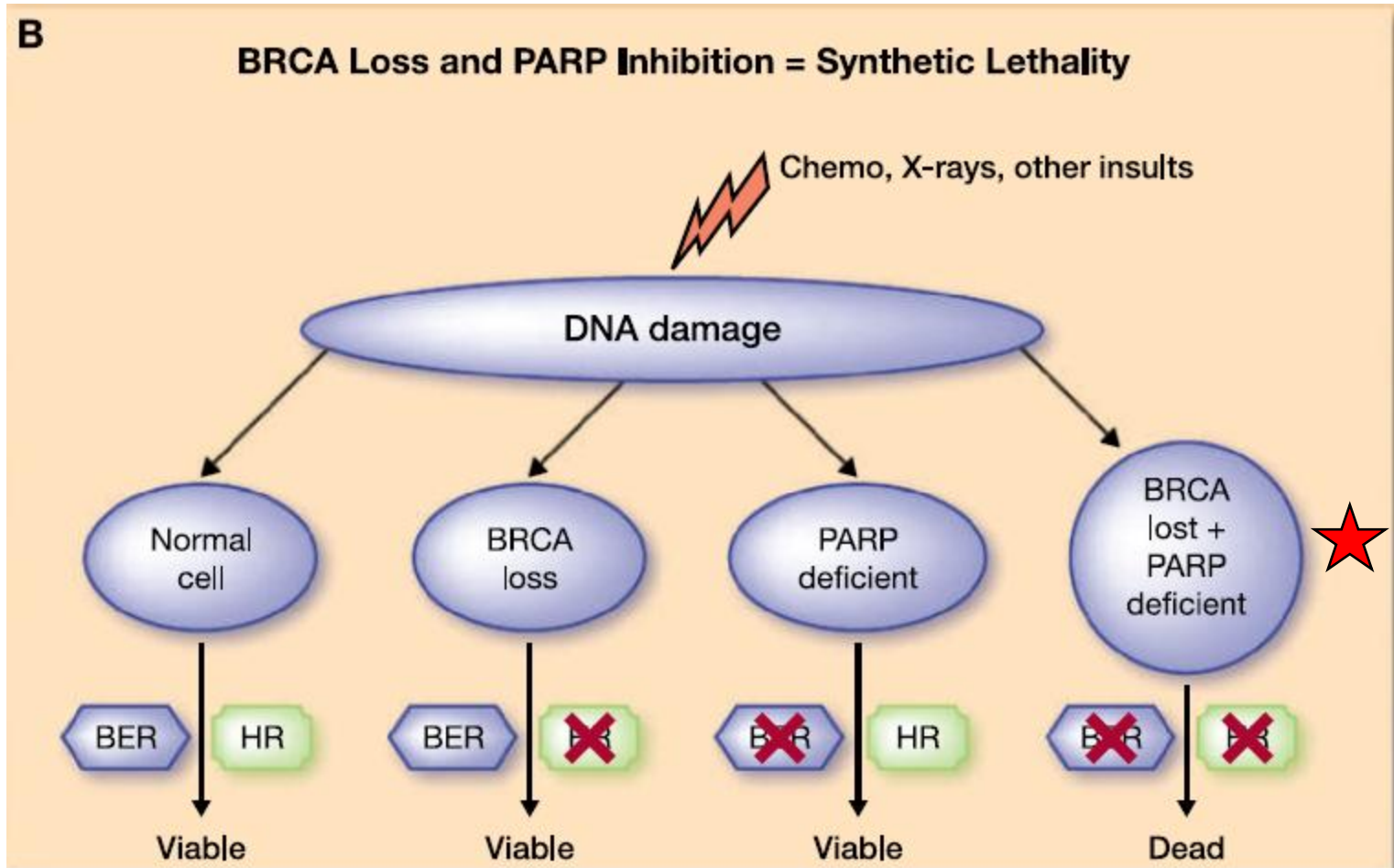
## Pt RO: Treatment

- Started on the BiPar study with gemcitabine, carboplatin, and PARP inhibitor
- Was stable on this for 1.5 years but then had to go off study because her low blood counts
- Unfortunately she has recently progressed and is currently on another clinical trial

# New Hope: PARP Inhibitors

- TN BC has clinical-pathological similarities with BRCA-mutation bc which have a “broken” type of DNA repair.
- PARP's are a family of enzymes involved in DNA repair.
- Hypothesis: preventing DNA repair via PARP inhibitors, in combination with the loss of DNA repair, will kill the tumor!

# PARP Inhibitors: Preclinical Data Supported the Hypothesis But Clinical Data Does Not!



Unfortunately no significant benefits of PARPi over chemotherapy alone to date

# New Potential Targets in TN Cancers: Ongoing Clinical Trials

- BRCA+ (PARPi)
- EGFR+ (Cetuximab, Gefitinib, Lapatinib)
- AR+ (Casodex, Abiraterone Acetate)
- SRC family of kinases+ (Dasatinib)
- Nuclear receptors (Various antagonists)

*Funded by Susan G Komen for the Cure, Texas CPRIT, and Pharmaceutical Industry*

# Summary and Clinical Implications

**The Myth:** TN breast cancer is defined by what it does NOT have (ER-/PR-/HER2-)

**The Fact:** We are defining TN by what it DOES have!

New targeted therapies for TN BC will result from funded preclinical studies and your active participation in clinical trials!

*Suzanne Fuqua, PhD*



*Julie Nangia, M.D.*