# Metastatic Breast Cancer in 2015

## Are we making progress?

Vernon Harvey
Auckland - November 2015


http://Nubiagroup-powerpoint-collection.blogspot.com/

# Systemic Management of Metastatic Breast Cancer

Remains incurable

Aims of therapy

- Quality of life
- Prolongation of life
- Identify 'best' therapy

How do we achieve this?

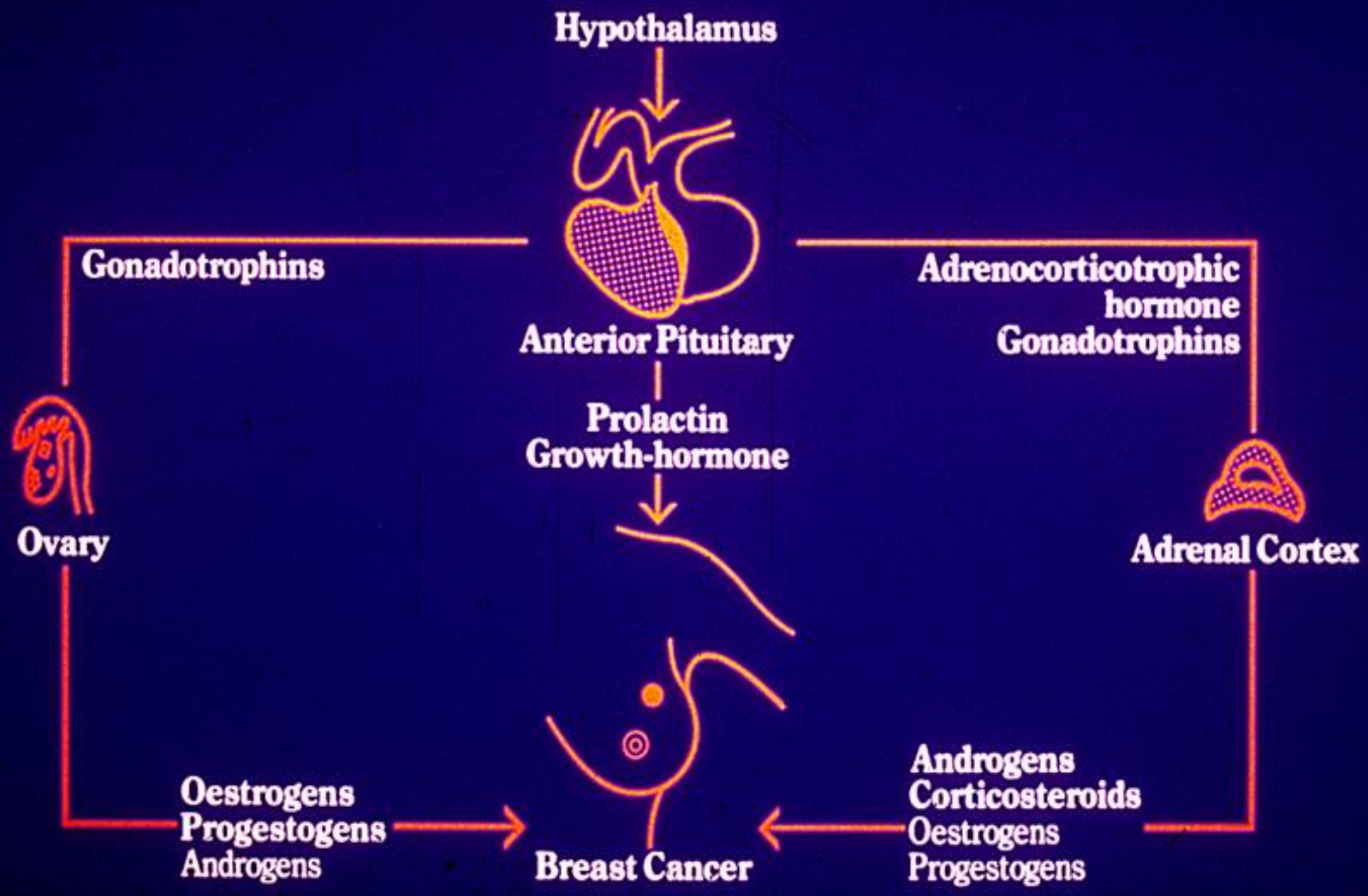
# Systemic Management of Metastatic Breast Cancer

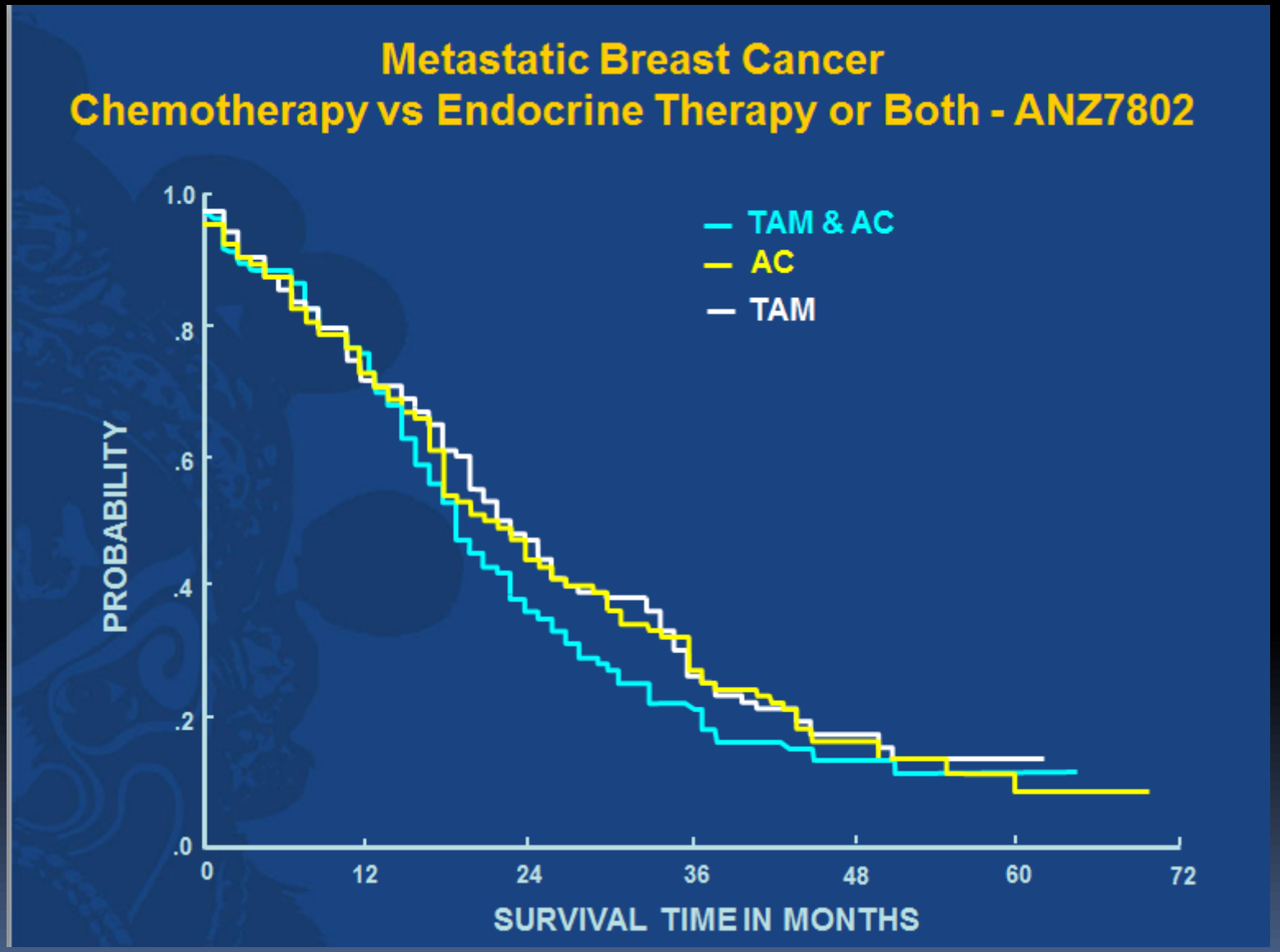
## Options

Hormone Therapy
Chemotherapy
Biological Therapy

Symptom Control

# THE ENDOCRINE ENVIRONMENT OF THE CANCEROUS BREAST




Metastatic Breast Cancer
Chemotherapy vs Endocrine Therapy or Both - ANZ7802
TAM & AC
AC
TAM
PROBABILITY
1.0
.8
.6
.4
.2
.0
0
12
24
36
48
60
72
SURVIVAL TIME IN MONTHS

# Metastatic Breast Cancer

## General Principles

Hormone therapy → Chemotherapy *

(with Herceptin if HER2+)

Symptom Control →

* Some prefer chemotherapy first for life threatening disease

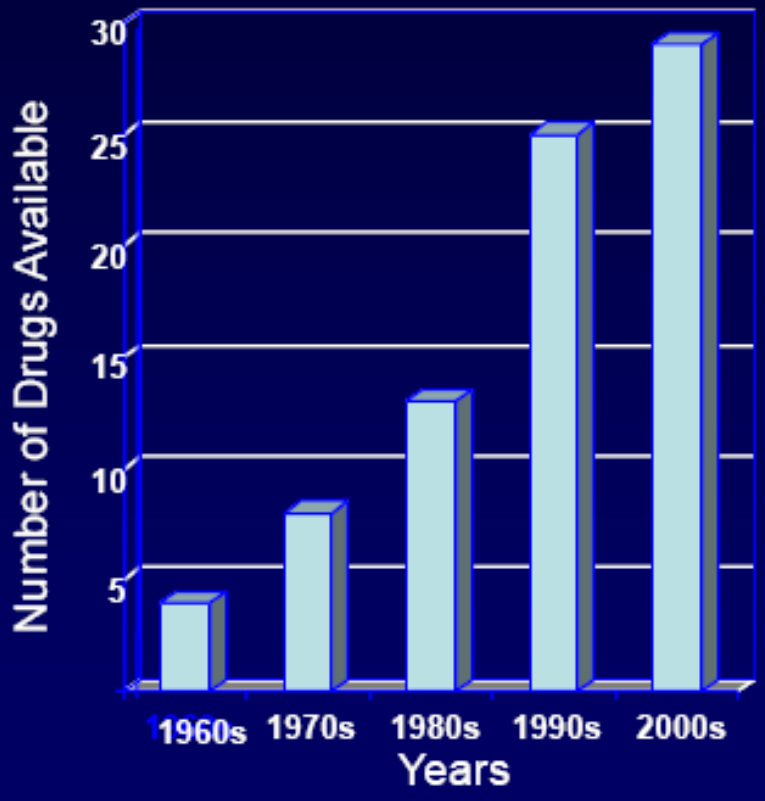
# Endocrine options in MBC

- **Premenopausal**
  - Ovarian Ablation
  - Tamoxifen
  - ?Ovarian Ablation and AI
- **Postmenopausal**
  - Aromatase Inhibitors
  - Tamoxifen
  - Progestogens
  - Faslodex

# Results of Hormone Treatment

- 60% response (if ER+)
- Average duration 9 to 12 months
- May respond to subsequent hormones

# Growing Number of Therapies




- 1950s: Cyclophosphamide, methotrexate
- 1960s: 5-fluorouracil
- 1970s: Doxorubicin, tamoxifen
- 1980s: Mitoxantrone, megestrol acetate, goserelin, leuprolide
- 1990s: Paclitaxel, docetaxel, vinorelbine, trastuzumab, capecitabine, gemcitabine, epirubicin, toremifene, anastrozole, letrozole, exemestane
- 2000s: *nab*-paclitaxel, lapatinib, bevacizumab, ixabepilone, eribulin. denosumab

U.S. Food & Drug Administration, 2008.

# Systemic Management of Breast Cancer

**Chemotherapy**

- CMF
- Adriamycin
- Taxanes
- Vinorelbine
- Capecitabine
- Combination chemotherapy
- Herceptin

# Results of Chemotherapy

50 - 60 % response

Average duration 9 to 12 months

Responses tend to get shorter

# Limitations of Chemotherapy

- No drug clearly superior
- Combinations not superior to sequential use (and more toxic)
- Higher doses not better
- Lower doses not “kinder”

# Metastatic Breast Cancer

**Endocrine Therapy**

**(ER and/or PR + only)**

Single drug

Sequential therapy

Continue to progression

**Chemotherapy**

**(ER/PR- or failed hormones)**

Single or combination

Sequential therapy

Duration limited by toxicity

**Achievements**

Control in 30-60%

Average duration 9- 12 mths

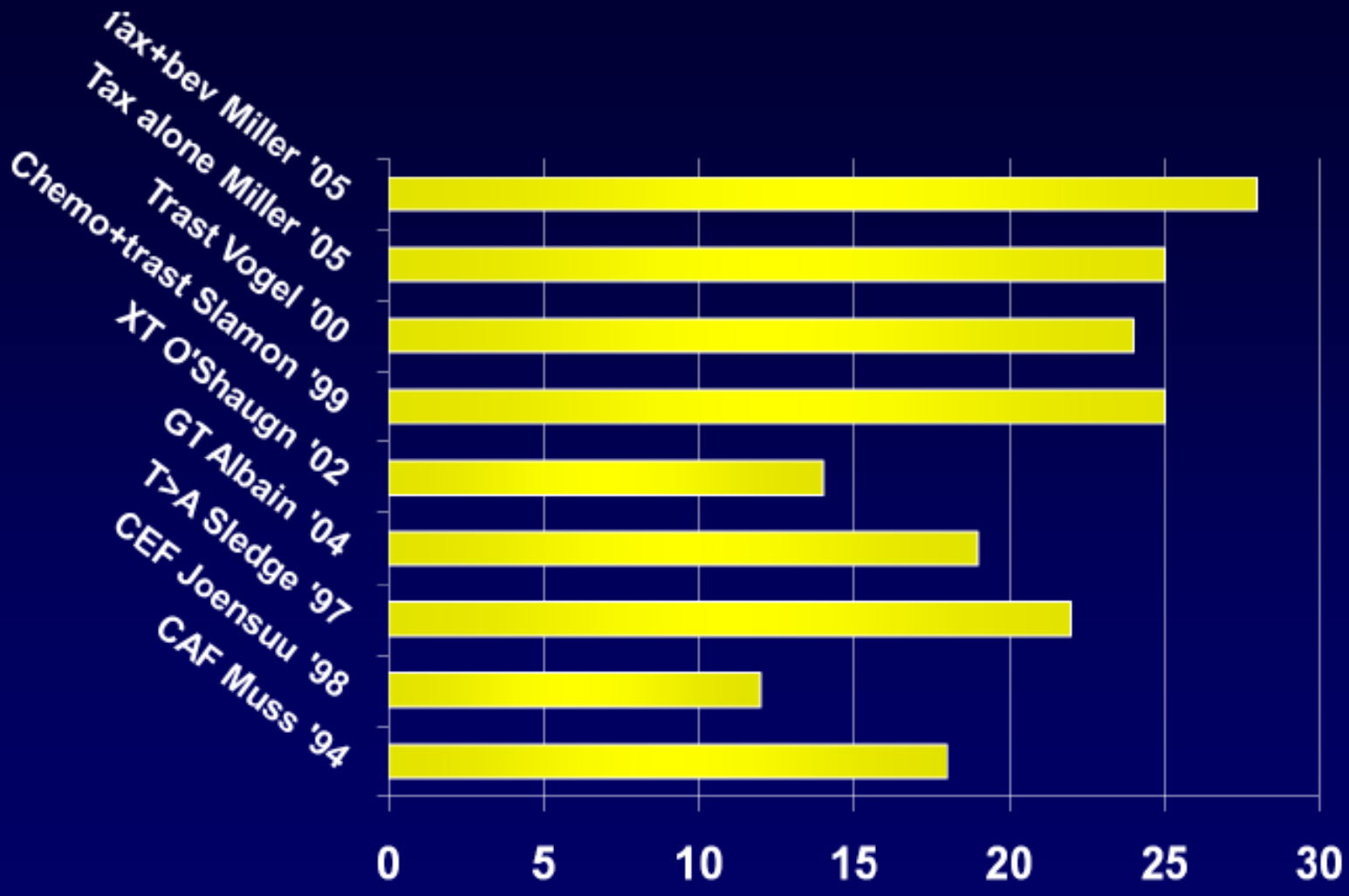
Wide variation

Control in 30-60%

Average duration 9-12 mths

Wide variation

# Overall Survival - Months




Courtesy Hy Muss

# Has anything changed?

## Metastatic Disease 2010

- **All therapy is palliative**
- Survival has increased
- Survival depends mostly on tempo
  - Biology of tumor key
- Goal of treatment
  - Control of disease and symptoms
  - Maximizing quality of life

    You can't improve on being asymptomatic

# Changing Perspectives

**Why?**

Numerous new medications
but limited improvements in survival
Enormous effort for limited benefit to date

**What has changed?**

Improved understanding of cancer biology
Greater recognition of therapeutic targets
Need to speed up drug development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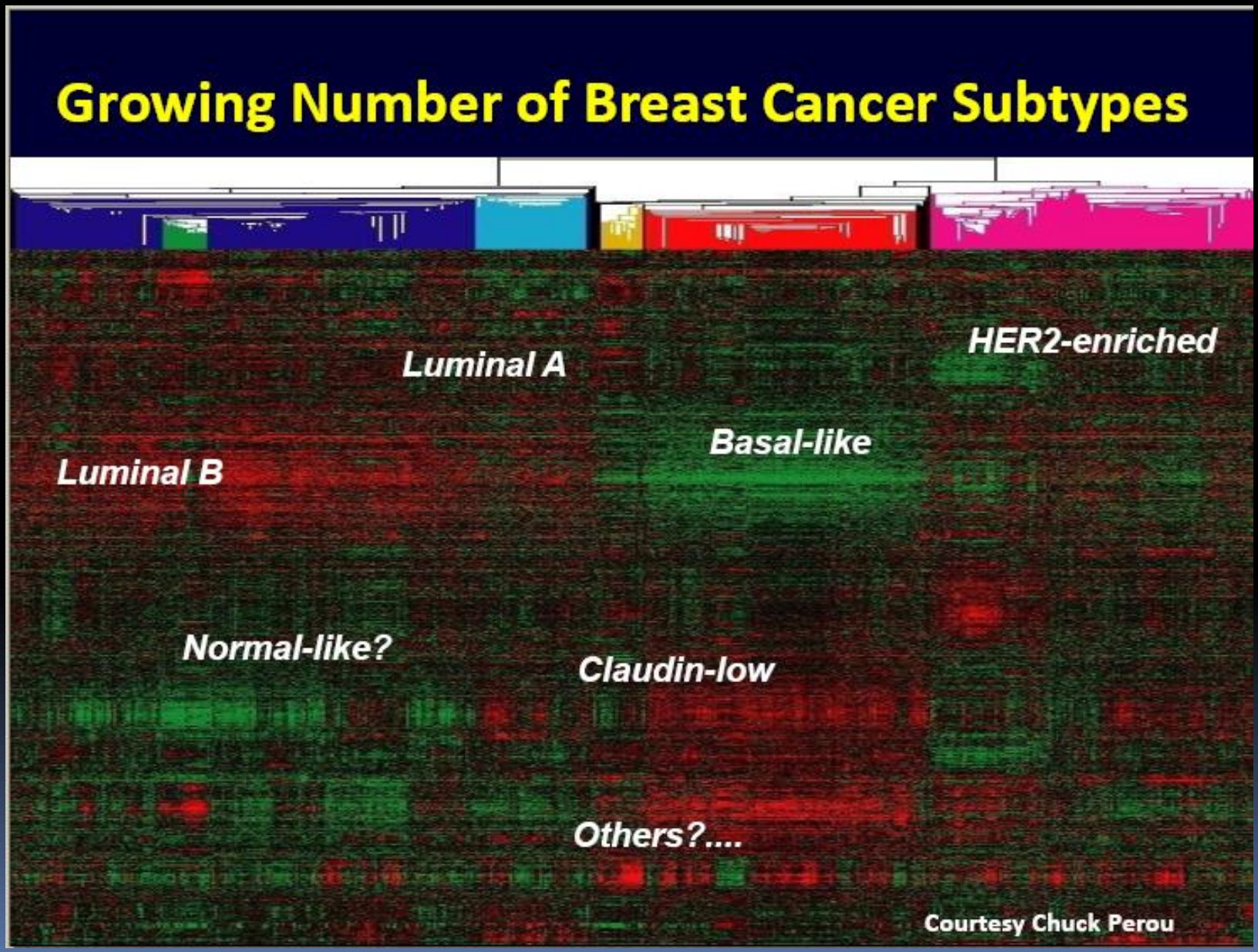
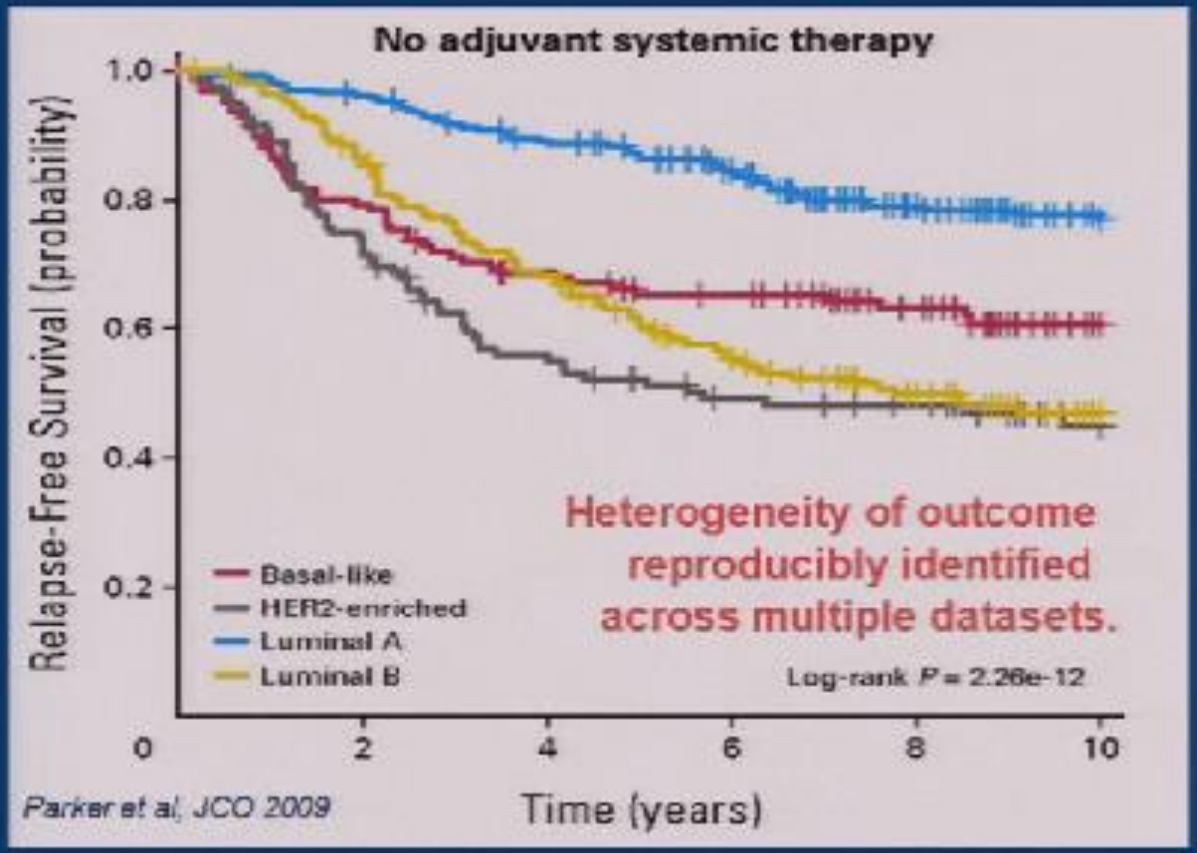
# Biology is Key

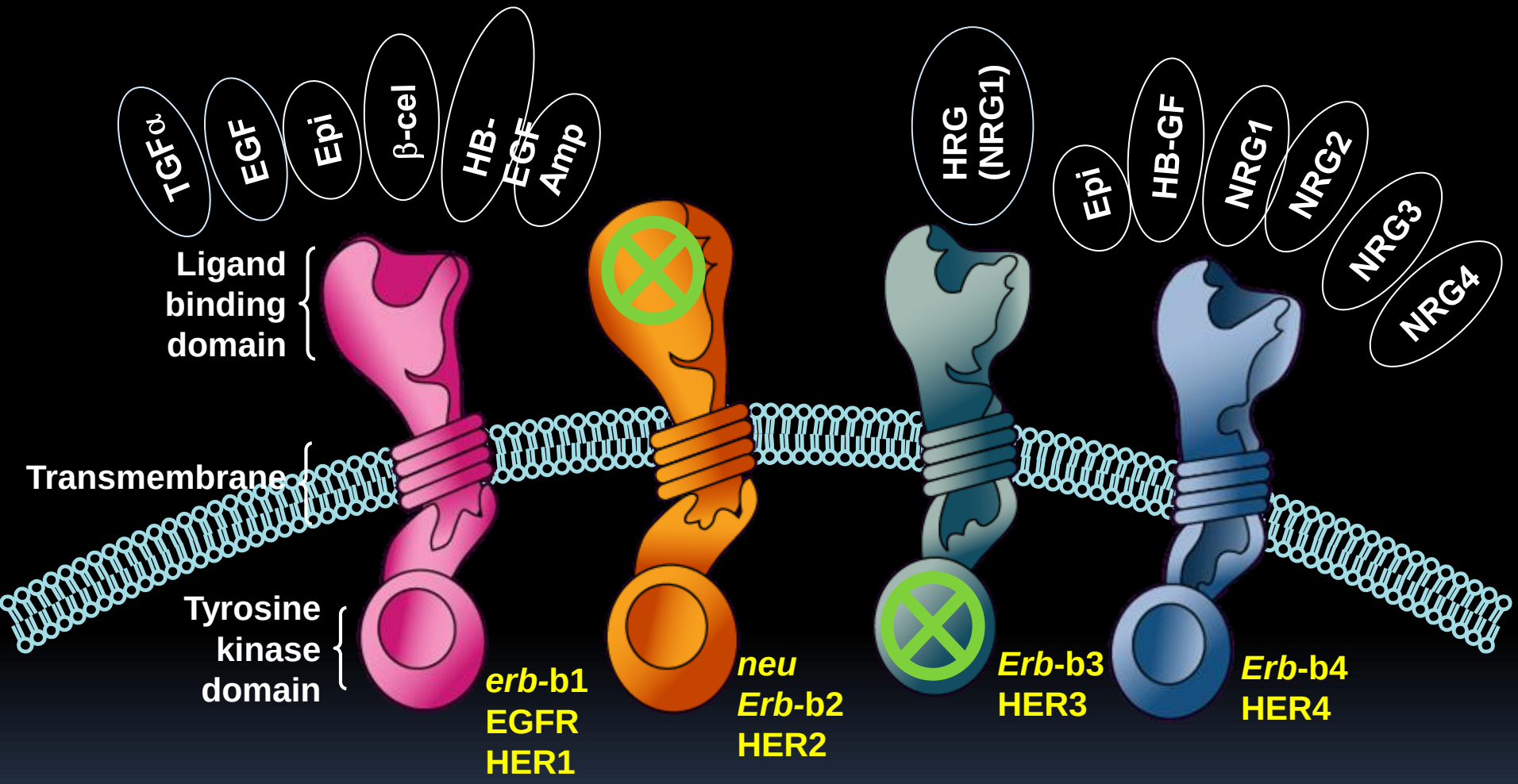


# Breast Cancer Subtypes and Prognosis



# The Herceptin Story

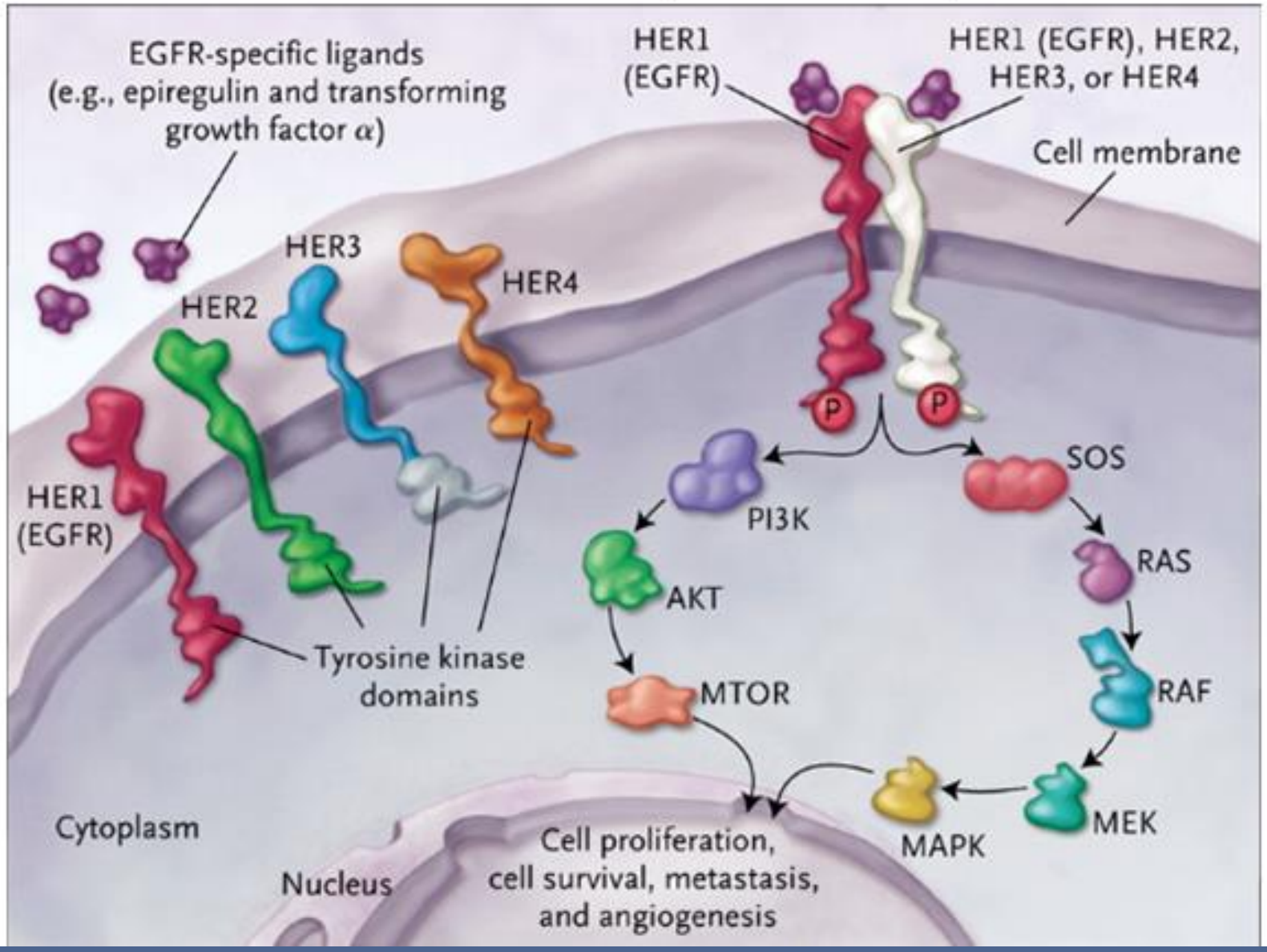
# The EGFR/HER Family



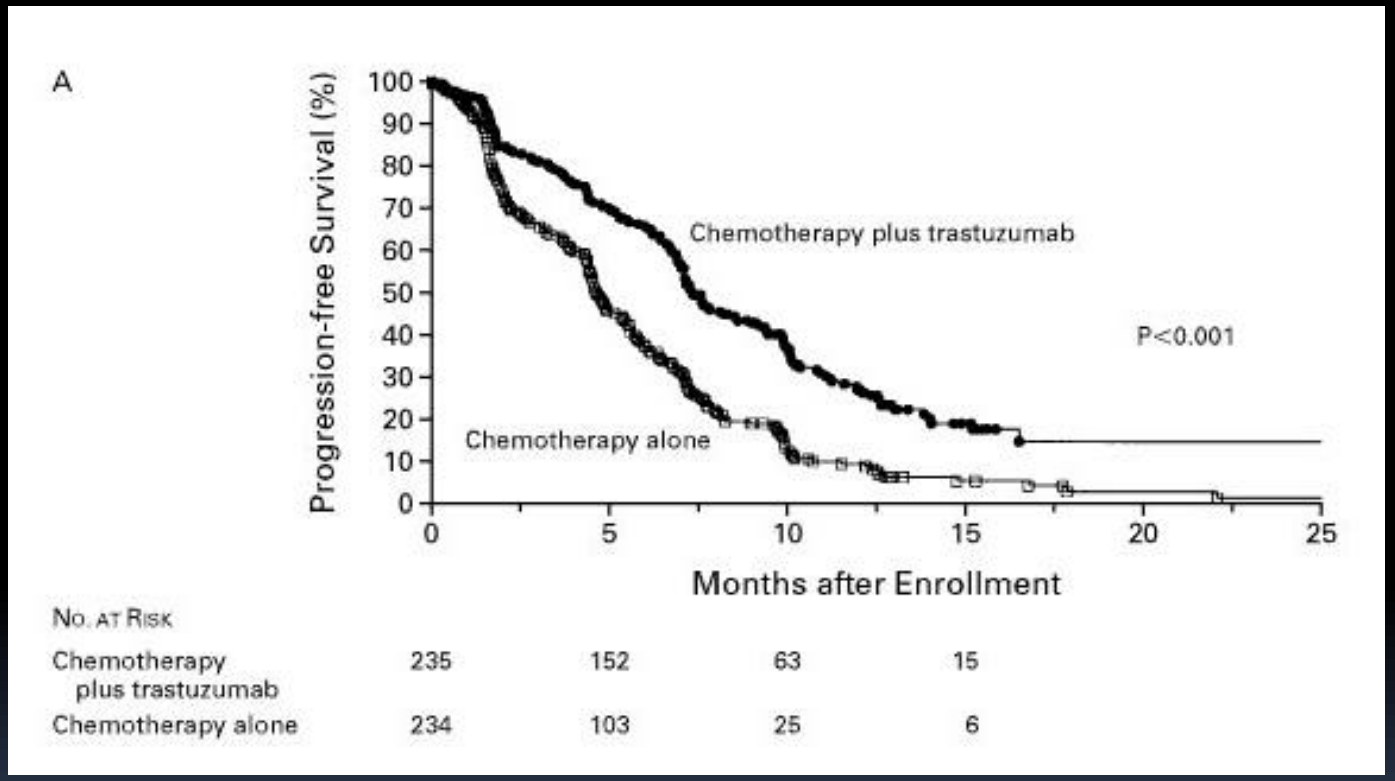


Mendelsohn and Baselga. *Oncogene.* 2000;19:6550.
Olayioye et al. *EMBO J.* 2000;19:3159.
Prigent and Lemoine. *Prog Growth Factor Res.* 1992;4:1.
Harari and Yarden. *Oncogene*. 2000;19:6102.
Earp et al. *Breast Cancer Res Treat.* 1995;35:115.

# The HER Receptor Family



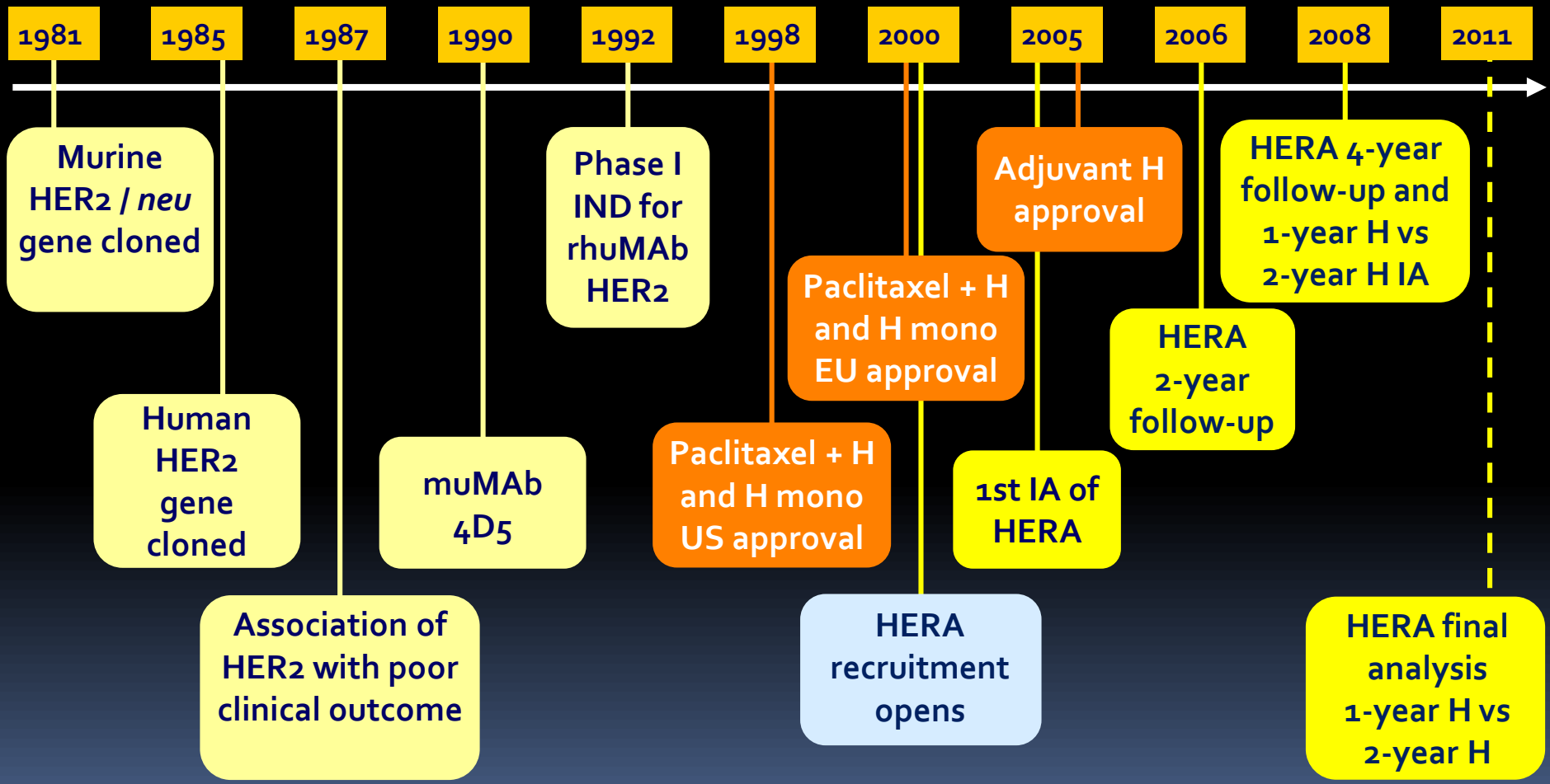
# Progression-free Survival in patients on Chemotherapy plus Trastuzumab or Chemotherapy Alone (Panel A) and Whether Anthracycline and Cyclophosphamide (Panel B) or Paclitaxel (Panel C)




Slamon D et al.
N Engl J Med 2001;344:783-792

The NEW ENGLAND JOURNAL of MEDICINE

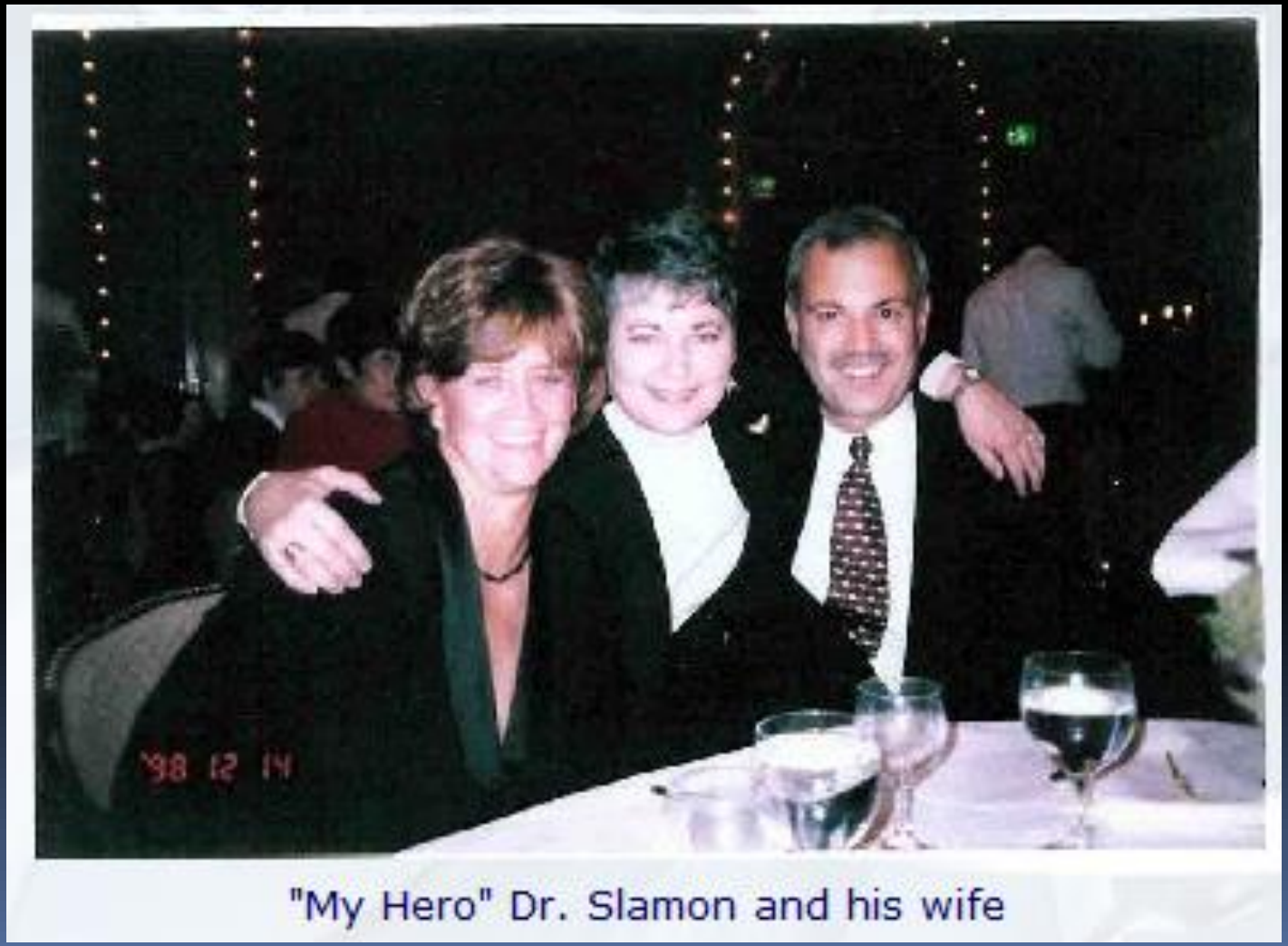
# The fascinating history of Herceptin




HER2, human epidermal growth factor receptor 2; H, Herceptin; IA, interim analysis

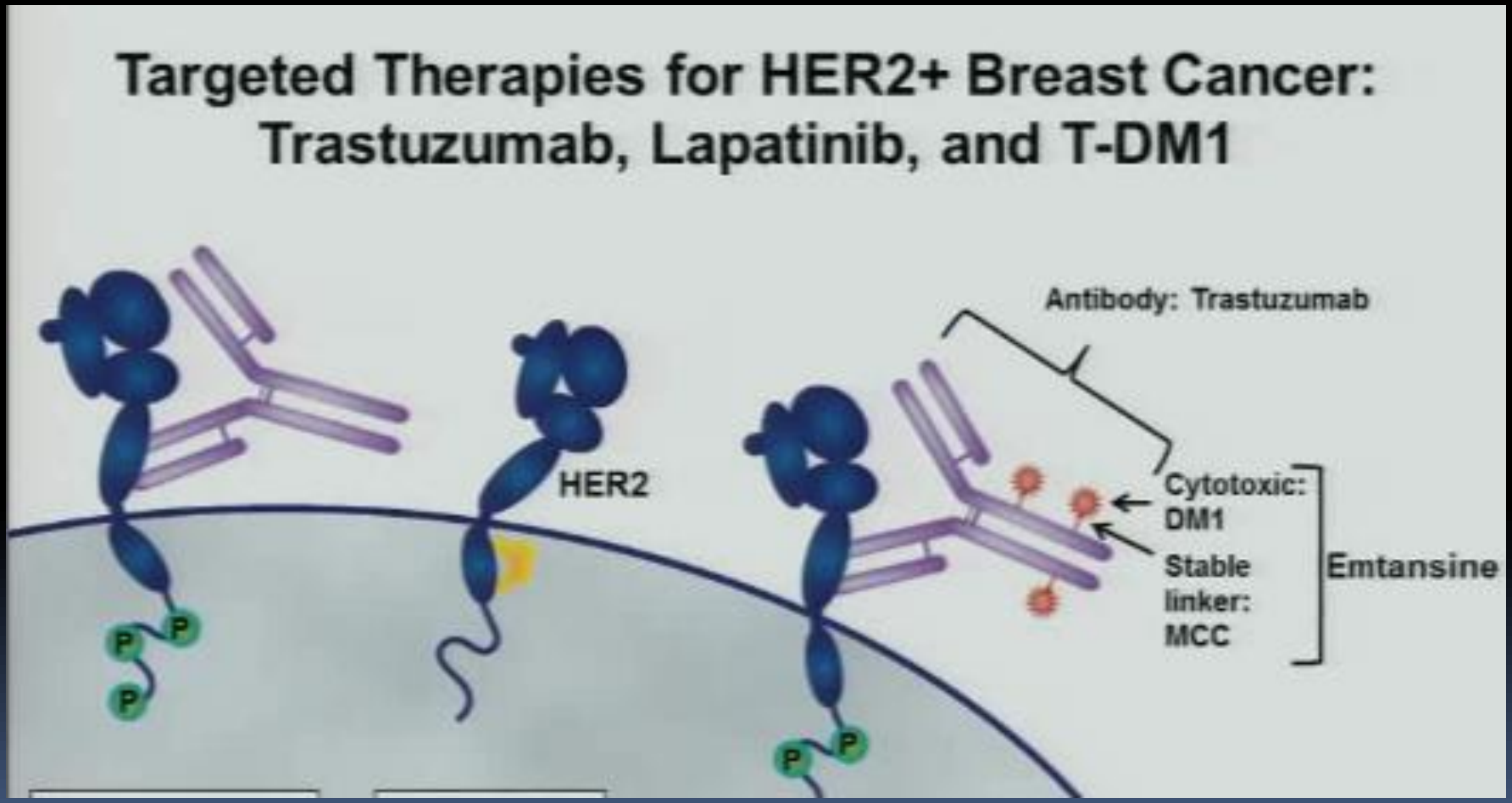
# Barbara Bradfield

The first patient with MBC treated with Herceptin – 10 years disease free

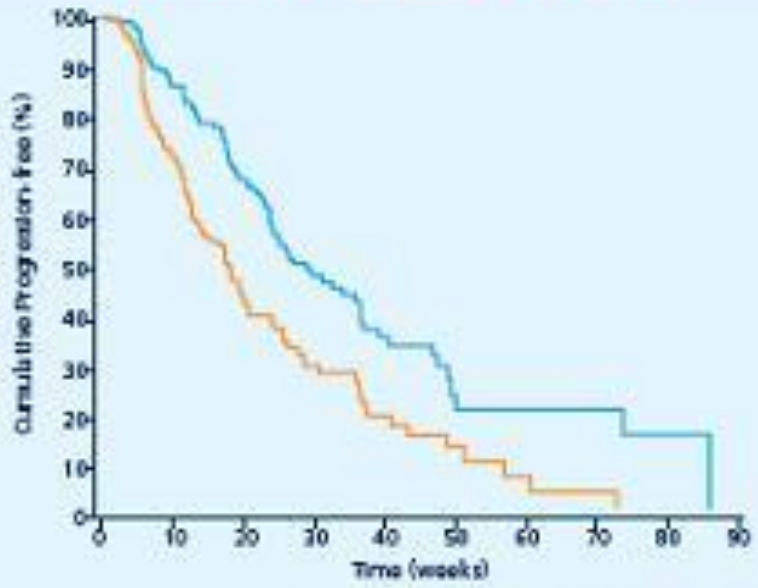



"My Hero" Dr. Slamon and his wife

# Lapatinib

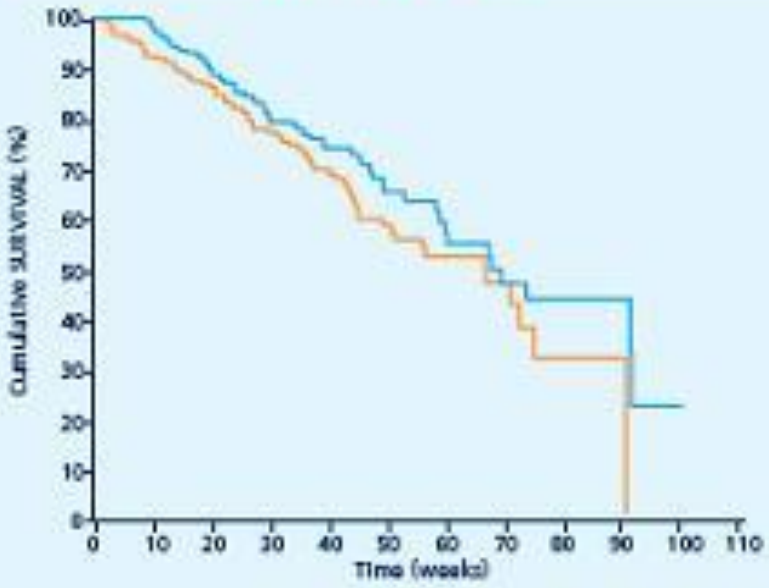

Targeted Therapies for HER2+ Breast Cancer:
Trastuzumab, Lapatinib, and T-DM1
Antibody: Trastuzumab
HER2
Cytotoxic:
DM1
Stable
linker:
MCC
Emtansine
P
P
P
P
P

## TIME TO PROGRESSION (ITT) By Independent Review



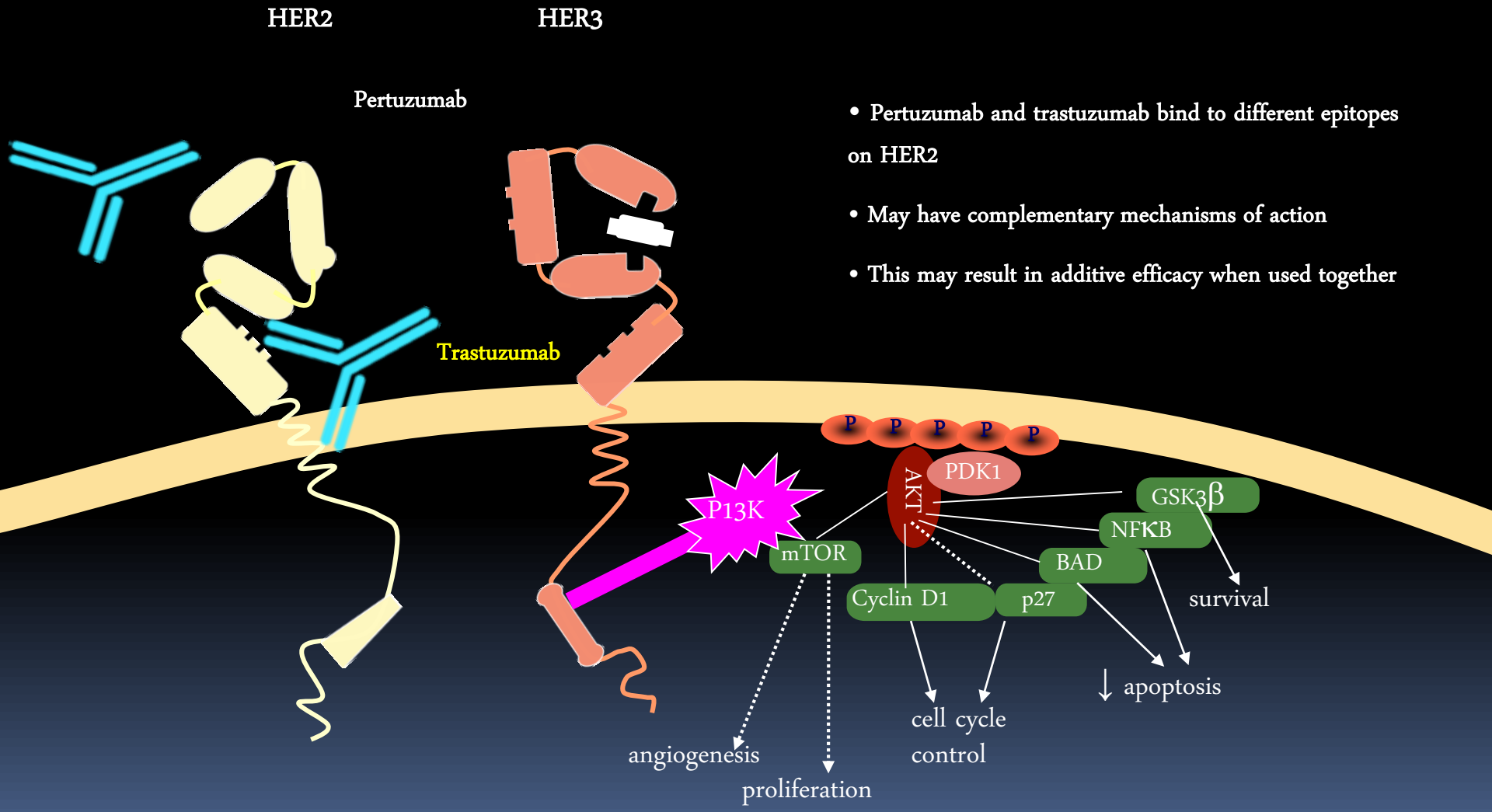

| | LAPATINIB + CAPECITABINE | [illegible] |
|---|---|---|
| NO. OF PATIENTS | 198 | 201 |
| PROGRESSED OR DIED | 82 (41%) | 102 (51%) |
| MEDIAN TTP, MO | 6.2 | 4.3 |
| HAZARD RATIO (95% CI) | 0.57 (0.43, 0.77) | |
| p-VALUE (LOG-RANK, 1-SIDED) | 0.00013 | |

## OVERALL SURVIVAL




| | LAPATINIB + CAPECITABINE | [illegible] |
|---|---|---|
| NO. OF PATIENTS | 198 | 201 |
| MEDIAN OVERALL SURVIVAL | 15.6 | 15.3 |
| HAZARD RATIO (95% CI) | 0.78 (0.55, 1.12) | |
| p-VALUE (LOG-RANK, 1-SIDED) | 0.177 | |

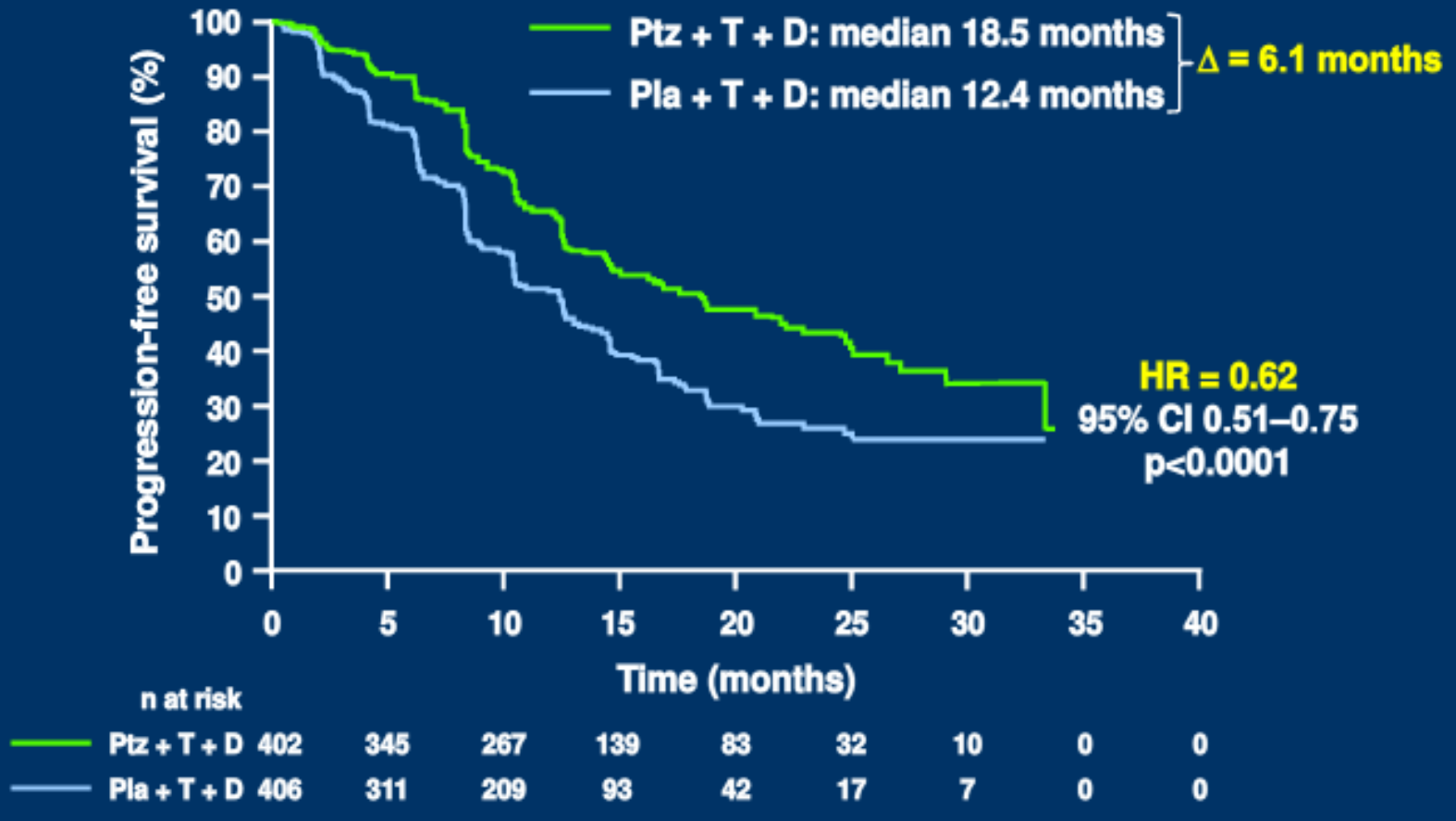
# Pertuzumab and trastuzumab: potential for additive efficacy




- Pertuzumab and trastuzumab bind to different epitopes on HER2
- May have complementary mechanisms of action
- This may result in additive efficacy when used together

# Primary endpoint: Independently assessed PFS

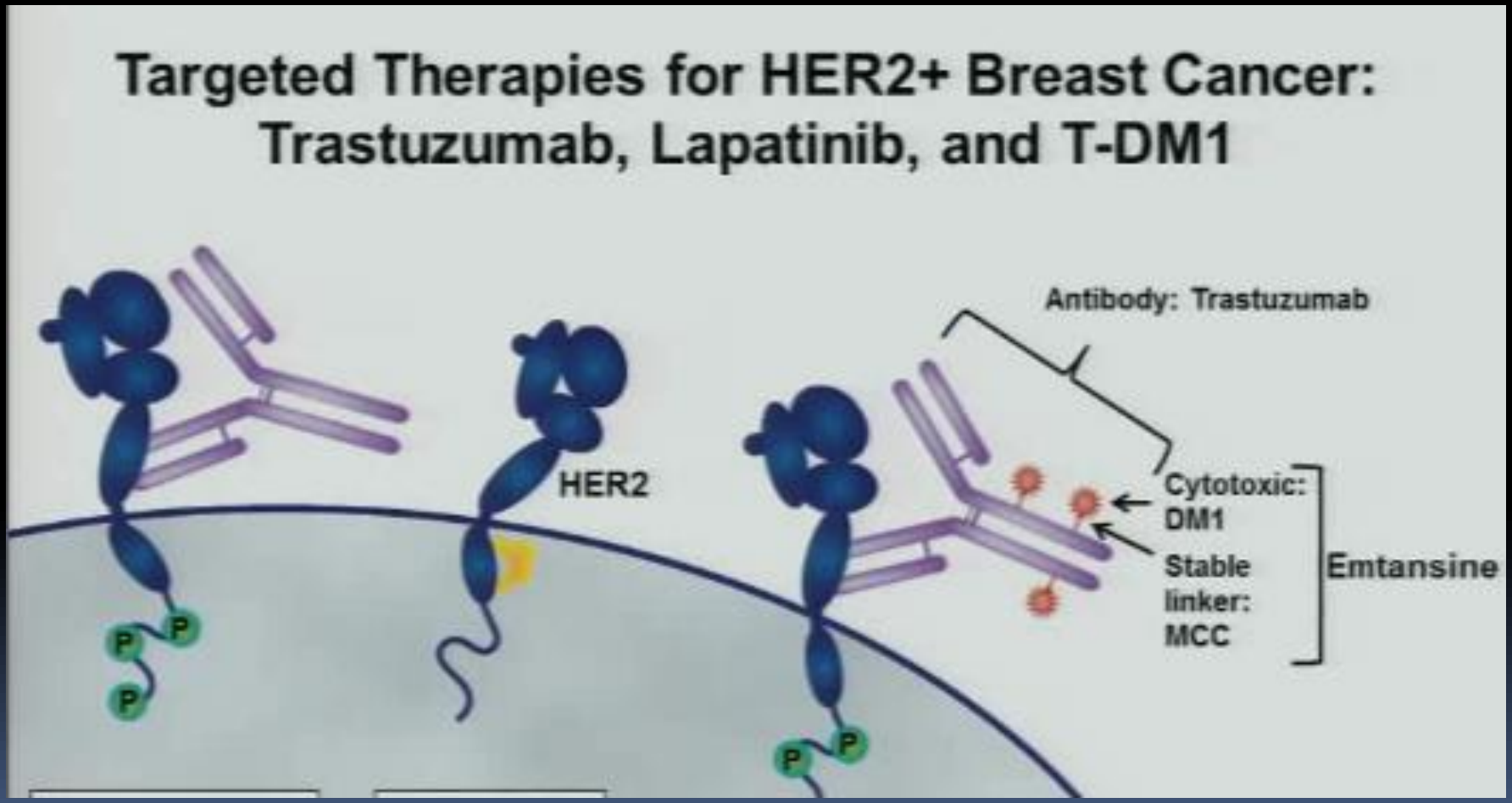
## *n = 433 PFS events*



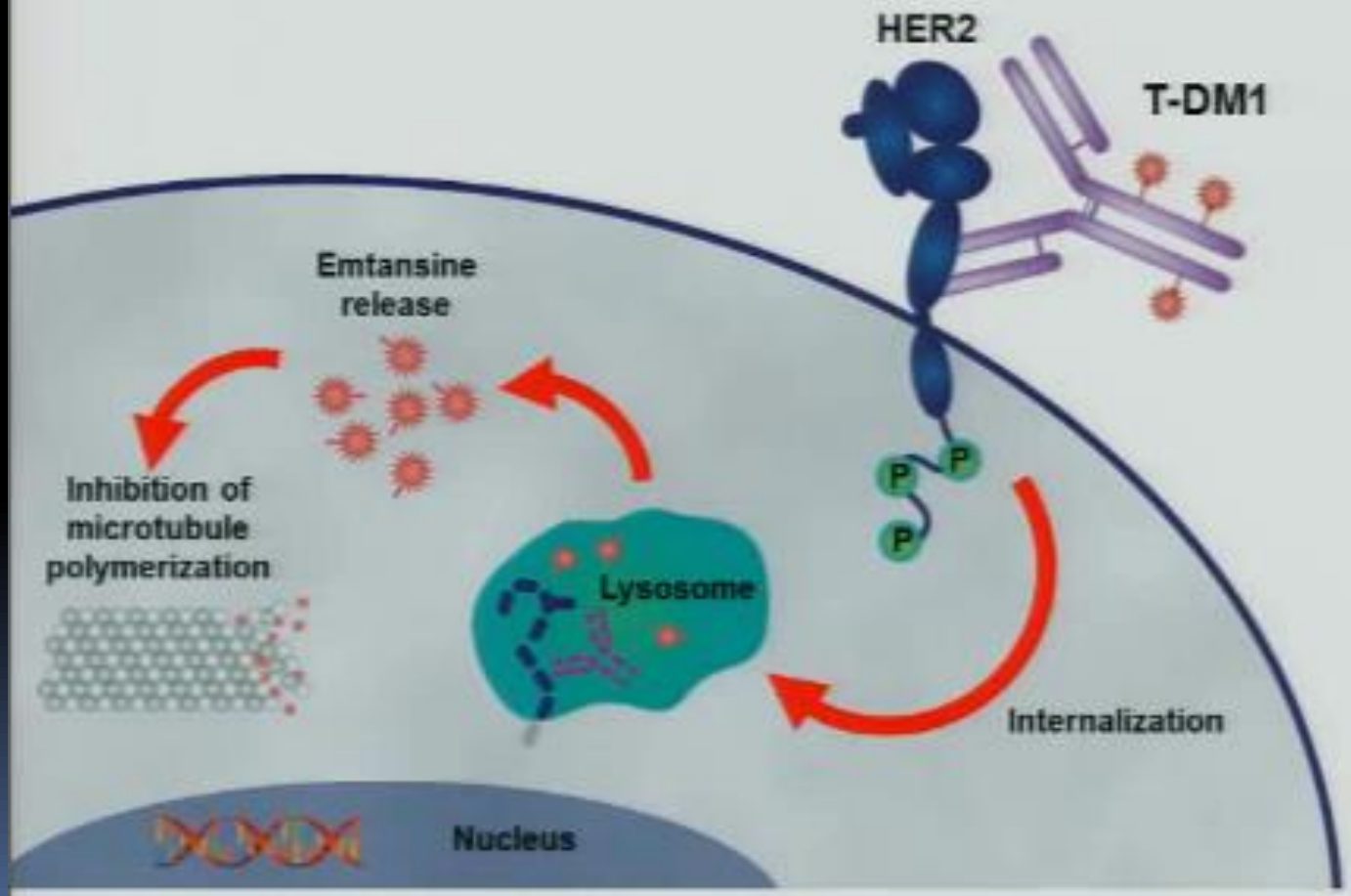

Stratified by prior treatment status and region

D, docetaxel; PFS, progression-free survival; Pla, placebo; Ptz, pertuzumab; T, trastuzumab

# Trastuzumab-Emtansine (T-DM1)



# T-DM1: Mechanism of Action




Adapted from LoRusso PM, et al. *Clin Cancer Res* 2011.

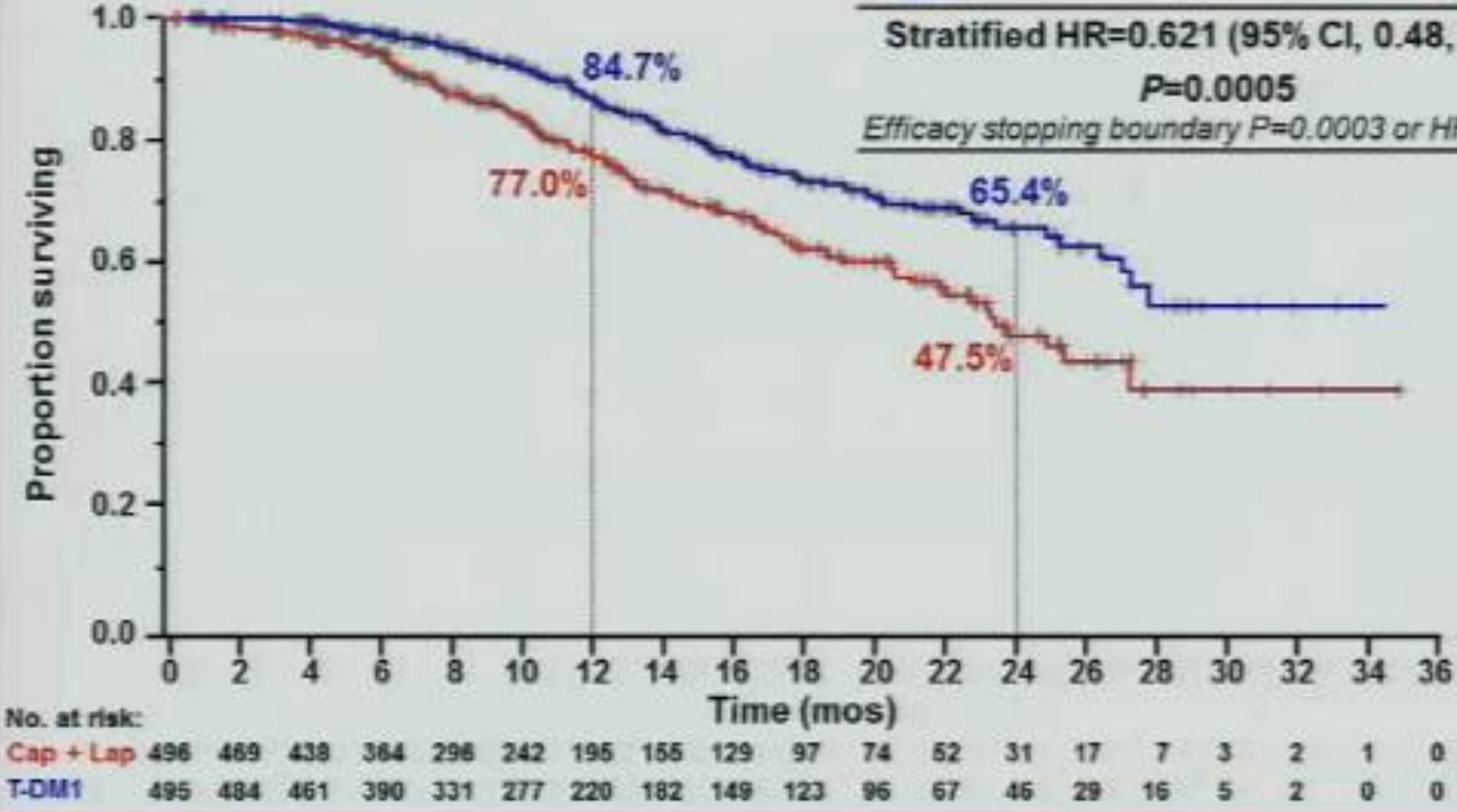
# Overall Survival: Interim Analysis

| | Median (mos) | No. events |
|---|---|---|
| Cap + Lap | 23.3 | 129 |
| T-DM1 | NR | 94 |

Stratified HR=0.621 (95% CI, 0.48, 0.81)

*P*=0.0005

*Efficacy stopping boundary P=0.0003 or HR=0.617*

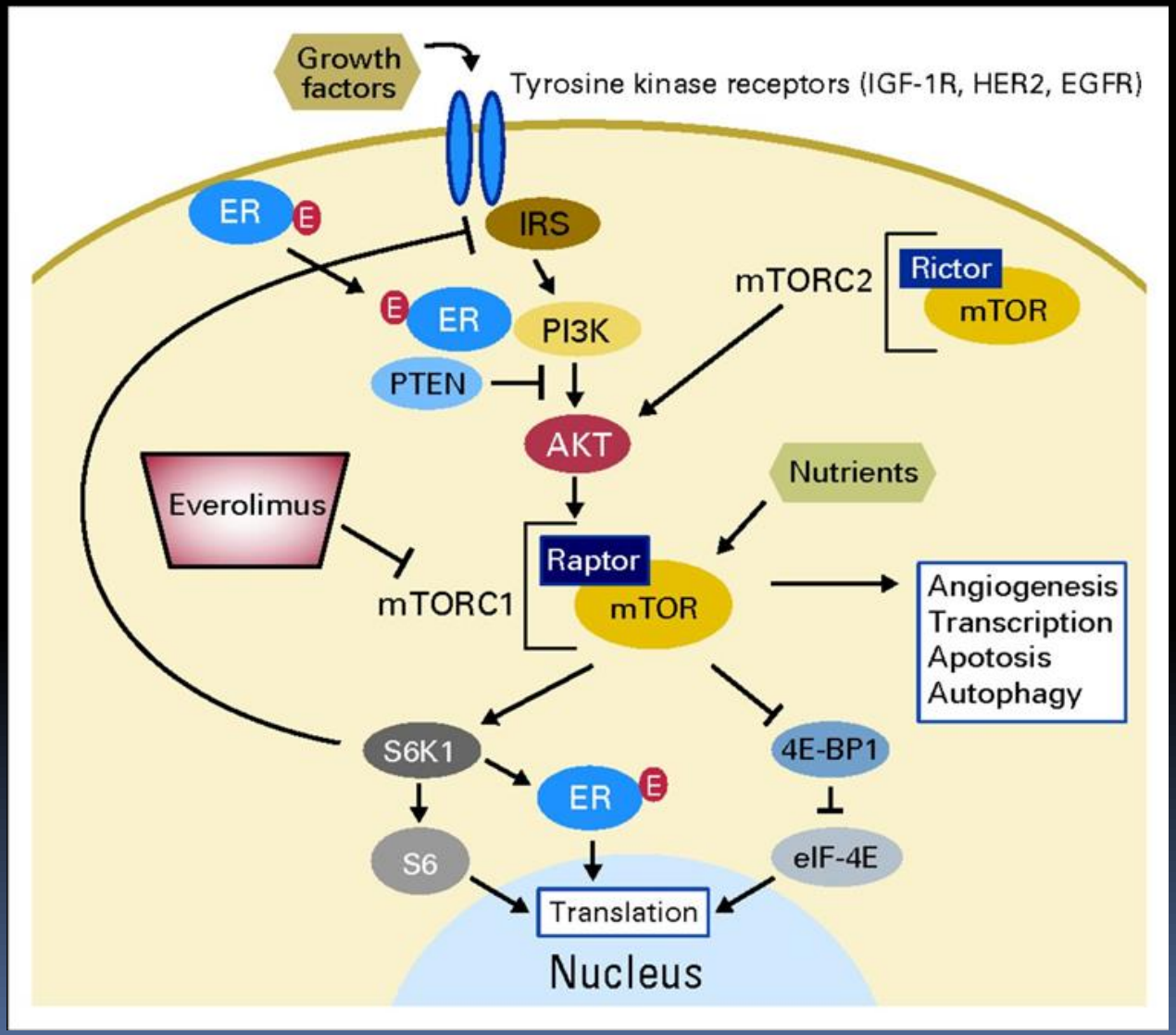



No. at risk:

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cap + Lap | 496 | 469 | 438 | 384 | 296 | 242 | 195 | 155 | 129 | 97 | 74 | 52 | 31 | 17 | 7 | 3 | 2 | 1 | 0 |
| T-DM1 | 495 | 484 | 461 | 390 | 331 | 277 | 220 | 182 | 149 | 123 | 96 | 67 | 46 | 29 | 16 | 5 | 2 | 0 | 0 |

Unstratified HR=0.63 (*P*=0.0005).
NR=not reached.

# Reversing Endocrine Resistance



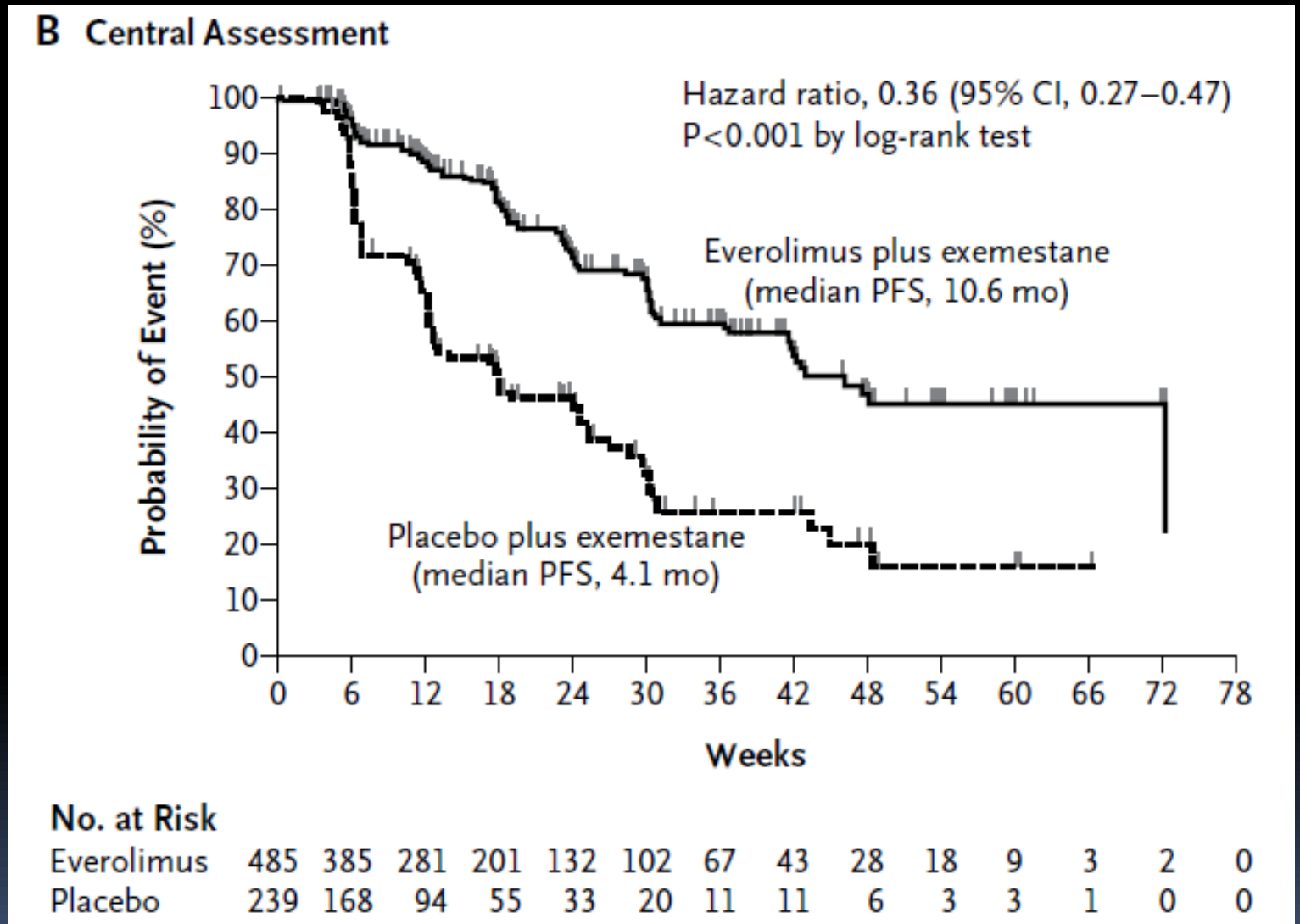
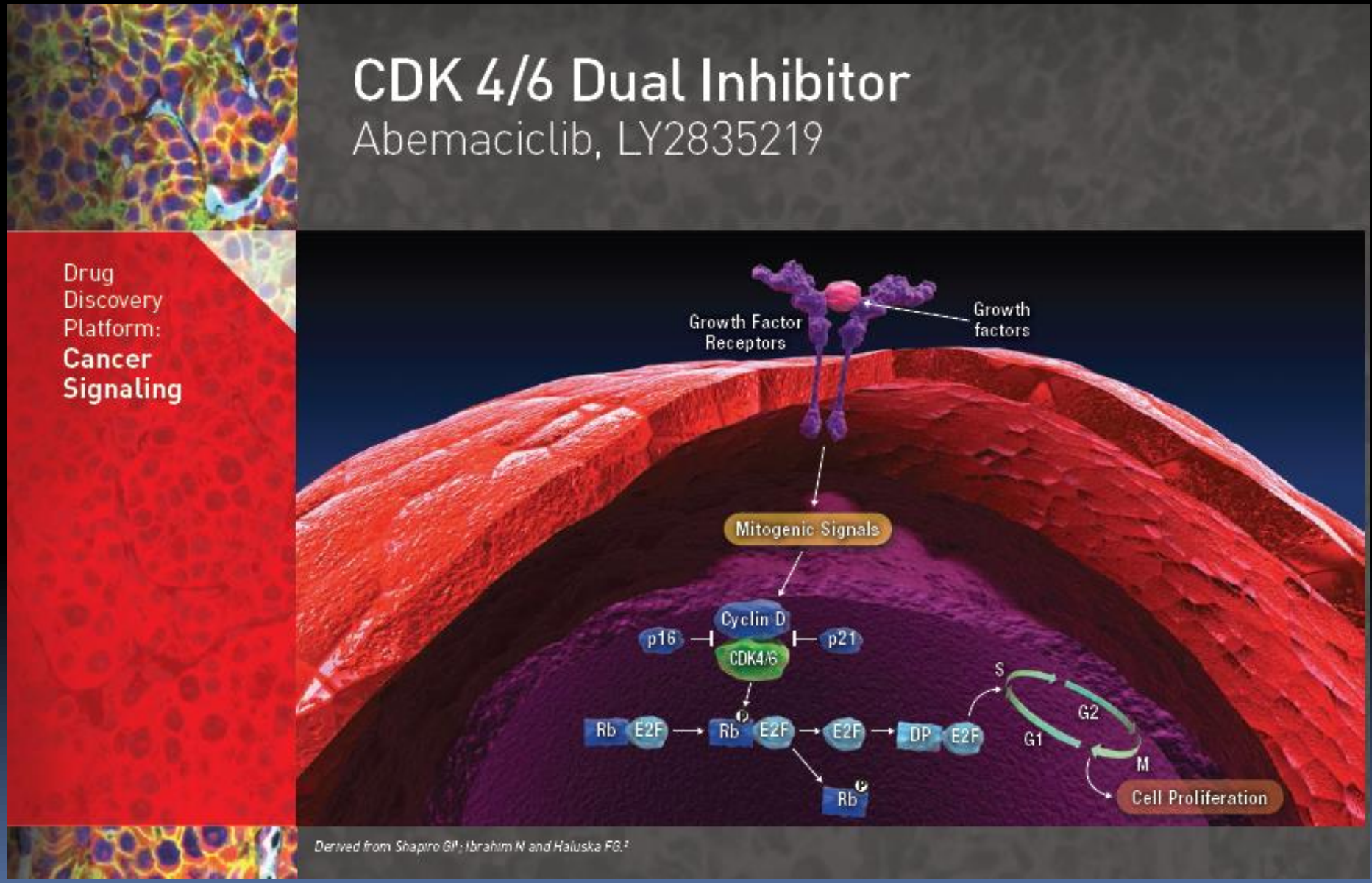


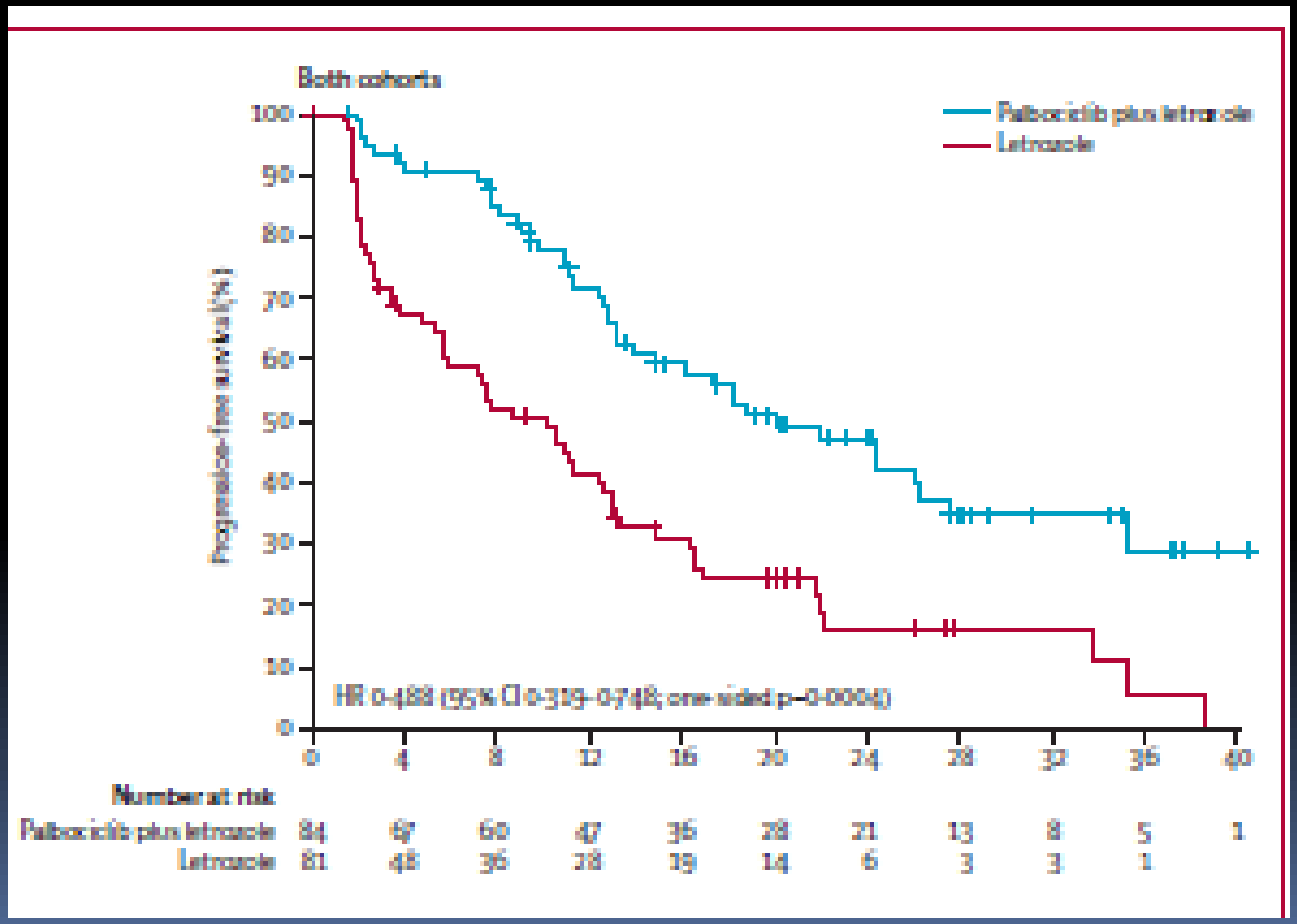

**Figure 1.** Kaplan–Meier Plot of Progression-free Survival.

# Reversing Endocrine Resistance



# Paloma 01 trial

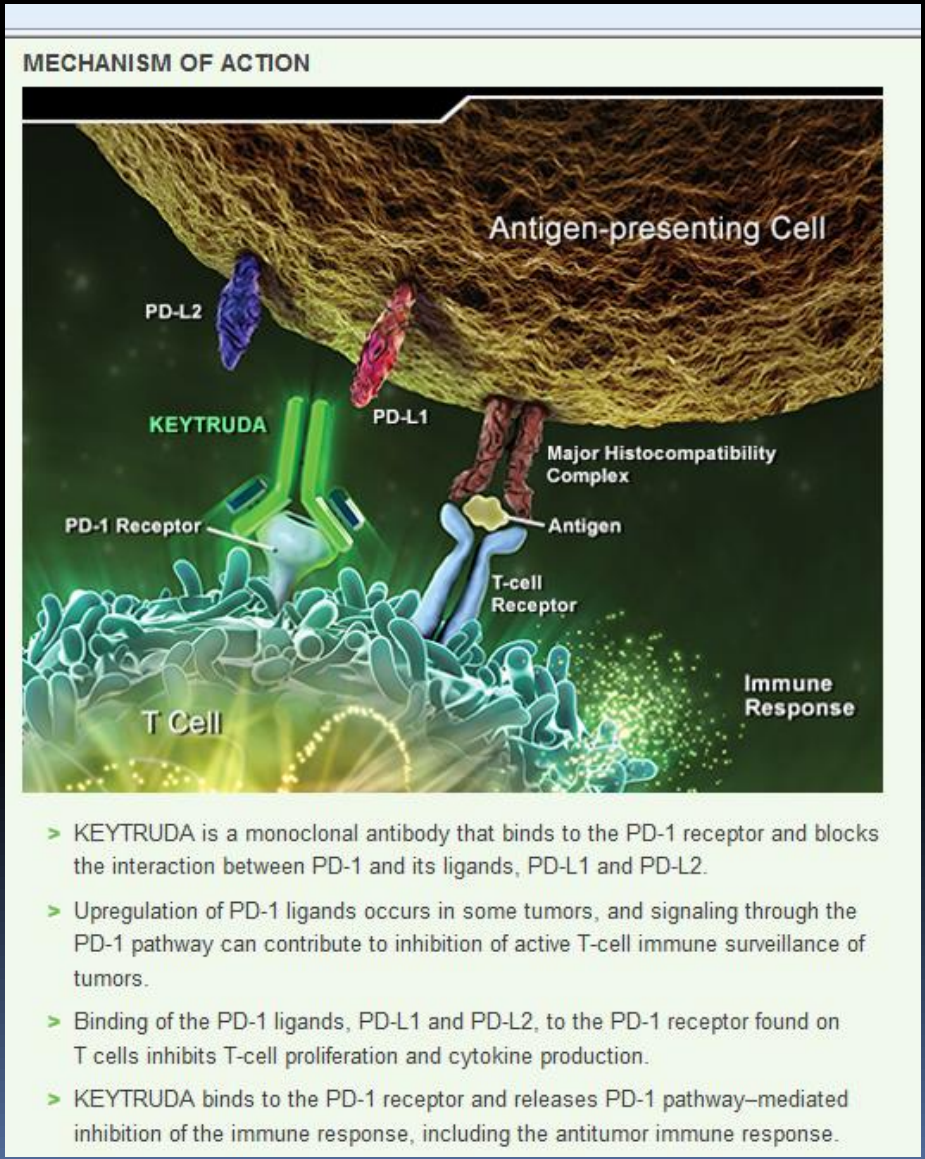
## Palbociclib + letrozole vs Letrozole



# Involving the Immune System

Disease shrinkage in 20% of triple negative breast cancer

Keynote 012 trial SABCS 2024



# We are moving forward……

but never as quickly as we want or patients need

# Systemic Management of Breast Cancer

**Additional Measures**

Radiation therapy

Orthopaedic procedures

Bisphosphonates

Pleurocentesis

Abdominocentesis etc

# And all the while……**LIVE**

SWEET LOUISE | POSITIVE LIVES WITH BREAST CANCER

**Thank you very much**