

# Metastatic breast cancer update

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# Today's agenda

- Discuss metastatic breast cancer
  - definition
- Translation of clinical trial results into standard care
  - What does it mean?
- New strategies and therapies
  - Exciting therapies in trials

# What is metastatic breast cancer?

- Breast cancer that has spread outside the lymph nodes in the neck
- Frequent question: If it spreads to the lungs does that mean I have lung cancer?
  - No, it is breast cancer.
  - Metastatic breast cancer is also called advanced breast cancer or stage 4 breast cancer

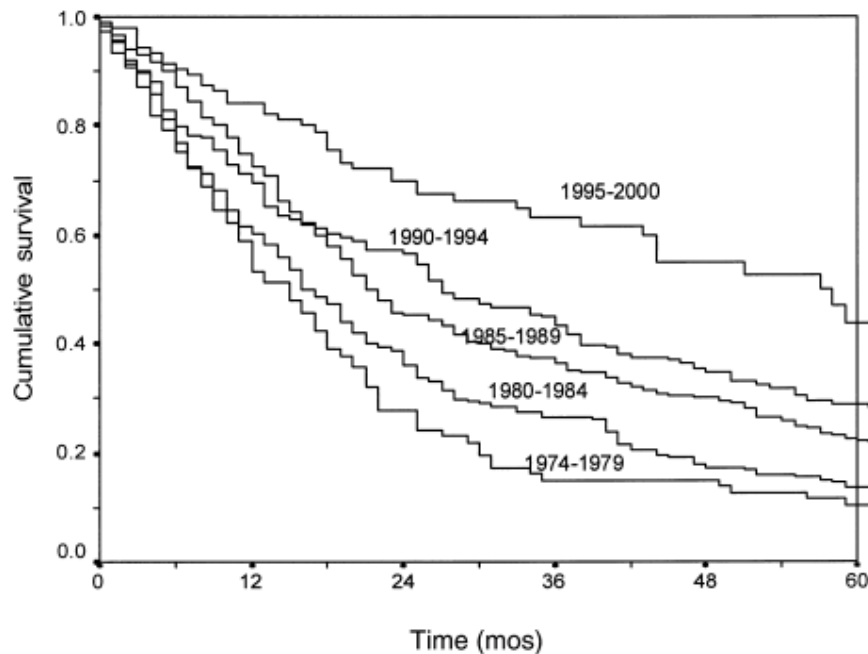
# Approach to stage 4 breast cancer

- Balancing needs to shrink tumor versus side effects of therapy.
- Studies have shown that giving more therapy to “eradicate” any visible tumor did not result in women with breast cancer living longer than those who got less intense therapy and had residual tumor.

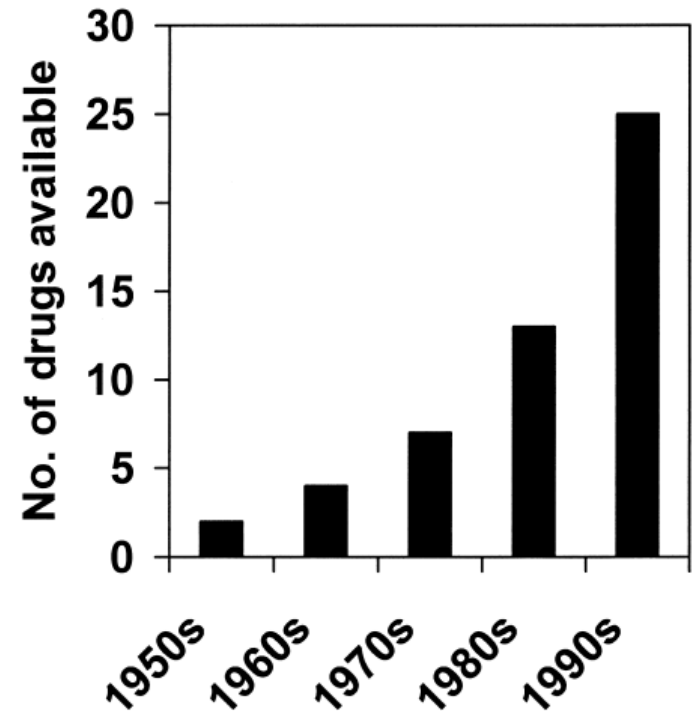
It is still important to expand the  
number of options.....

# Stage 4 Breast Cancer

- Relapse rate over time



Year of recurrence associated with a trend towards improved overall survival



- 1950s: cyclophosphamide, methotrexate
- 1960s: 5- fluorouracil, vinblastine, vincristine, fluoxymesterone
- 1970s: doxorubicin, mitomycin-C, tamoxifen
- 1980s: mitoxantrone, etoposide, aminoglutethimide, megestrol acetate, goserelin, leuprolide
- 1990s: paclitaxel, docetaxel, vinorelbine, gemcitabine, trastuzumab, capecitabine, epirubicin, pamidronate, toremifene, anastrozole, letrozole, exemestane

**Result: the more options the  
better**

How do we maximize this?

# 2013: Trends in breast cancer therapy

Metastatic Breast Cancer  
Moving towards targeted  
therapy

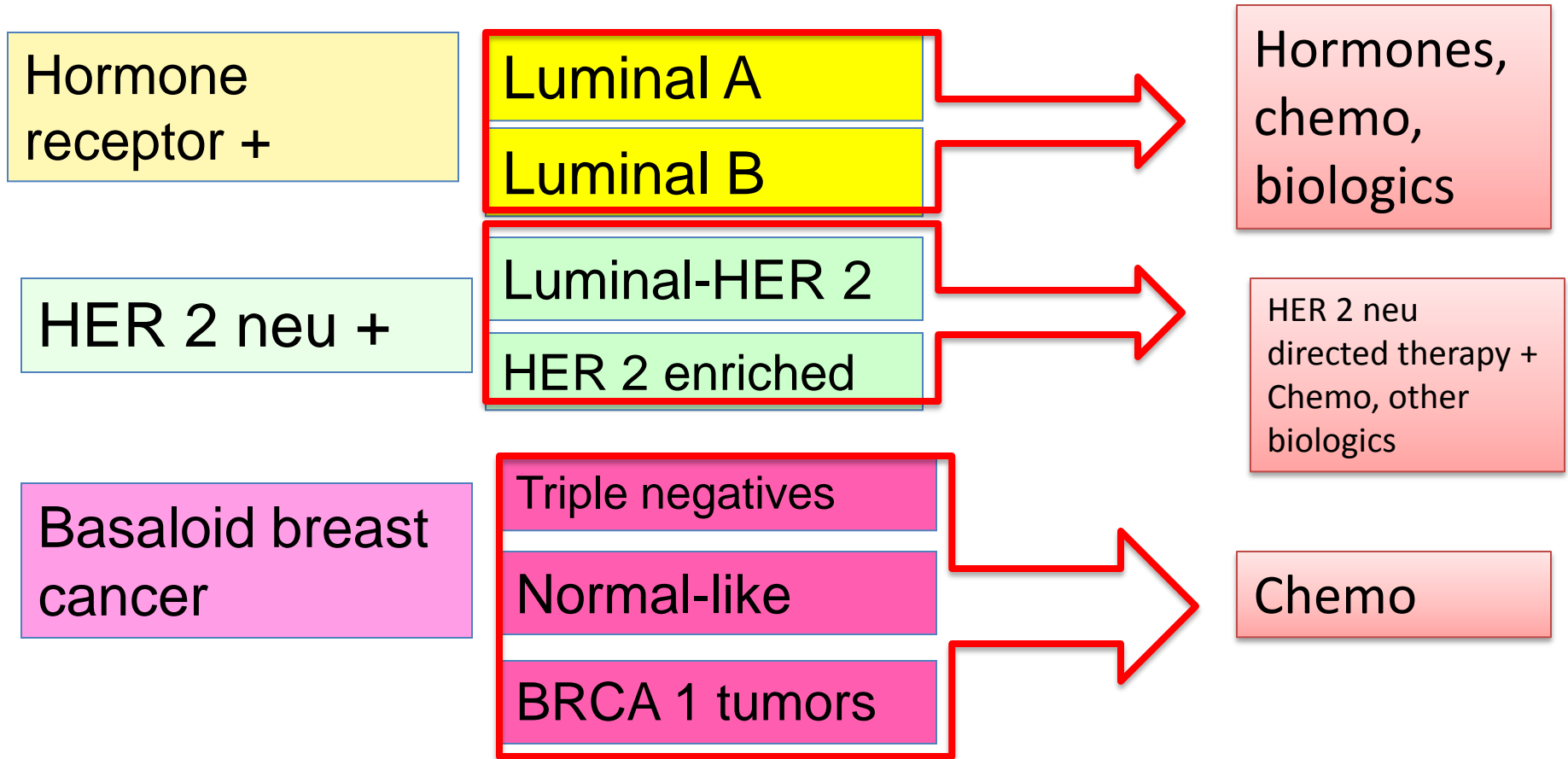


Molecular subtypes  
playing a bigger role





# 2012: Approach to pts with metastatic breast cancer



# Treatment options Stage 4 breast cancer

Standard treatments

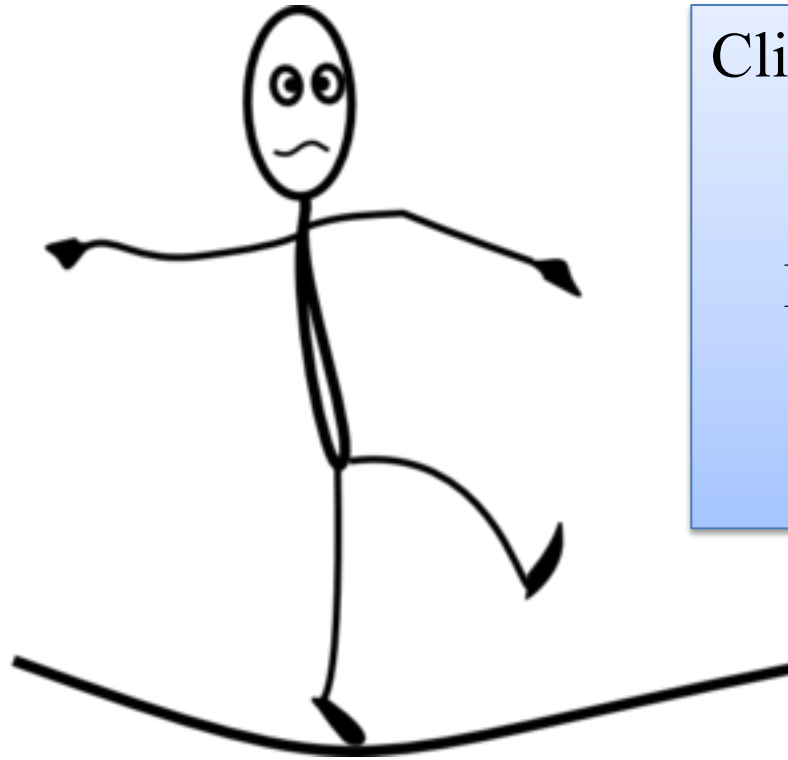
1. Chemotherapy
2. Hormonal therapy
3. Radiation therapy
4. Biologic therapy

Clinical Trials

1. Phase I trials
2. Phase II trials
3. Phase III trials

# Picking a treatment

## So many choices....



Clinical symptoms  
Side effects  
QOL issues  
Practical issues  
Prior therapies

Efficacy =>< Toxicity Equation

# Most recent NCCN list

## CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER<sup>1</sup>

### Preferred Single Agents

#### *Anthracyclines*

- Doxorubicin
- Epirubicin
- Pegylated liposomal doxorubicin

#### *Taxanes*

- Paclitaxel
- Docetaxel
- Albumin-bound paclitaxel

#### *Anti-metabolites*

- Capecitabine
- Gemcitabine

#### *Other microtubule inhibitors*

- Vinorelbine
- Eribulin

### Other Single Agents

- Cyclophosphamide
- Mitoxantrone
- Cisplatin
- Etoposide (po) (category 2B)
- Vinblastine
- Fluorouracil CI
- Ixabepilone

### Preferred Agents With Bevacizumab<sup>2</sup>

- Paclitaxel

### Preferred Chemotherapy Combinations

- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- AT (doxorubicin/docetaxel; doxorubicin/paclitaxel)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)

### Other Combinations

- Ixabepilone + capecitabine (category 2B)

### Preferred First-line Agents For HER2-positive Disease

- Pertuzumab + trastuzumab + docetaxel (category 1)
- Pertuzumab + trastuzumab + paclitaxel

### Other First-line Agents For HER2-positive Disease

#### *Trastuzumab with:*

- Paclitaxel ± carboplatin
- Docetaxel
- Vinorelbine
- Capecitabine

### Agents For Trastuzumab-exposed HER2-positive Disease

- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents

# Let's talk about HER 2 neu directed therapy

Many new drugs recently approved

# HER 2 neu based therapy

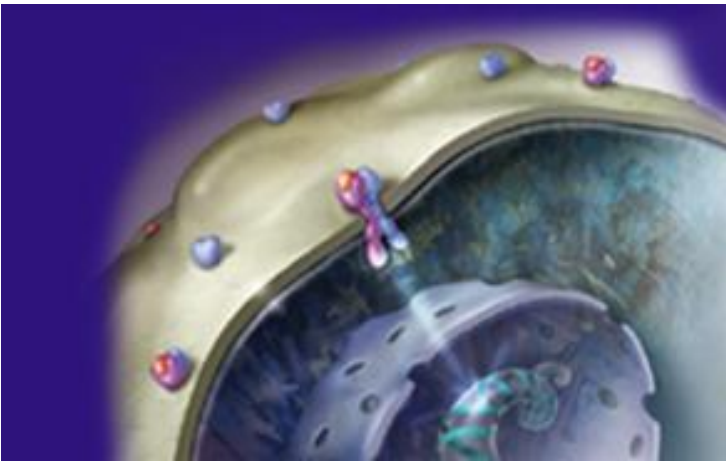
Trastuzumab

Lapatinib

Pertuzumab

TDM1

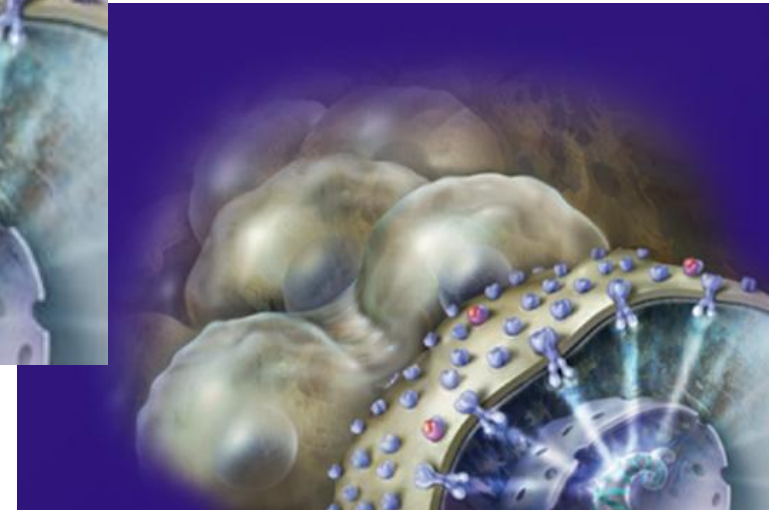
# HER2 Overexpression Leads to Increased Cell Proliferation



Normal



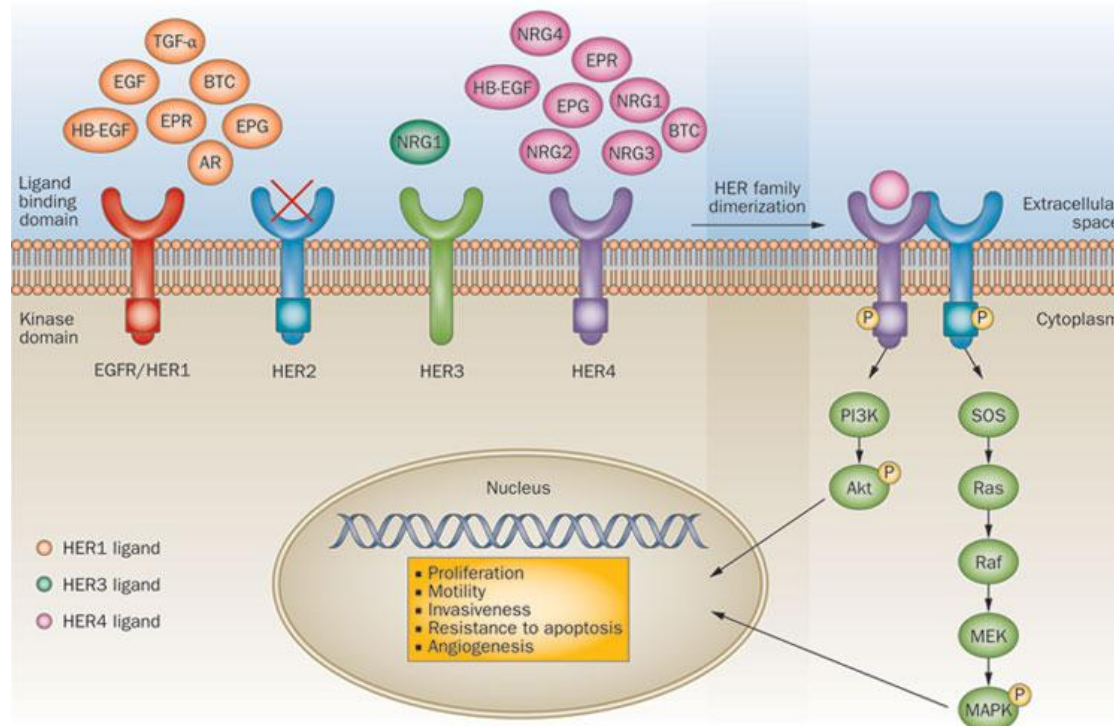
Overexpressed HER2



Excessive cellular division



## Figure 1 Heterodimer formation of members of the HER family and downstream signaling

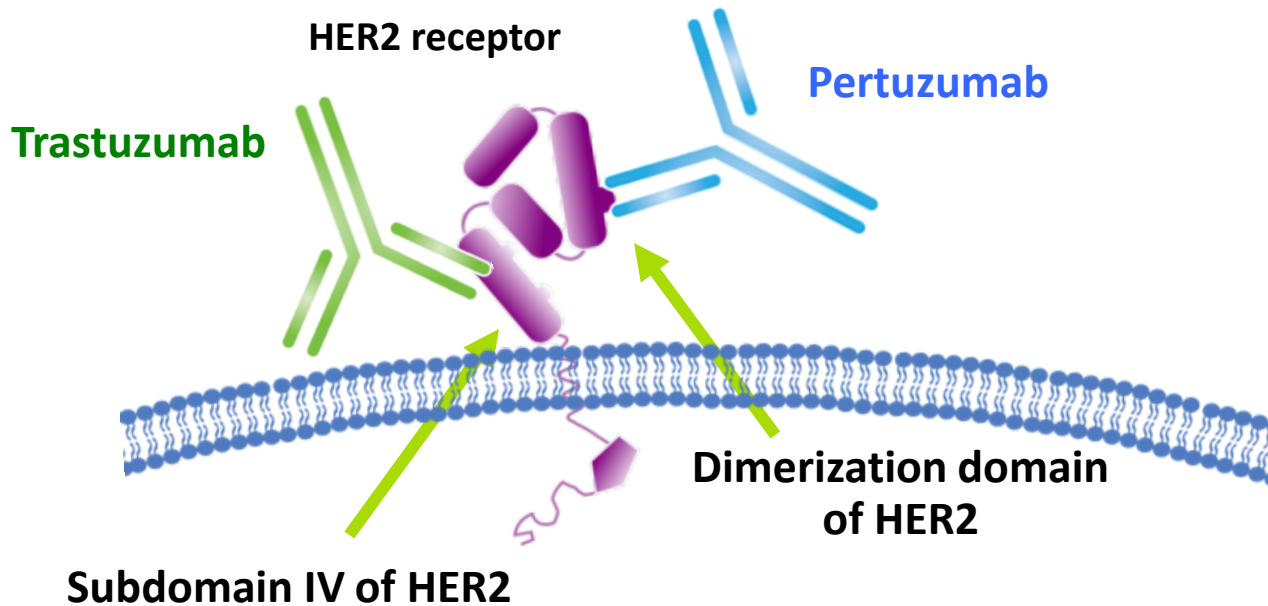


Arteaga, C. L. *et al.* (2011) Treatment of HER2-positive breast cancer: current status and future perspectives *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2011.177

# HER 2 neu + Breast cancer

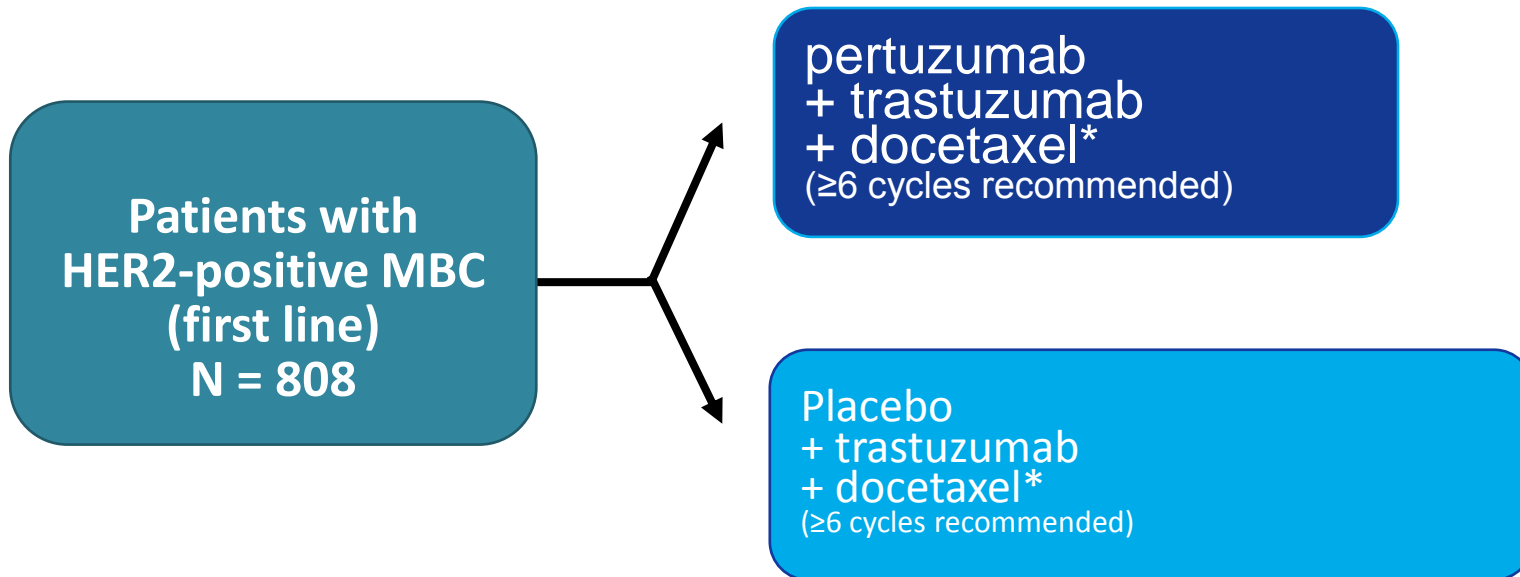
- Herceptin
- Lapatinib
- Pertuzumab: approved 6/2012
- TDM1: approved 2/2013
- Neratinib: soon
- Afatinib: soon
- HSP90 inhibitors: soon too.

# Pertuzumab



- Monoclonal Ab with a distinct binding site to trastuzumab
- Prevents HER2 receptor dimerization
- Thought to provide more complete HER2 receptor blockade and to decrease resistance
- Recently approved in combination with trastuzumab and docetaxel as first line therapy for HER2 positive metastatic breast cancer

# Cleopatra Study

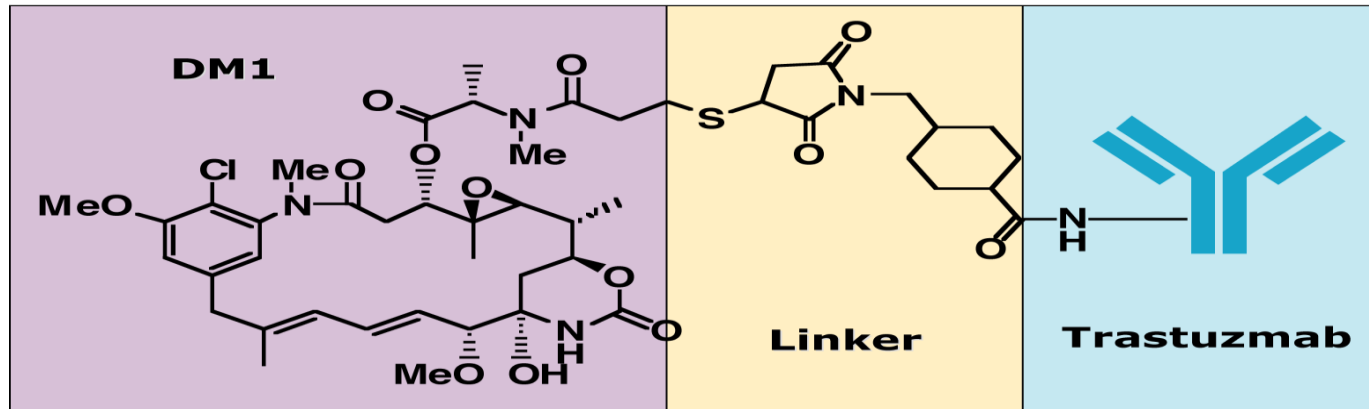


Improvement in PFS ( 6 mos) and OS ( HR 0.64)

•<6 cycles allowed for unacceptable toxicity or PD; >6 cycles allowed at investigator discretion.

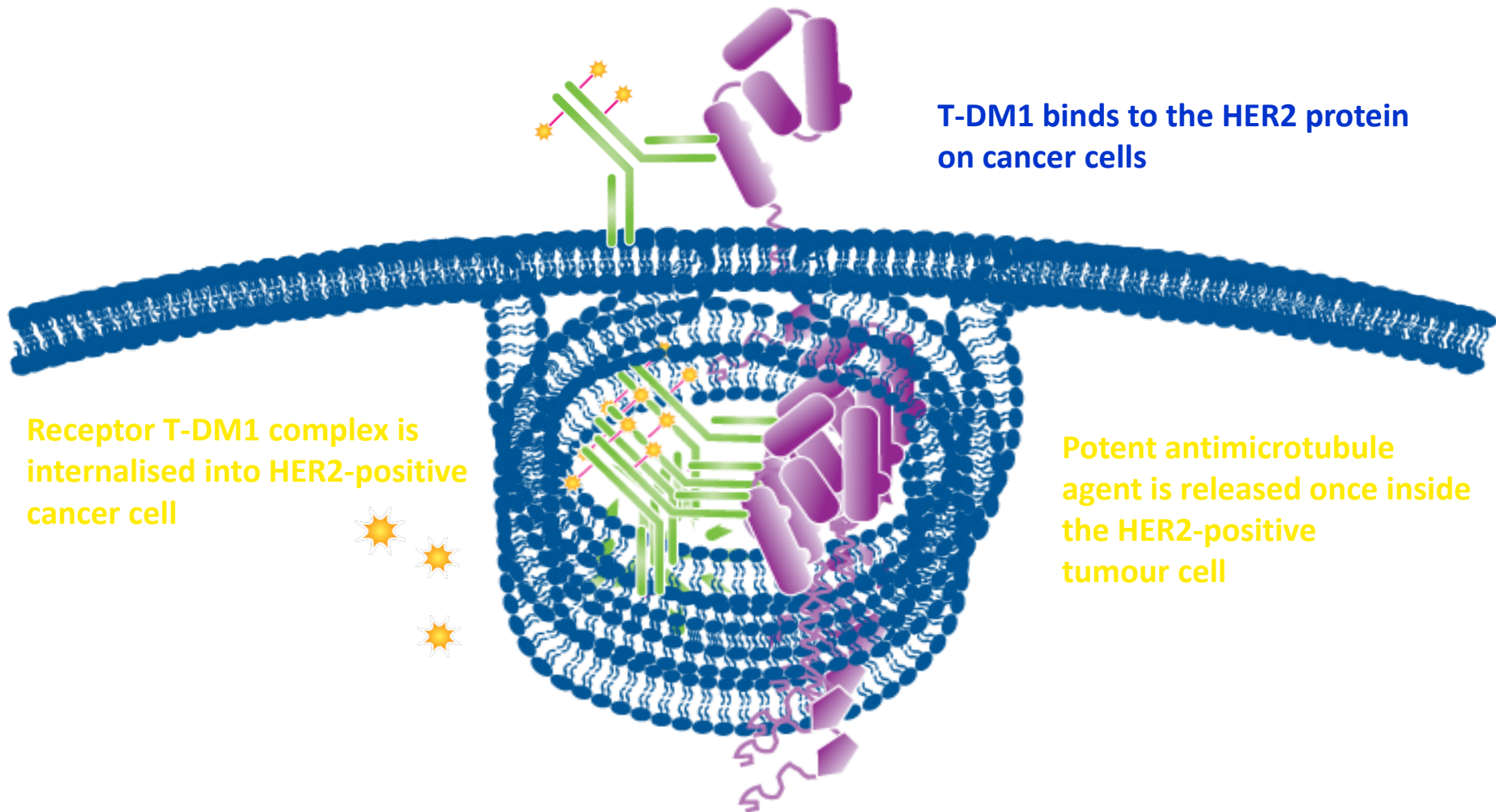
Baselga J et al. *N Engl J Med.* 2012;366:109-119.

# T-DM1 (ado-trastuzumab emtansine).

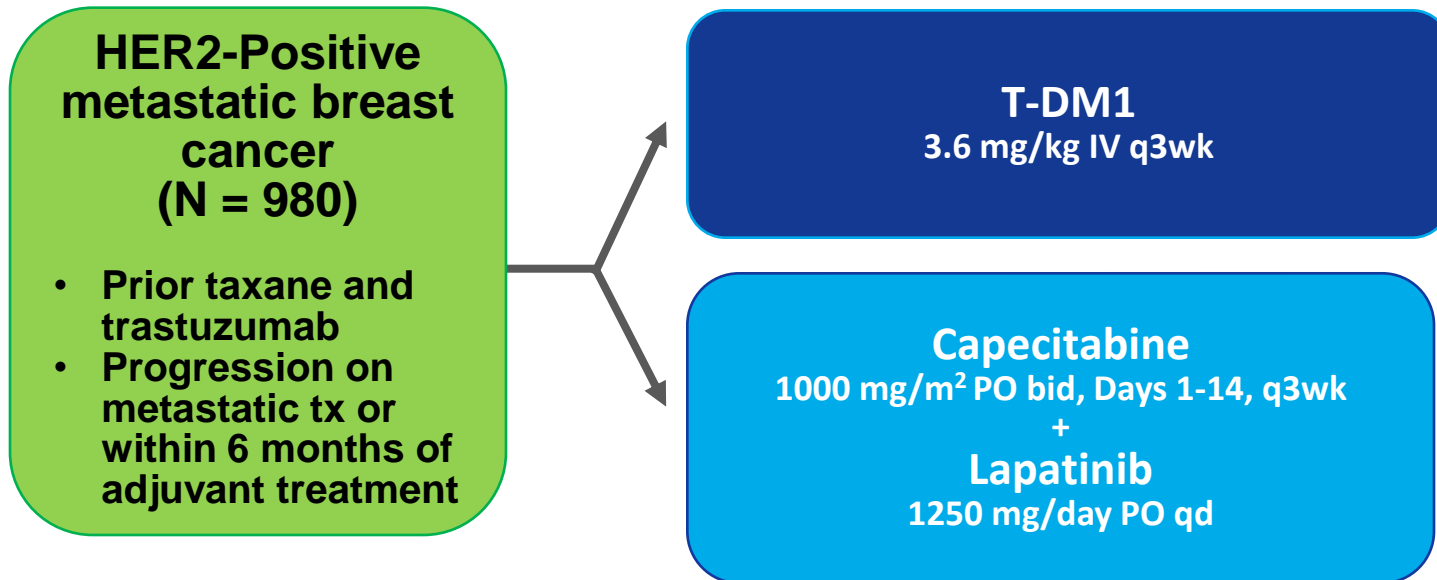


- Antibody drug conjugate
- Trastuzumab linked to a potent antimicrotubule agent (derivative of maytansine)
- After binding to HER2, T-DM1 undergoes receptor-mediated internalization, resulting in intracellular release of DM1
- Delivers highly potent chemotherapy only to HER2 overexpressing cells
- Approved for therapy of metastatic HER2 positive breast cancer previously treated with a taxane and trastuzumab

# T-DM1 Mechanism of action



# EMILIA Study Design



Improvement in PFS ( 30%) and OS ( 5 months)

Hormone receptor positive  
breast cancer



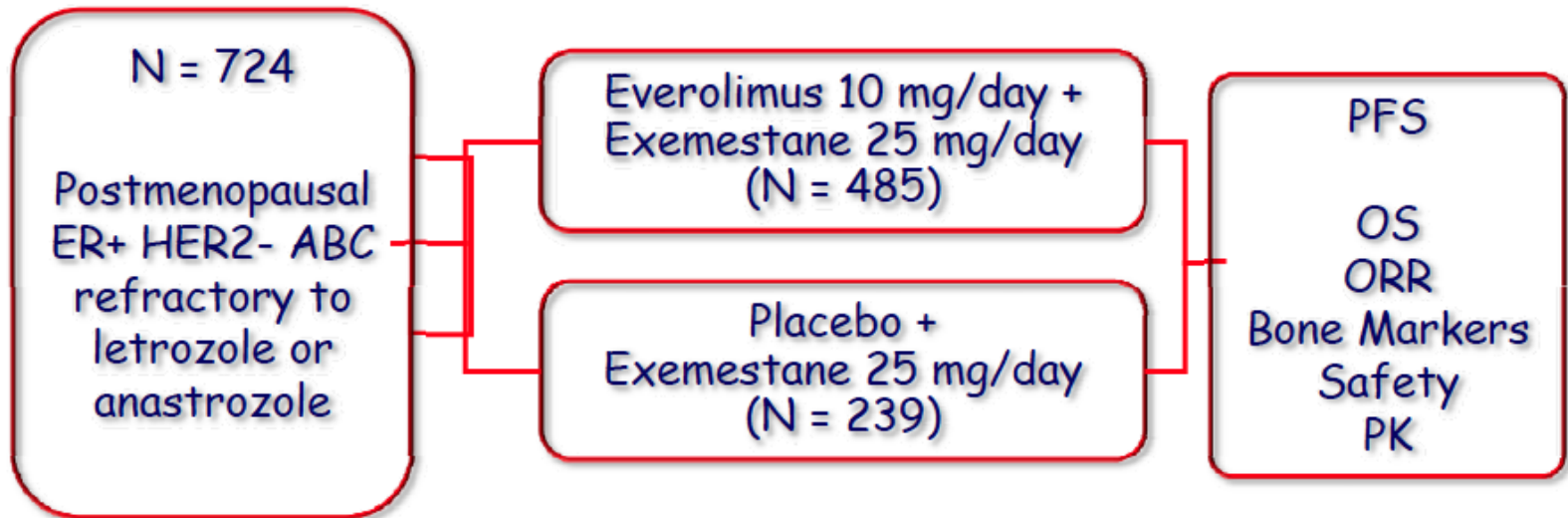
# Options for hormone positive breast cancer

- Definition: Estrogen and or progesterone receptor >1%
- SERMS: tamoxifen or toremifene
- Aromatase inhibitors:
  - Letrozole
  - Anastrozole
  - Exemestane
- Estrogen Receptor Downregulators
  - fulvestrant

# Latest finding in hormone receptor positive BC

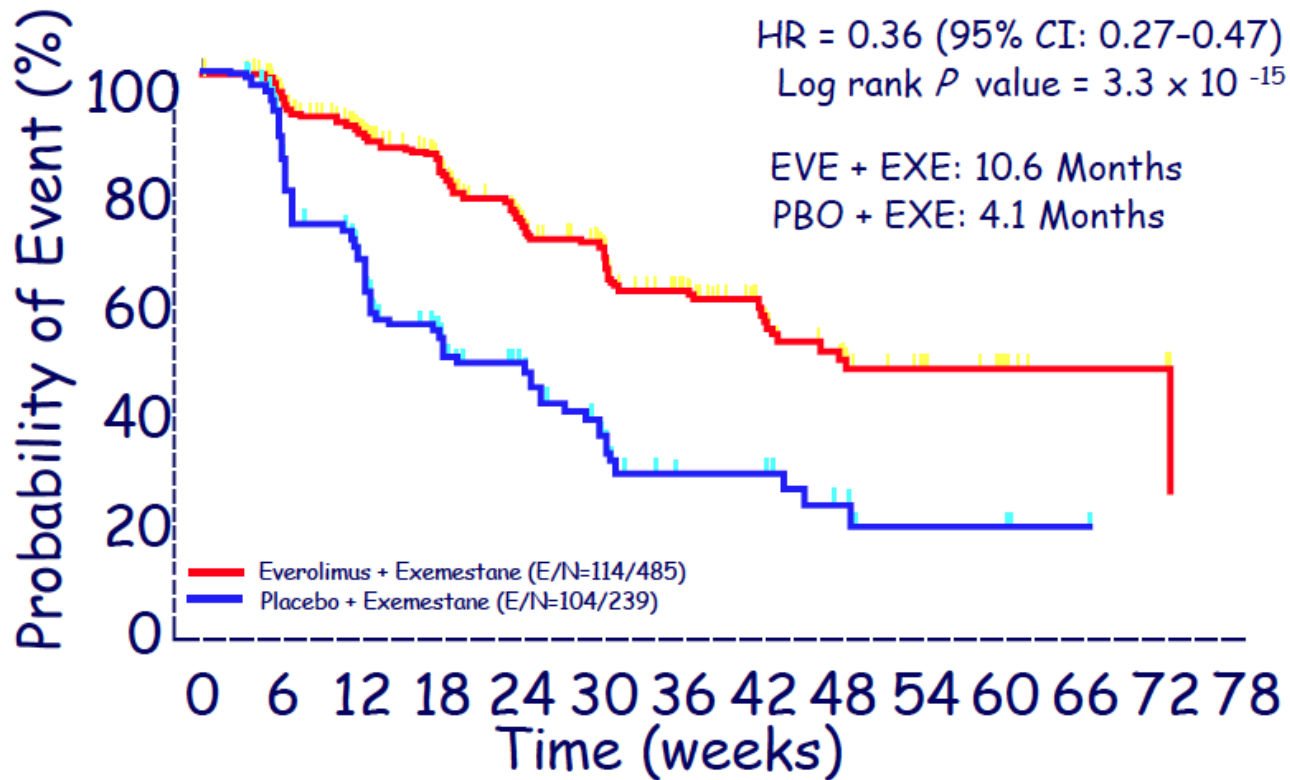
Use of everolimus to reverse  
endocrine resistance

# BOLERO-2: Trial Design



- Stratification:
  1. Sensitivity to prior hormonal therapy
  2. Presence of visceral disease
- No cross-over

## BOLERO-2: Addition of everolimus to exemestane improves PFS in HR+ MBC

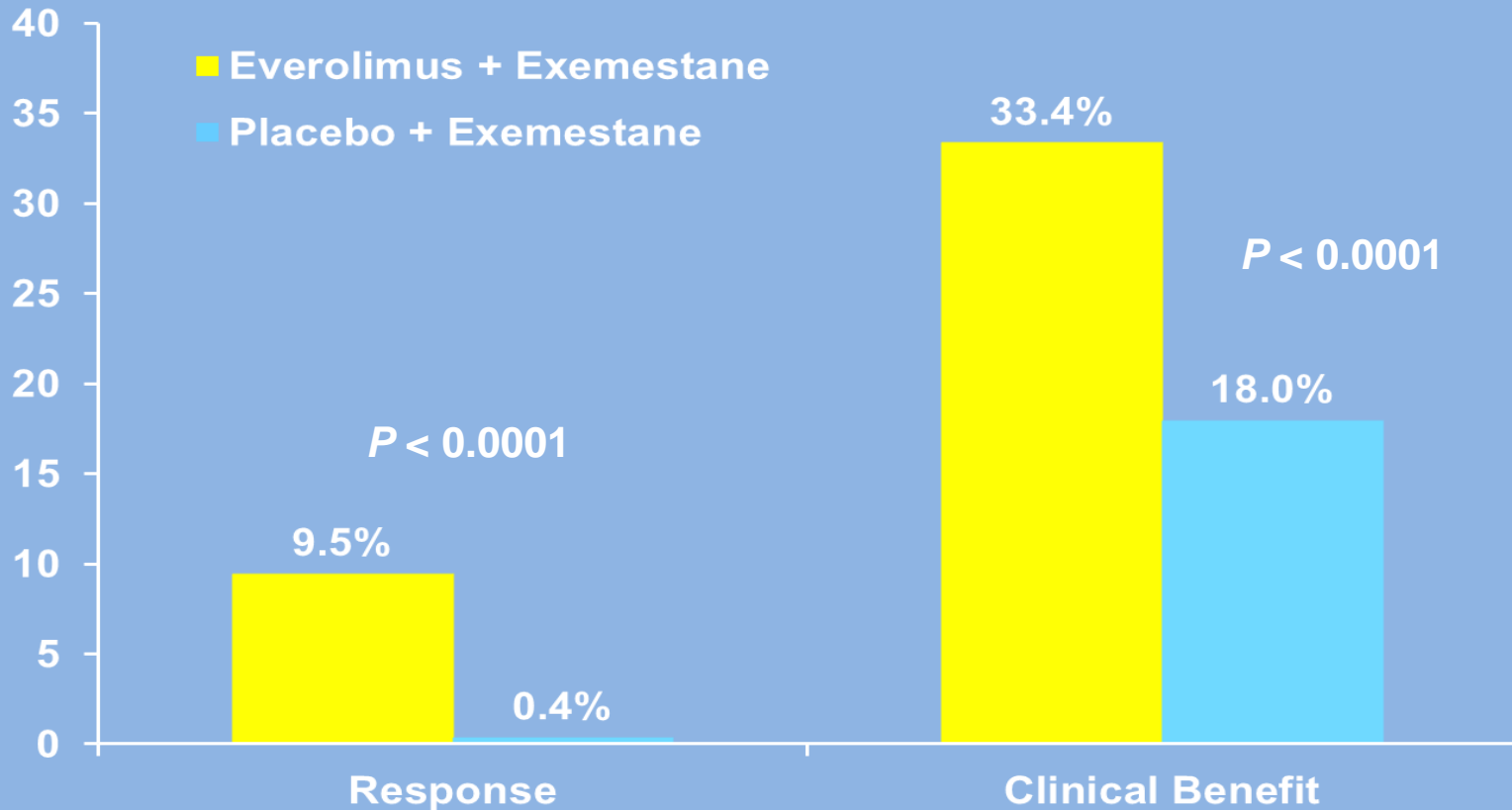


Baselga et al ESMO 2011; NEJM 2012

# BOLERO-2: Most Common G3/4 AEs

	Everolimus + Exemestane (N = 482), %			Placebo + Exemestane (N = 238), %		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
<b>Stomatitis</b>	<b>56</b>	<b>8</b>	<b>0</b>	<b>11</b>	<b>1</b>	<b>0</b>
<b>Fatigue</b>	<b>33</b>	<b>3</b>	<b>&lt;1</b>	<b>26</b>	<b>1</b>	<b>0</b>
<b>Dyspnea</b>	<b>18</b>	<b>4</b>	<b>0</b>	<b>9</b>	<b>1</b>	<b>&lt;1</b>
<b>Anemia</b>	<b>16</b>	<b>5</b>	<b>&lt;1</b>	<b>4</b>	<b>&lt;1</b>	<b>&lt;1</b>
<b>Hyperglycemia</b>	<b>13</b>	<b>4</b>	<b>&lt;1</b>	<b>2</b>	<b>&lt;1</b>	<b>0</b>
<b>AST</b>	<b>13</b>	<b>3</b>	<b>&lt;1</b>	<b>6</b>	<b>1</b>	<b>0</b>
<b>Pneumonitis</b>	<b>12</b>	<b>3</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>

# BOLERO-2: Overall Response Rate and Clinical Benefit Rate by Local Assessment



# BOLERO-2: Summary

- Addition of everolimus to exemestane prolongs PFS in patients with ER+ HER2- breast cancer refractory to initial non-steroidal aromatase inhibitors
  - Local: median 6.9 vs 2.8 months, HR = 0.43,  $P < 0.0001$
  - Central: median 10.6 vs 4.1 months, HR = 0.36,  $P < 0.00$
- Benefit is observed in all subgroups
- Adverse events are consistent with previous experience with everolimus including stomatitis, fatigue and hyperglycemia

# Everolimus

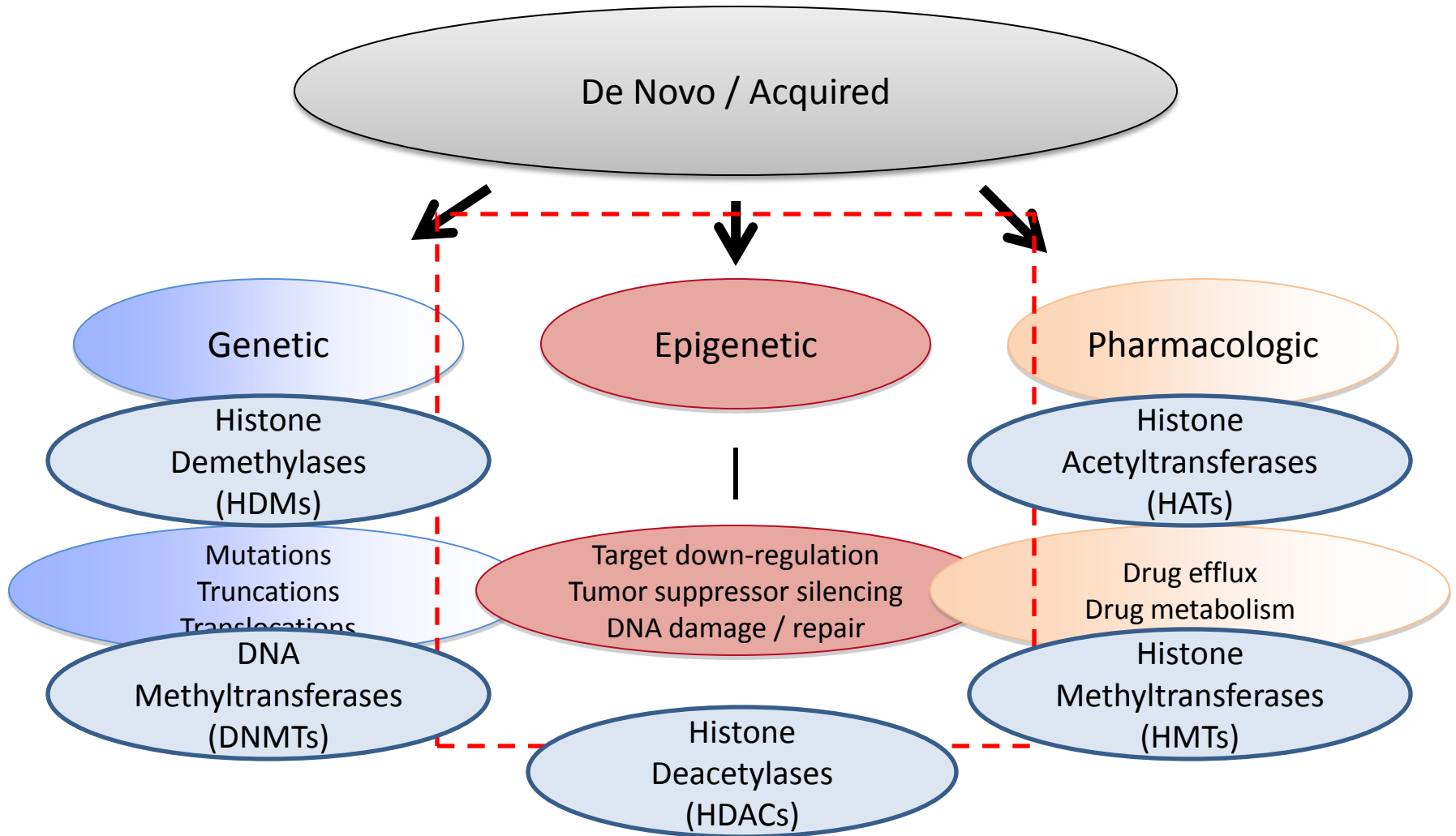
- Similar results seen when combined with tamoxifen
- Much smaller benefit when combined with vinorelbine and trastuzumab(herceptin)



# New things to watch in clinical trials

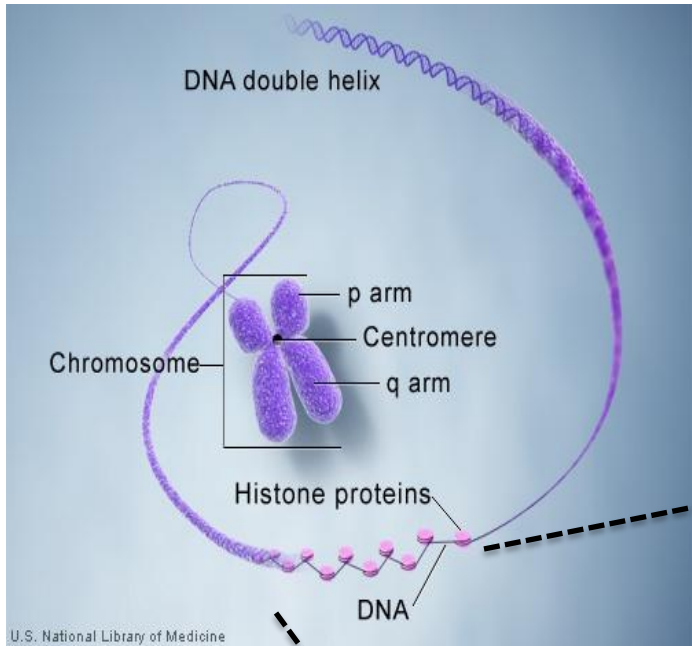
- Addition of HDAC inhibitors

# Drug Resistance is Multi-factorial



# HDAC Inhibitors Mechanism of Action

HDACi 'open up' the structure of DNA



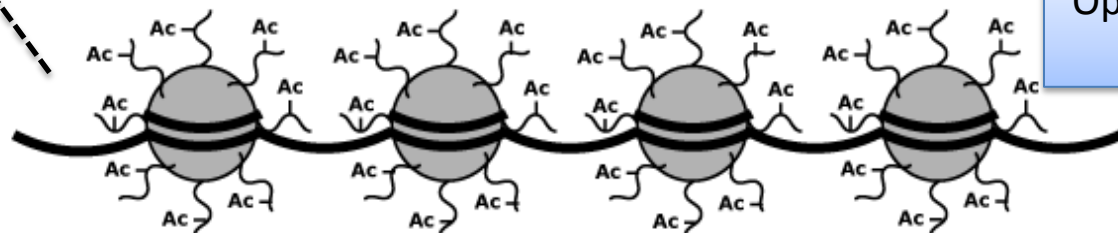
Closed chromatin = Genes off

HDAC Inhibitors (HDACi)

Histone acetyltransferases (HATs)

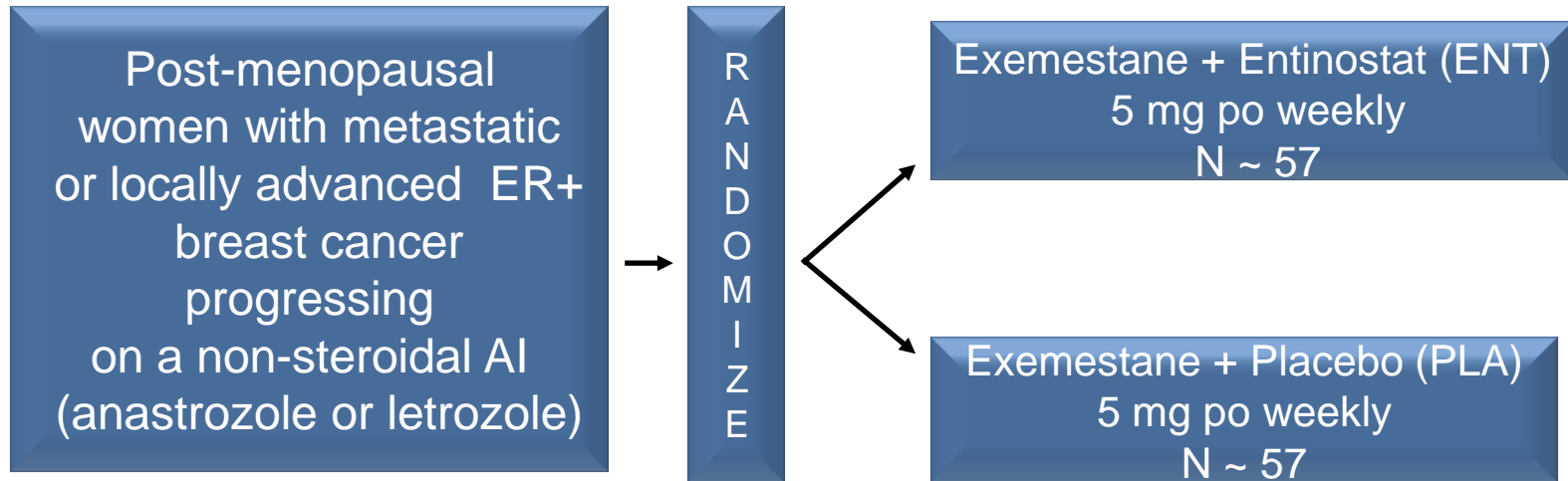
Histone deacetylases (HDACs)

Open chromatin = Genes on



# ENCORE 301 Study Design

Hypothesis: Entinostat re-sensitizes tumors to aromatase inhibitors (AI)



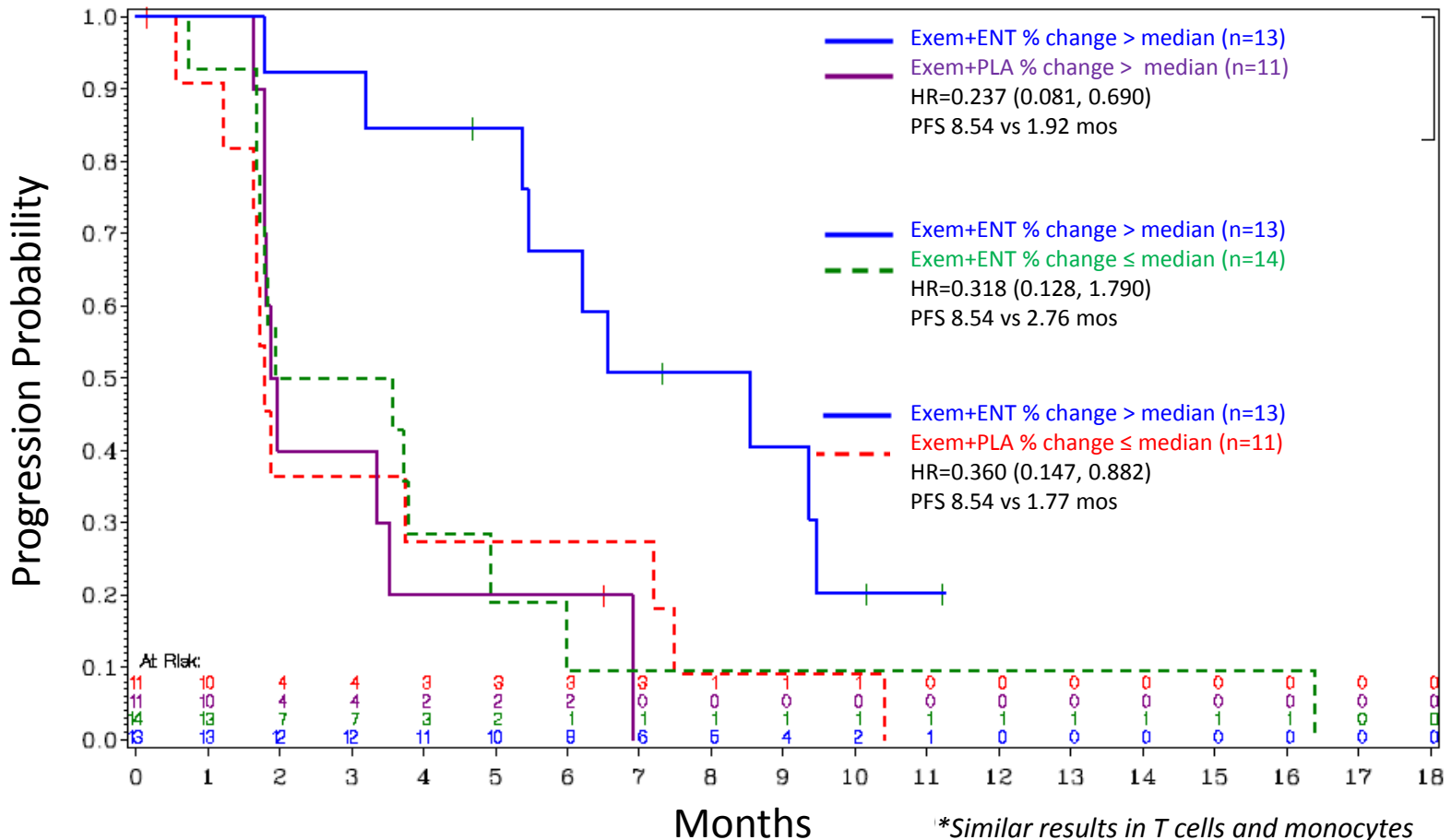
## Stratification Factors:

- AI disease progression (Adjuvant vs MBC setting)
- Bone only disease (yes / no)
- Geographic region (North America vs EU/Russia)

Randomized, **double-blind**, placebo-controlled  
Endpoints include: 1<sup>o</sup> PFS, 2<sup>o</sup> ORR and CBR; Exploratory Endpoint - OS

# PFS Greatest in Exemestane+Entinostat in Subjects Who Hyperacetylate

## PFS by Treatment and Change in B-cell % Acetylation\*



# ENCORE 301 Conclusions: Exemestane+Entinostat

- Improved PFS
  - This combination may allow patients to remain on hormonal therapy longer, delaying the need for chemotherapy
- Trend in OS benefit
  - An exploratory endpoint with data that is still maturing
- Well tolerated
  - Safety profile consistent with previous studies
- Increased PFS in subjects who hyperacetylate
  - First randomized study to demonstrate an association between an HDAC inhibitor induced acetylation and clinical outcomes
- These results support plans for the global, pivotal Phase 3 study due to begin enrollment in early 2012

Triple negative breast cancer

# Triple negative

- Definition: Lack ER, PR and HER 2 neu
- What we know:
  - Not all created equal
  - Some overlap: basaloid and TNBC
- Is BRCA 1 associated TNBC different?
  - Maybe, not sure yet
  - Differential response to PARPinhibitors



# Drugs in clinical trials

# PARP inhibitors

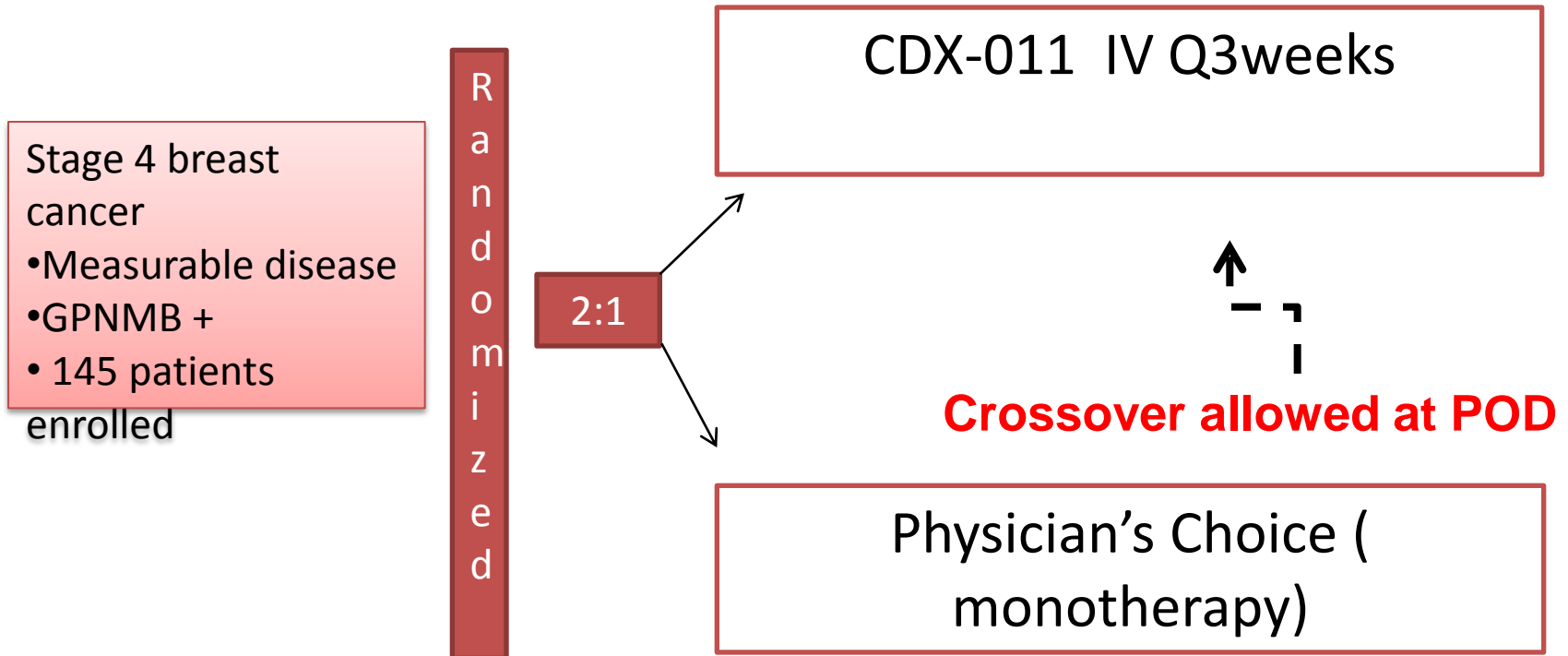
- Exploit vulnerability of cells that lack the machinery to repair themselves
- Explored in TNBC and BRCA1/2 mutation carrier
- Still finding its way TNBC but BRCA1/2 look excellent
- Examples: iniparib, olaparib and velaparib

glembatumumab vedotin

CRO11-vcMMAE

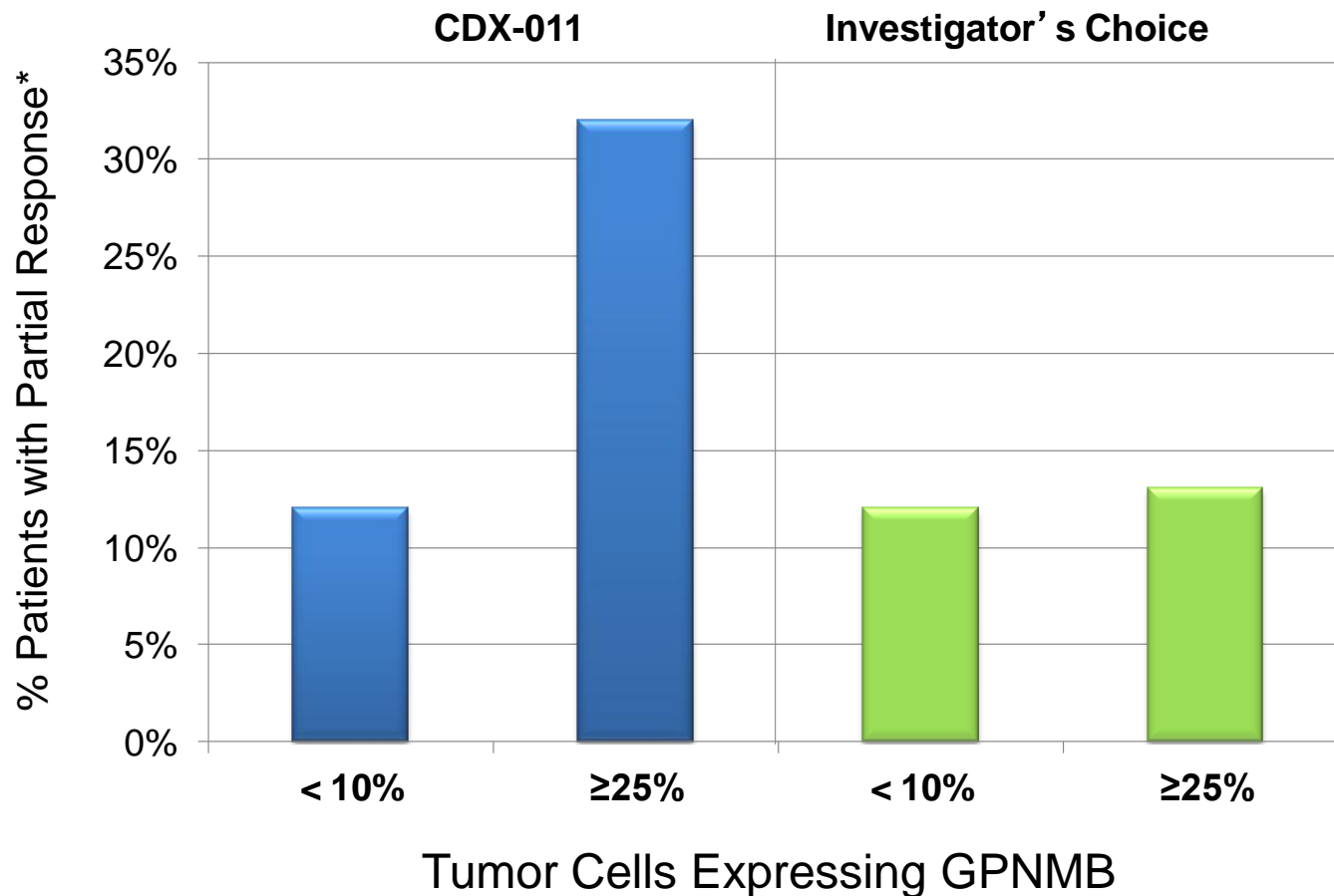


# Randomized Phase II trial of CDX-011 (CR011-vcMMAE) in Patients with Advanced GPNMB-expressing Breast Cancer



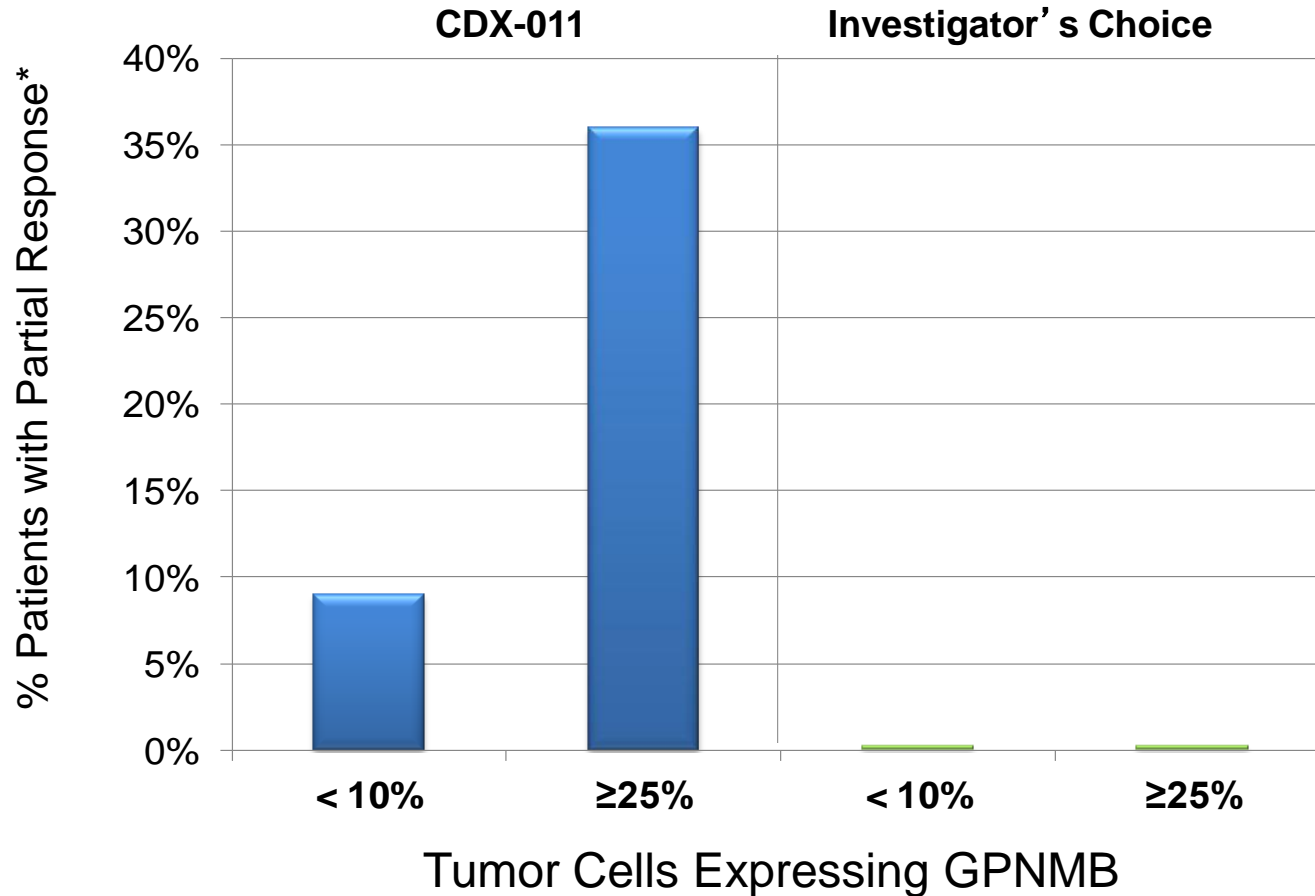
Trial completed in January 2012 and WCMC was the lead institution

# EMERGE: Correlation of Response and GPNMB Expression



\* Including confirmed and unconfirmed PR

# EMERGE: Triple-Negative Patients Correlation of Response and GPNMB Expression



\* Including confirmed and unconfirmed PR

# Glembatumumab vedotin:

- Promising activity in patients with TNBC
- Next trial soon.....



# New Strategies

## Work in Progress:

To understand why BC spreads

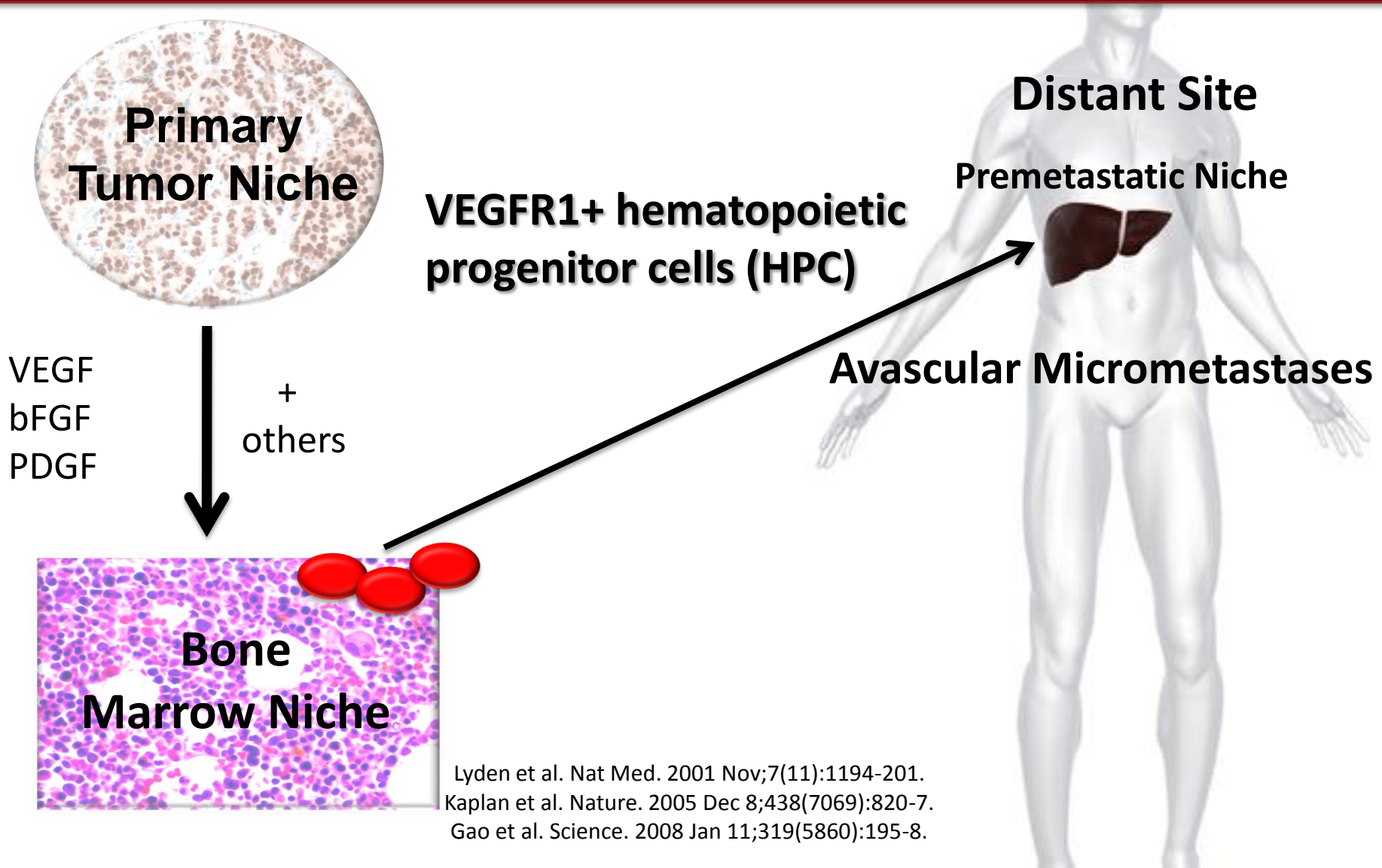
Strategy to influence the microenvironment and prevent relapse

# Research question

- Why can a tumor be dormant and occult for years in BC and then recur?
  - What are the processes that facilitate this process?
  - Are there any strategies that can interrupt this process pre-clinically that can be replicated clinically?

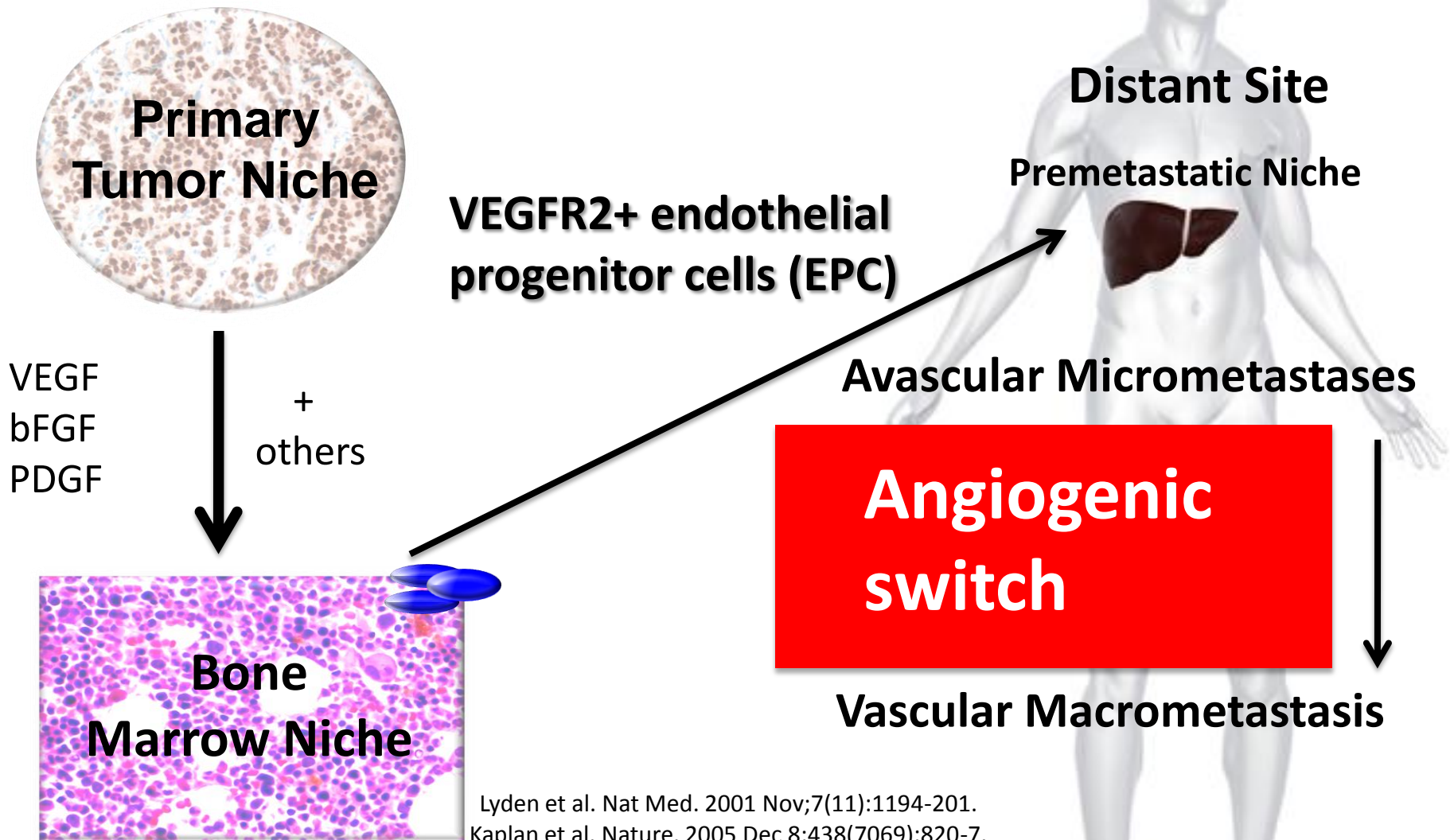
Maintaining dormancy= cure

# Preclinical models of metastatic progression



Lyden et al. Nat Med. 2001 Nov;7(11):1194-201.  
Kaplan et al. Nature. 2005 Dec 8;438(7069):820-7.  
Gao et al. Science. 2008 Jan 11;319(5860):195-8.

# Preclinical models of metastatic progression



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Does what happen in mice happen in women with breast cancer?



# Are these pre-clinical models relevant to patients with breast cancer?

Observational Study

- What is the natural history of EPCs and HPCs in adjuvant BC patients and metastatic cancer response and progression over time

Clinical Study

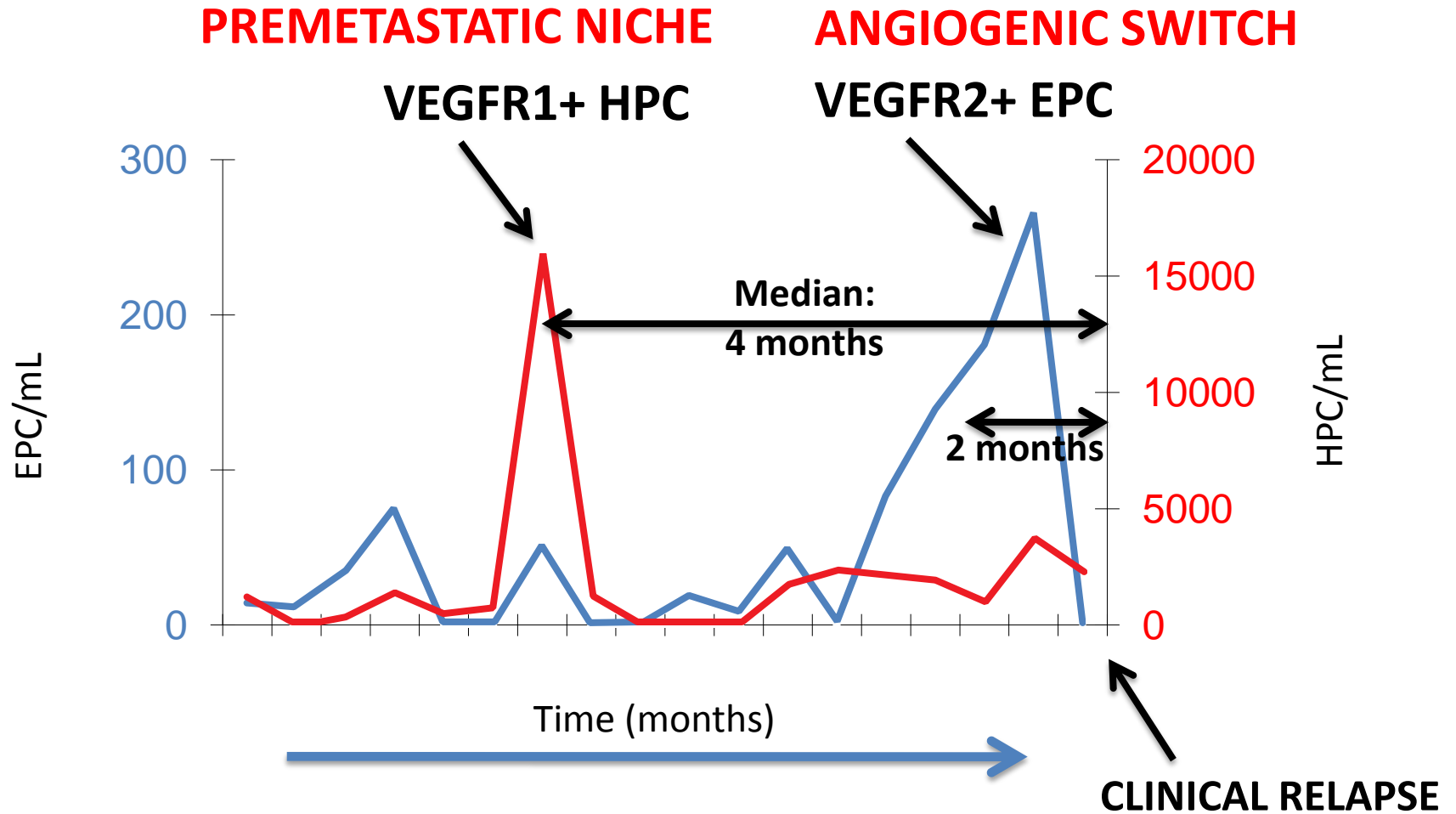
- Decrease EPCs in women with BC at high risk of relapse

EPCs- CD45<sup>dim</sup>, CD133+, VEGFR2+ cells; HPCs- CD34+, VEGFR1+

# Results

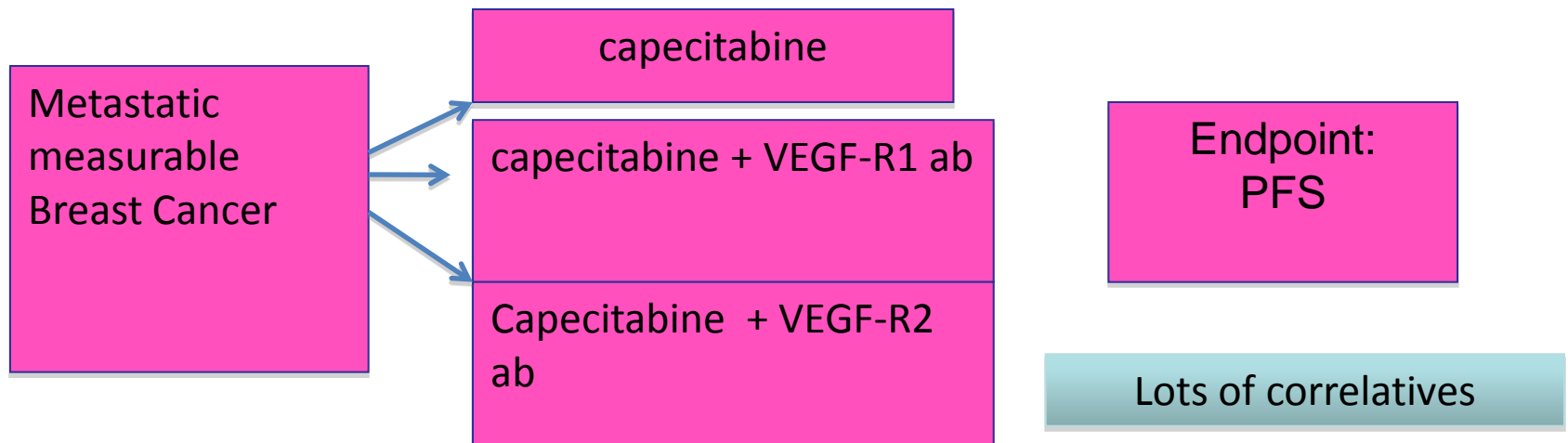
- Study group 132 patients
- There was a surge in VEGFR1+ cells followed by a surge in VEGFR2+ cells followed by a clinical relapse
- Targets for therapy

# Identical pattern of HPC surge preceding EPC surge prior to overt relapse in only relapsed patients





# Completed Clinical Study:



## Opportunity:

To understand the role of VEGFR 1 and VEGFR2 bone marrow derived cells in metastatic breast cancer

Potential translation: maintenance of tumor dormancy...

Does what happen in mice happen in women with breast cancer? **I think so!**



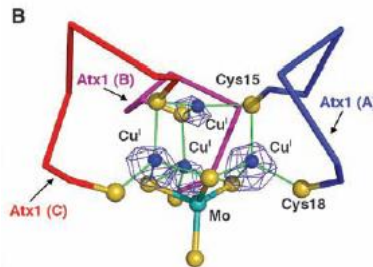
Can we impact the EPCs  
(microenvironment) in a high risk  
population?

TM study

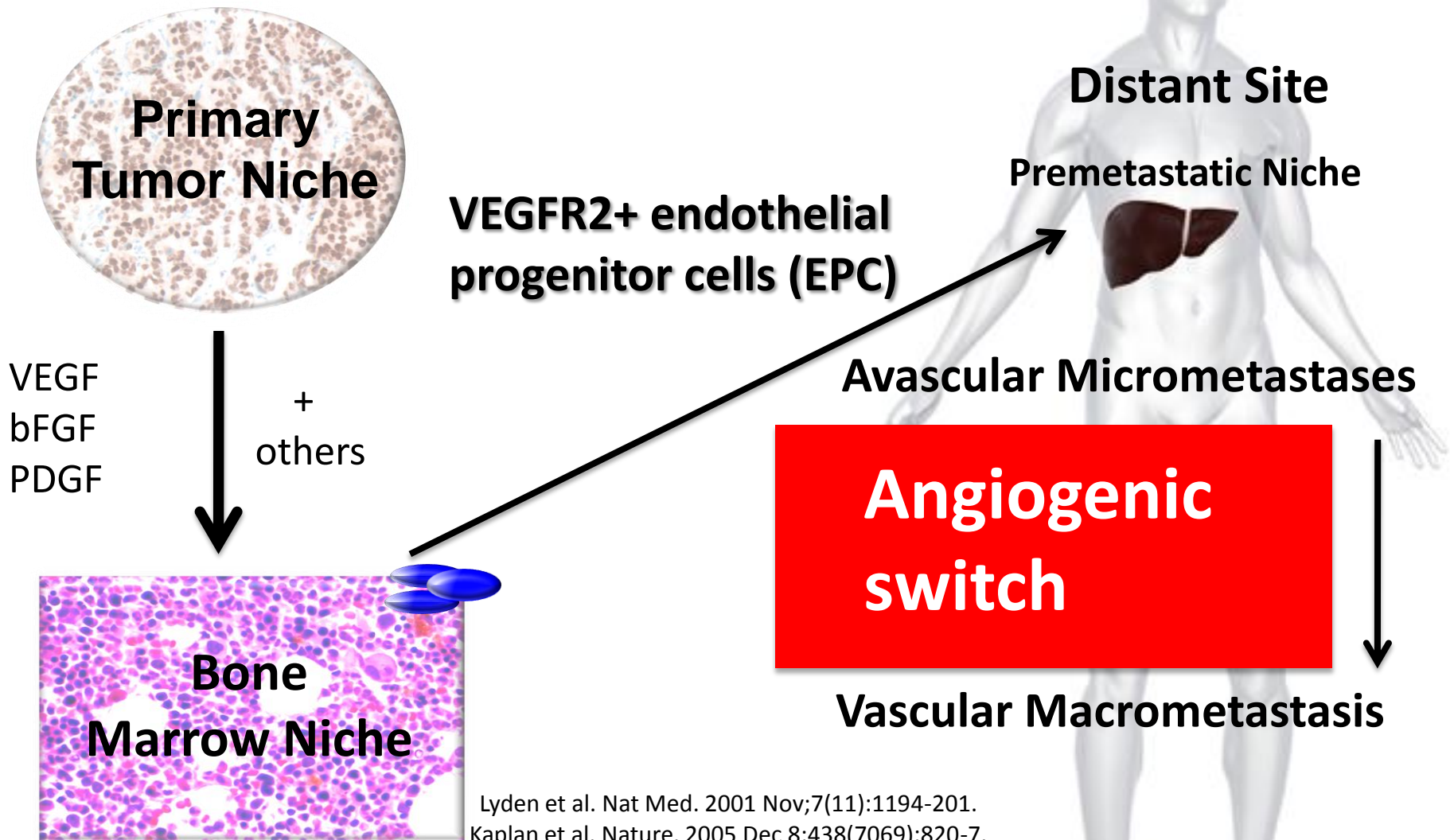
( phase II study of tetrathiomolybdate in BC pts at high risk of relapse)

# Tetrathiomolybdate (TM)

- TM is an oral copper chelator
- Copper is required for angiogenesis, endothelial cell migration and proliferation
- Copper deficiency inhibits angiogenesis and shrinks tumors
- Clinical trials of TM (phase I and II) show that TM is safe. Efficacy has been variable.

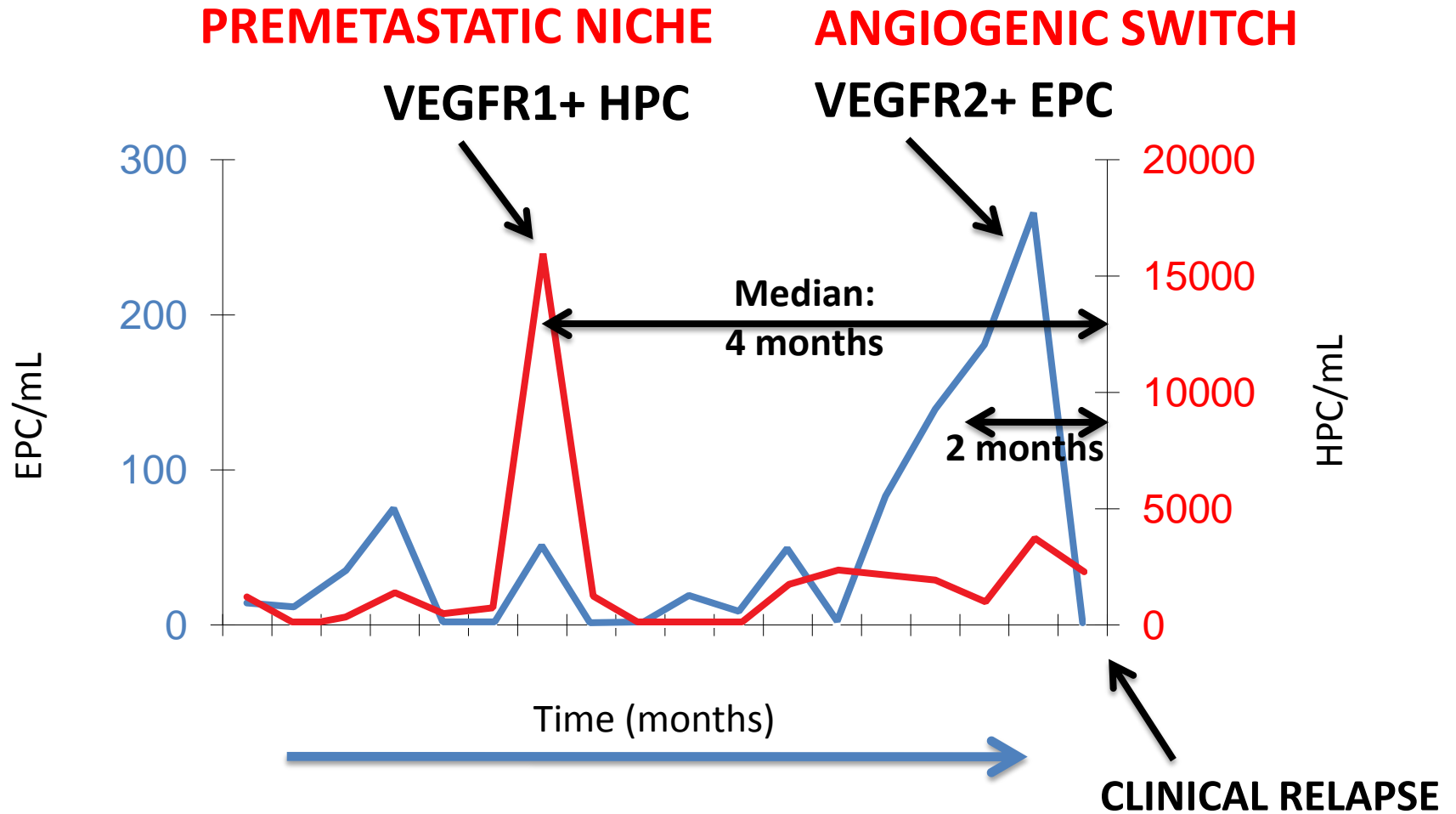


# Preclinical models of metastatic progression



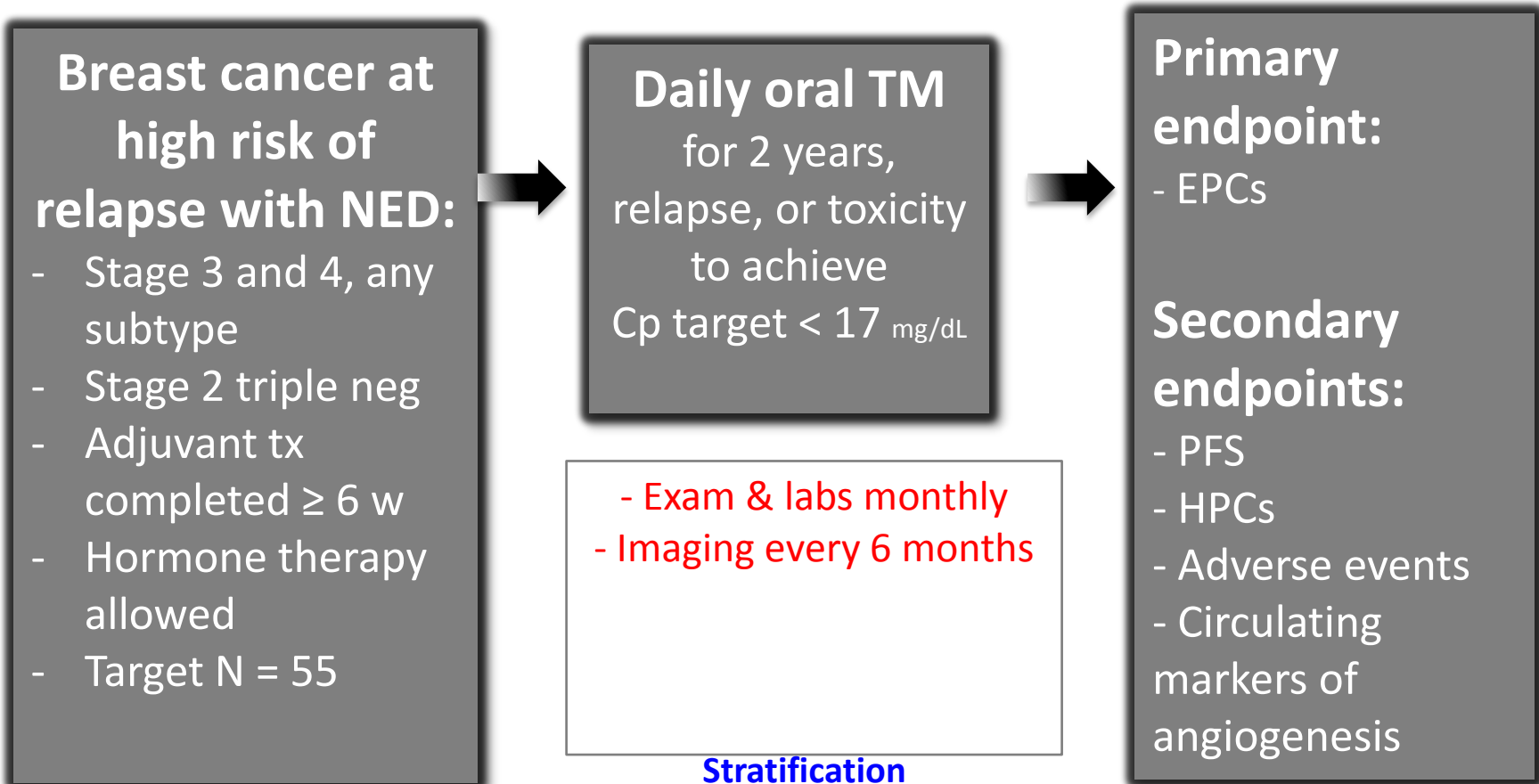
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# Identical pattern of HPC surge preceding EPC surge prior to overt relapse in only relapsed patients



# Phase 2 study of TM

## Open-label, single-arm phase II trial



### Stratification

- Copper depletion
- Molecular subtype

**Accrual:** June 2007 - ongoing

# Preliminary results

- TM is safe and well tolerated
- TM copper depletes most patients
- If copper depleted, reduces EPCs
- Went back into lab and figured out additional effects
- Will hopefully continue to move forward



The End!  
Thanks for listening