



Personalized Therapy for Breast Cancer in the Era of Molecular Cancer Medicine

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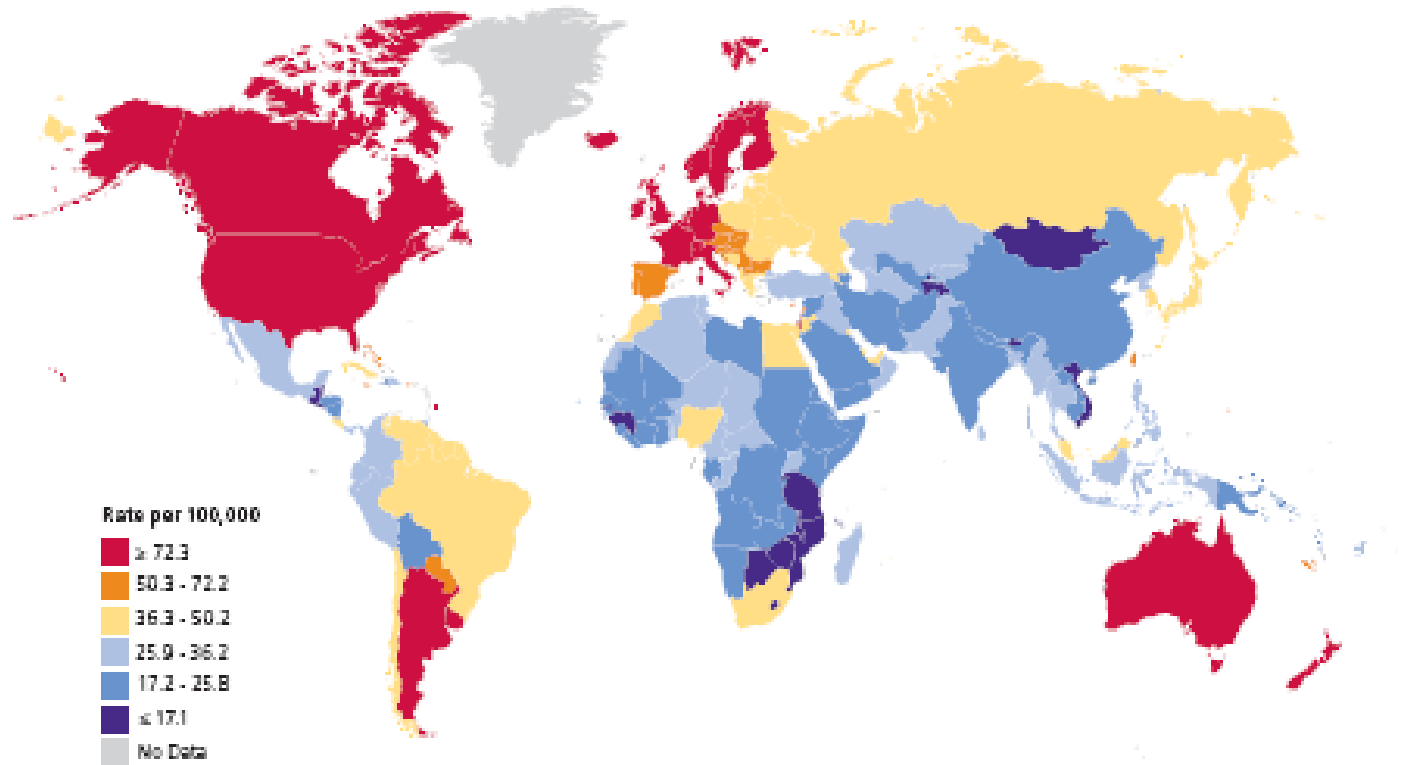
Director, University of Pittsburgh Cancer Institute

and UPMC CancerCenter



Breast Cancer—A Global Challenge

Figure 4. International Variation In Age-standardized Breast Cancer Incidence Rates, 2008



Source: GLOBOCAN 2008.

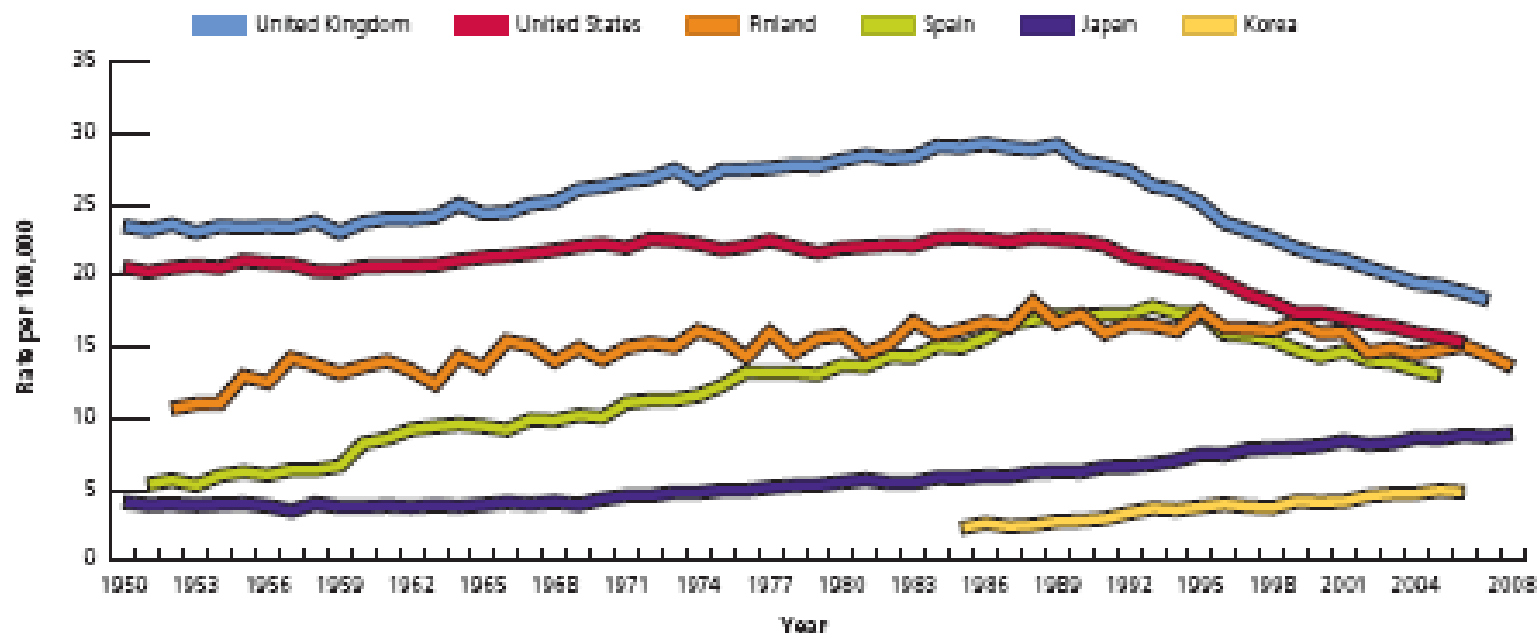


www.cancer.org

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Changing Landscape of Breast Cancer

Figure 5. Trends in Age-standardized Female Breast Cancer Death Rates in Select Countries



Source: WHO Mortality Database.



www.cancer.org

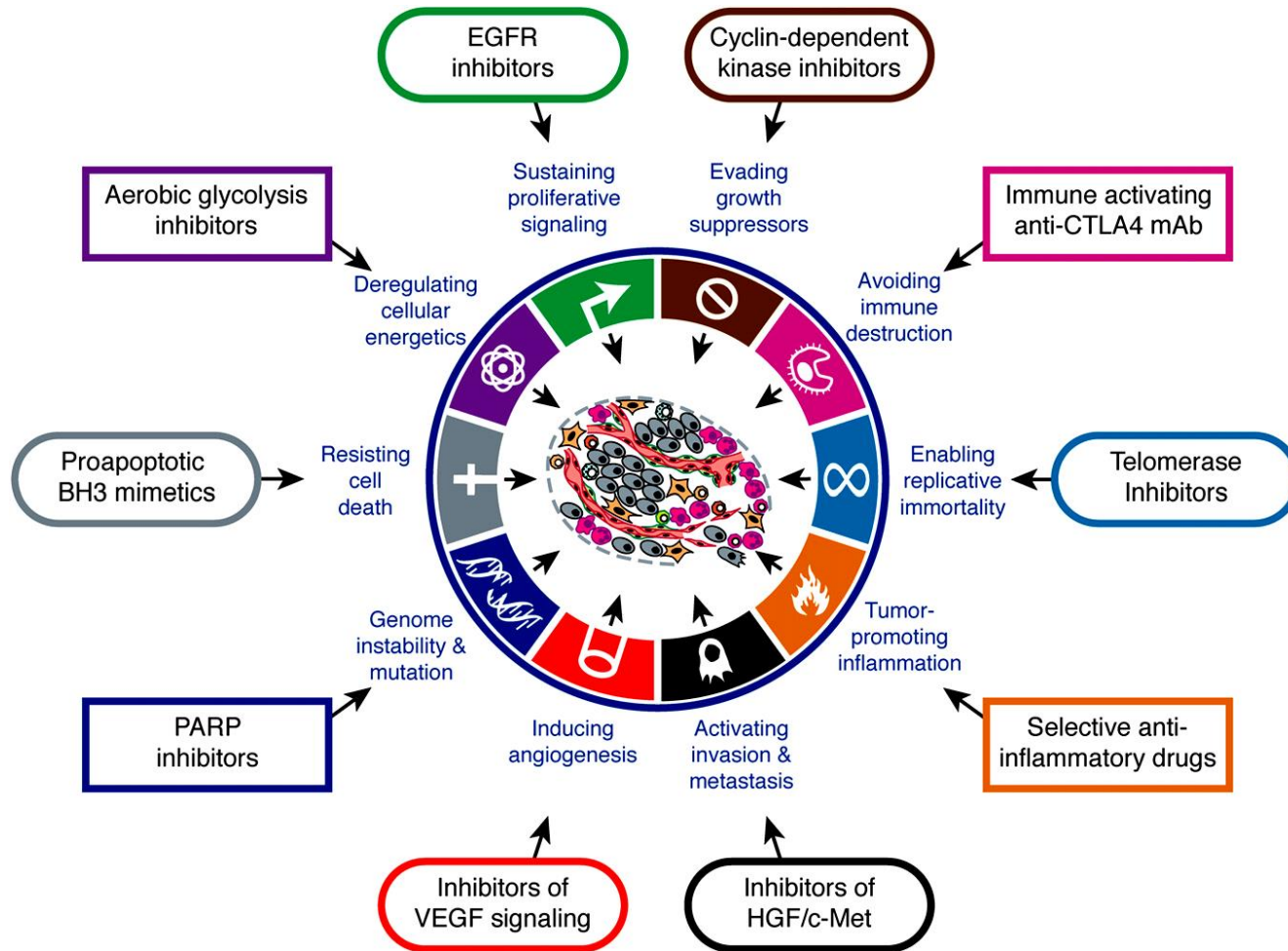
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Many Names---One Goal

- **Personalized**
- **Molecularly informed**
- **Individualized**
- **Tailored**
- **Stratified**
- **Precision**



Hallmarks of Cancer



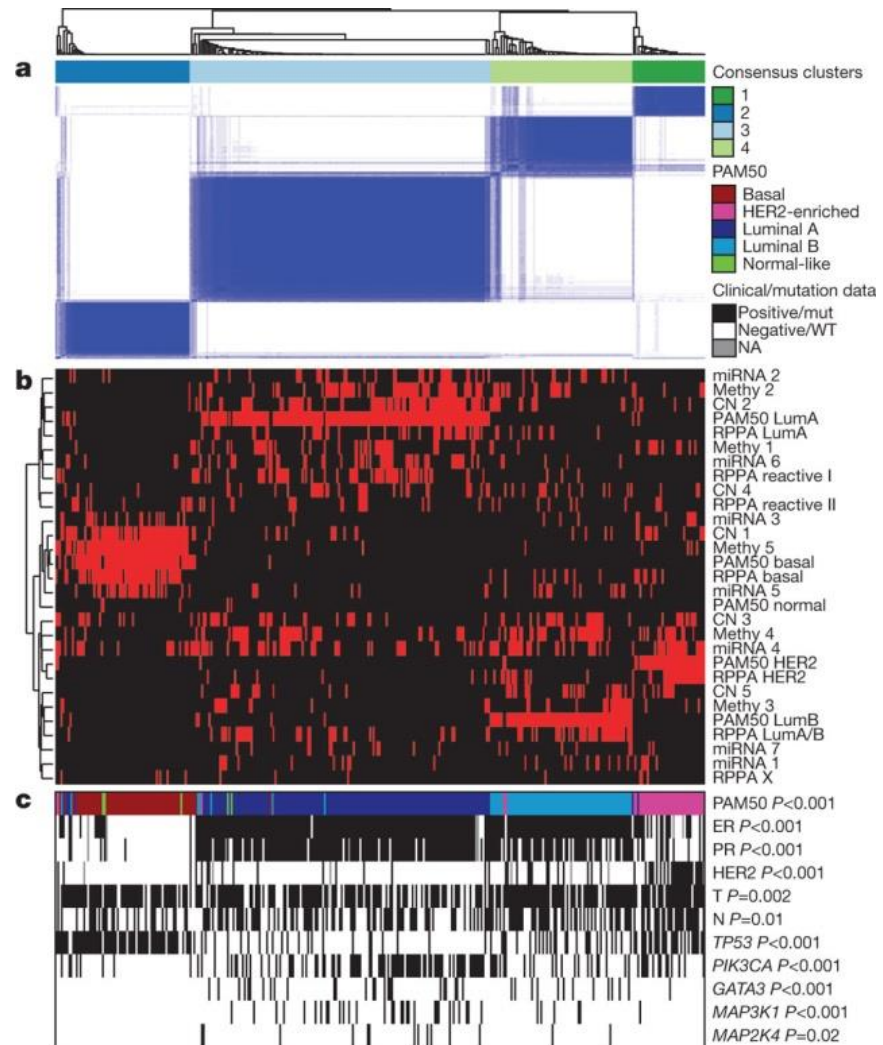
Weinberg and Hanahan, Cell, 2011



Coordinated Analysis of Breast Cancer Subtypes Defined from Multiple Genomic/Proteomic Platforms

463 patients with:

- mRNA expression array
- DNA methylation
- SNP array
- miRNA sequence
- Whole exome sequencing
- RPPA



TCGA, Nature, 2012

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Topics for Today

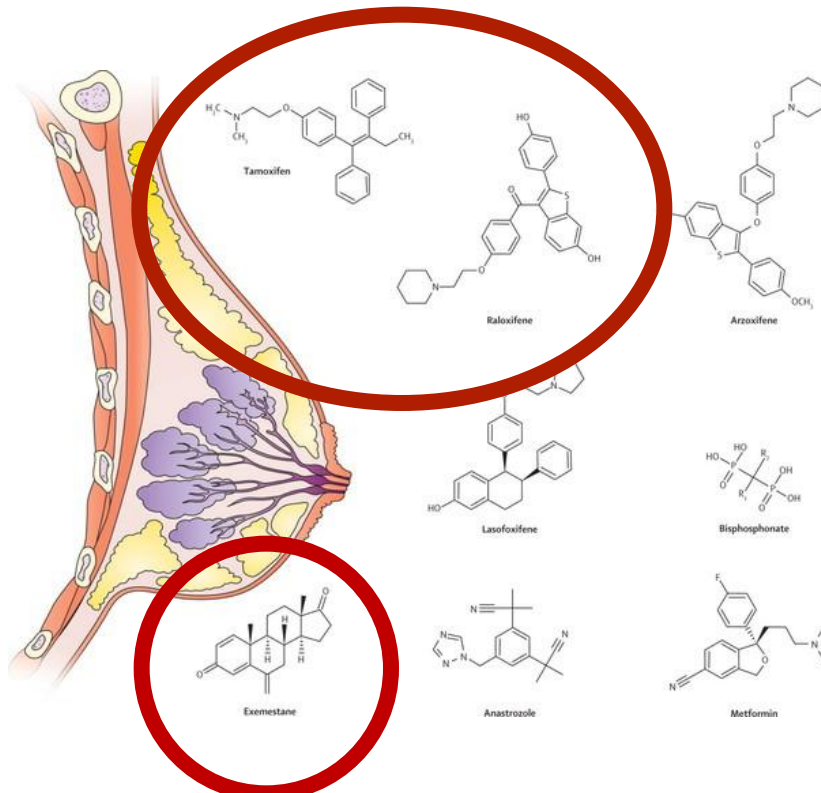
- **A plea for prevention**
- **Tailoring local therapy**
- **Hormone-responsive breast cancer**
- **HER-2 positive breast cancer**
- **Other systemic approaches**



Potential Methods for Breast Cancer Prevention

Pharmacological

Lifestyle



- Limit use of HRT
- Avoid alcohol
- Maintain normal BMI
- Exercise

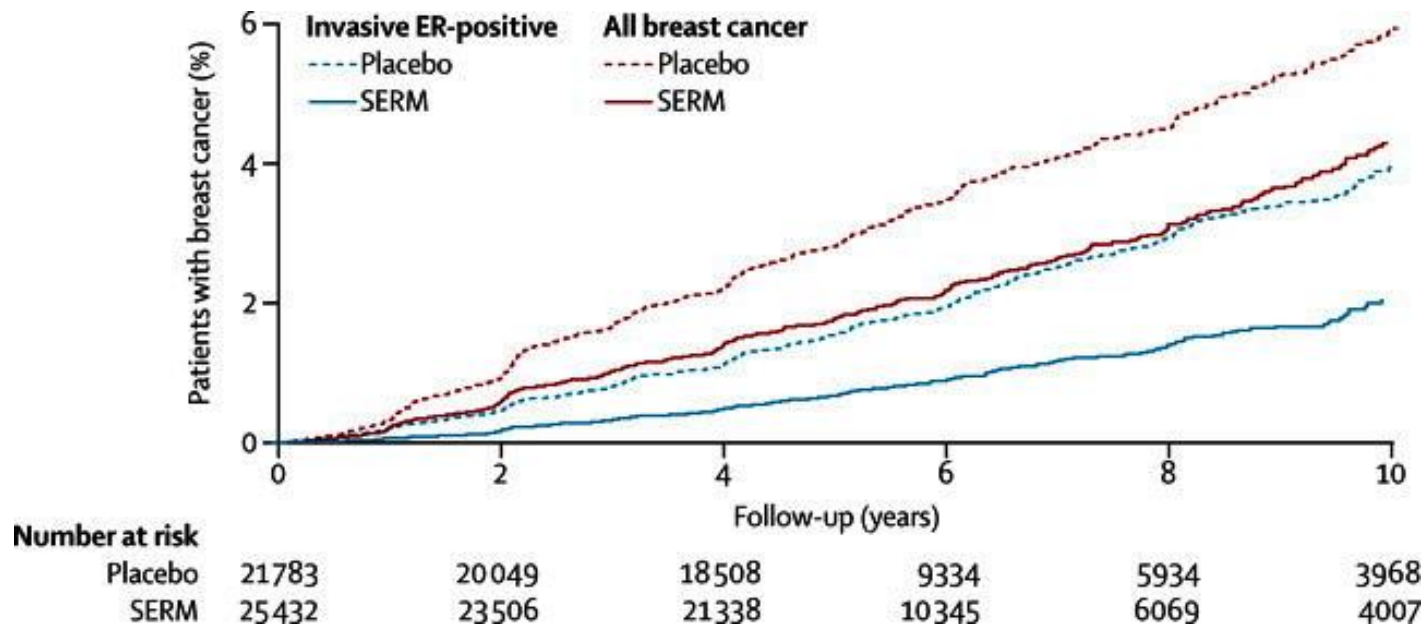
Cuzick et al, Lancet Oncology, 2011

Metaanalysis of SERM Prevention Trials

9 trials of 83,399 women with 65 mo median followup

HR=0.62

NNT=42



Cuzick et al, Lancet, 2013



Some Guidance about Use of Preventive Agents

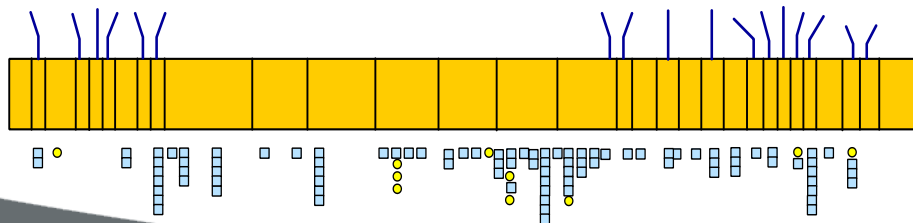
Agency	Recommendation
US FDA	Tamoxifen approved for high risk > 34 years Raloxifene approved for high risk post
USPSTF (2002)	Discuss tamoxifen with high risk women Against for normal/low risk women
ASCO (2013)	Discuss tamoxifen for high risk pre Discuss tamoxifen or raloxifene or AI for high risk post
NCCN (2012)	Discuss tamoxifen for high risk pre Discuss tamoxifen or raloxifene or exemestane for high risk post

ASCO, Visvanathan et al, J Clin Oncol, 2013



BRCA1/2 Testing

- From identification of genetic loci to clinical test
- Impact of prophylactic mastectomy and oophorectomy demonstrated
- Role of additional screening and prevention strategies—MRI for breast screening
- Testing should be offered to appropriate candidates
- Ongoing deciphering of repair pathway defects
- Role of PARP inhibitors for treatment?



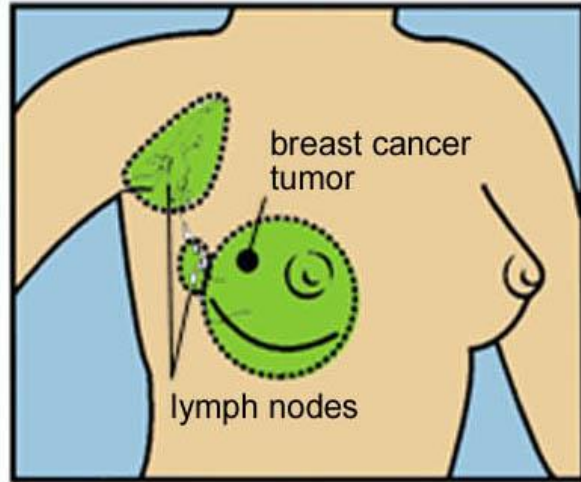
Topics for Today

- A plea for prevention
- **Tailoring local therapy**
- Hormone-responsive breast cancer
- HER-2 positive breast cancer
- Other systemic approaches

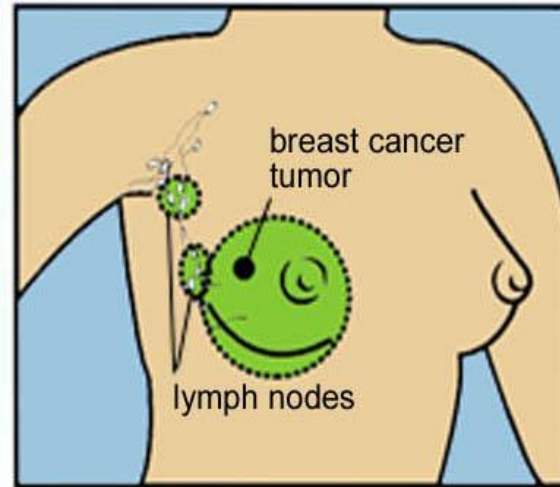


Limiting Local Therapy

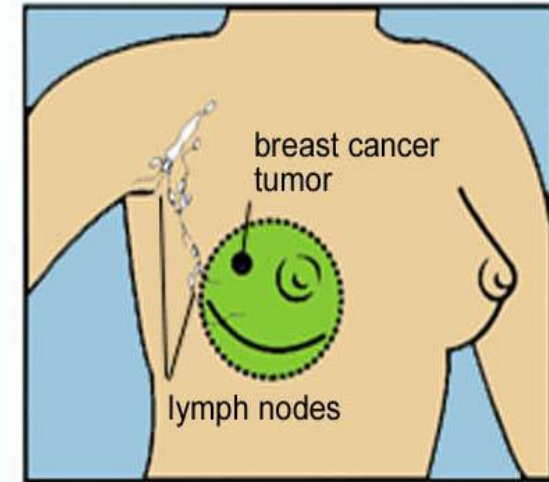
RADICAL MASTECTOMY



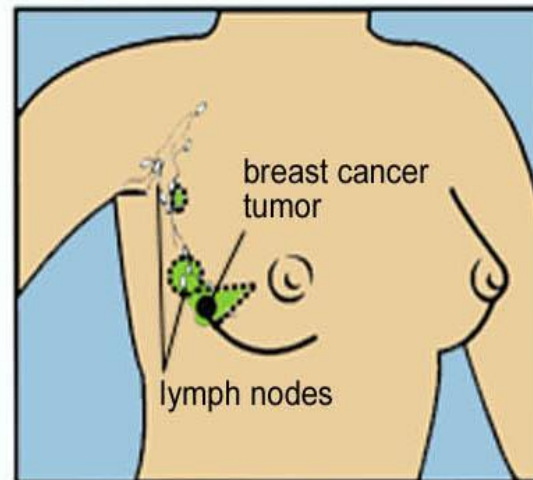
MODIFIED RADICAL MASTECTOMY



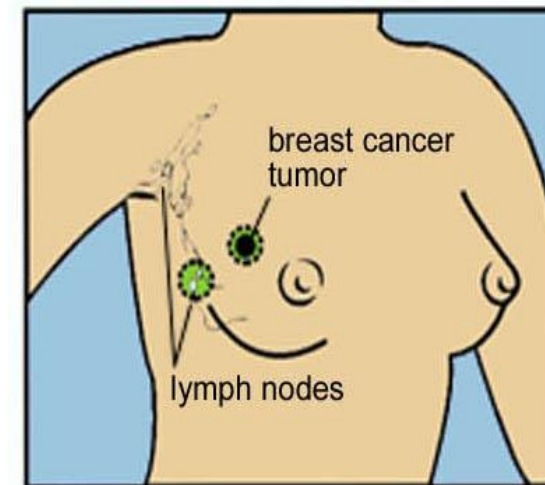
TOTAL MASTECTOMY



PARTIAL MASTECTOMY



LUMPECTOMY



- www.bhset.org

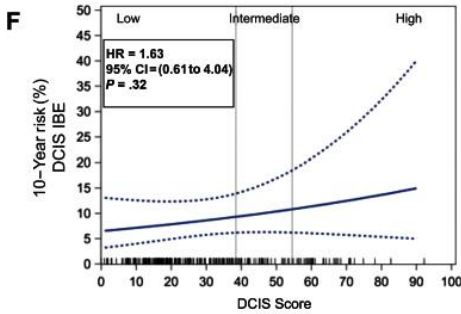
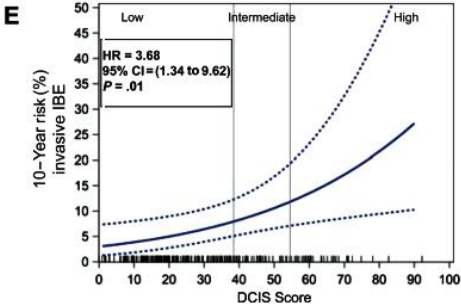
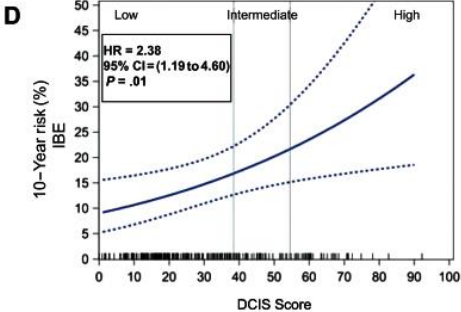
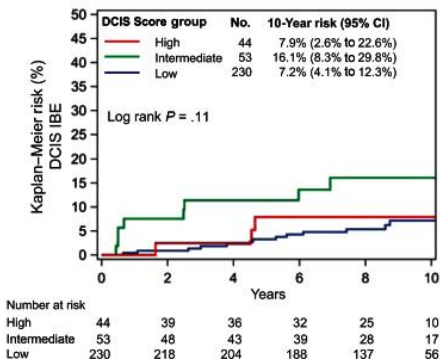
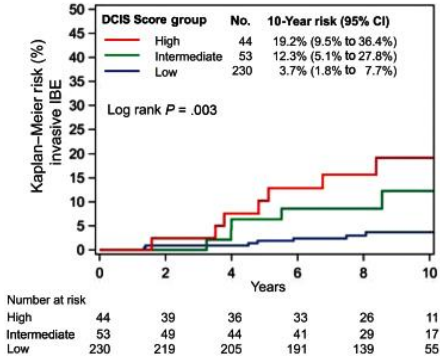
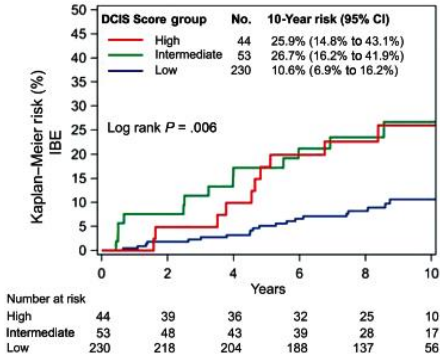
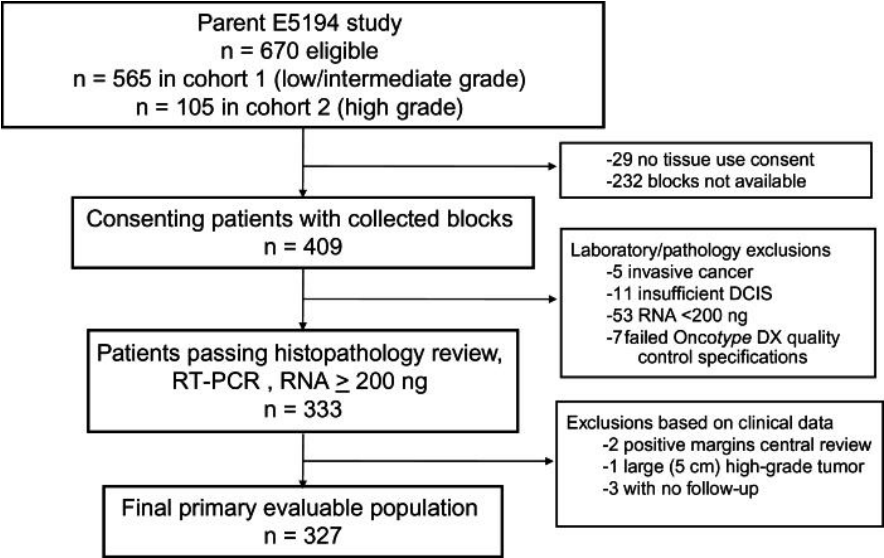
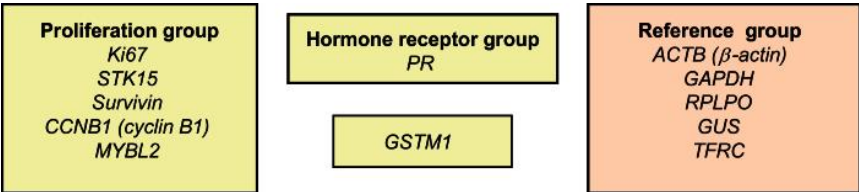


Directions in Tailored Local Therapy

- **Ability to omit axillary dissection for positive sentinel nodes**
- **Use of accelerated breast radiotherapy**
- **Omit radiotherapy after lumpectomy for older women with early stage HR-positive breast cancer receiving endocrine therapy (Hughes et al, JCO, 2013)**
- **Omit radiotherapy for certain DCIS**



Use of a DCIS Score to Predict Invasive Recurrence with Lumpectomy Alone for DCIS—E5194



Solin et al JNCI, 2013

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Randomized Trials of 10 vs 5 Years of Adjuvant Tamoxifen

Trial	Patient Number
ECOG, Scottish, NSABP B-14	1588
ATLAS	11646
aTTom	6953
Total	20187

ATLAS, Lancet, 2013 aTTom, ASCO, 2013

Outcomes in ATLAS and aTTom Trials of 10 vs 5 years of Tamoxifen

	Breast Cancer Mortality	Overall Survival
Years 5-9	0.97 (0.84-1.15)	0.99 (0.89-1.10)
Years 10+	0.75 (0.65-0.86)*	0.84 (0.77-0.93)*
All years	0.85 (0.77-0.94)*	0.91 (0.84-0.97)*

* P < 0.05 favoring 10 years



Summary of Reported Adjuvant Aromatase Inhibitor Trials

Trial	Time Since Random Assignment											
	-5	-4	-3	-2	-1	0	1	2	3	4	5	
Primary Adjuvant												
ATAC¹¹ 60-month strategy; median follow-up 100 mos Postmenopausal, HR (+)												→ TAM → ANA → TAM + ANA
BIG 1-98⁹ 60-month strategy Median follow-up 76 mos (monotx), 71 mos (switching) Postmenopausal, HR (+)												→ LET → TAM → LET (2 yrs), TAM (3 yrs) → TAM (2 yrs), LET (3 yrs)
ABCSG-12²² 36 month strategy Median follow-up 47.8 mos Premenopausal, ER and/ or PR (+)												→ TAM + GOS → ANA + GOS → TAM + GOS + ZOL → ANA + GOS + ZOL
Sequencing												
ABCSG-8⁵⁹ Primary random assignment 60 month strategy; median follow-up 72 mos Postmenopausal, ER(+)/PR(+), no chemo												→ TAM → TAM (2 yrs), ANA (3 yrs)
ITA¹¹² Randomly assigned to 2-3 yrs tx (5 yrs total) Median follow-up 64 mos Postmenopausal, ER(+), Node (+)					TAM (2-3 yrs) →							→ TAM → ANA
TEAM³¹ Primary random assignment 60 month strategy; Follow-up 61 mos Postmenopausal, ER and/or PR (+)												→ TAM (2½ yrs), EXE (2½ yrs) → EXE
IES¹¹³ Randomly assigned to 2-3 yrs tx (5 yrs total) Median follow-up 55.7 mos Postmenopausal, ER(+) or unknown					TAM (2-3 yrs) →							→ TAM → EXE
NSAS BC-03⁹ Randomly assigned to 1-4 yrs tx (5 yrs total) Median follow-up 42 mos Postmenopausal					TAM (1-4 yrs) →							→ TAM → ANA
ARNO 95¹¹⁴ Randomly assigned to 3 yrs tx (5 yrs total) Median follow-up 30.1 mos Postmenopausal, hormone responsive					TAM (2 yrs) →							→ TAM → ANA
Extended Adjuvant												
MA.17¹¹⁵ 5 yrs of TAM, randomly assigned to 60 mos of tx Median follow-up 64 mos Postmenopausal, HR(+)					TAM →							→ LET → Placebo
ABCSG-6a¹¹⁶ 5 yrs TAM, randomly assigned to 36 mos of tx Median follow-up 62.3 mos Postmenopausal, endocrine responsive					TAM →							→ ANA → Placebo
NSABP B-33¹⁷ 5 yrs of TAM, randomly assigned to 60 mos of tx Median follow-up 30 mos Postmenopausal, ER or PR (+)					TAM →							→ EXE → Placebo

• **Absolute Gain in DFS at 3-6 Years**

Primary 2-4 %

Switch 3-5%

Extended 6%

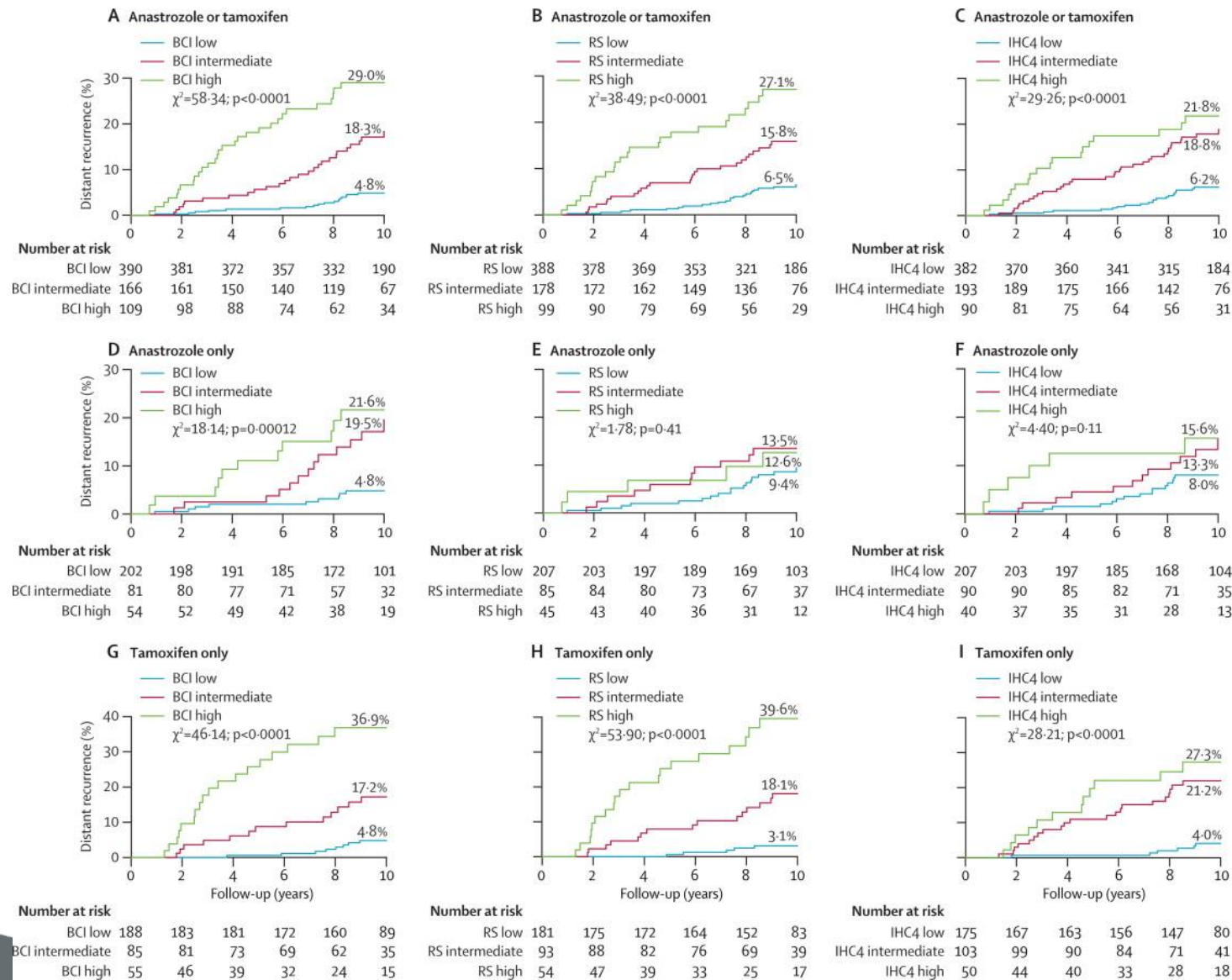
Burstein et al, J Clin Oncol, 2010

Challenges in Optimal Endocrine Therapy

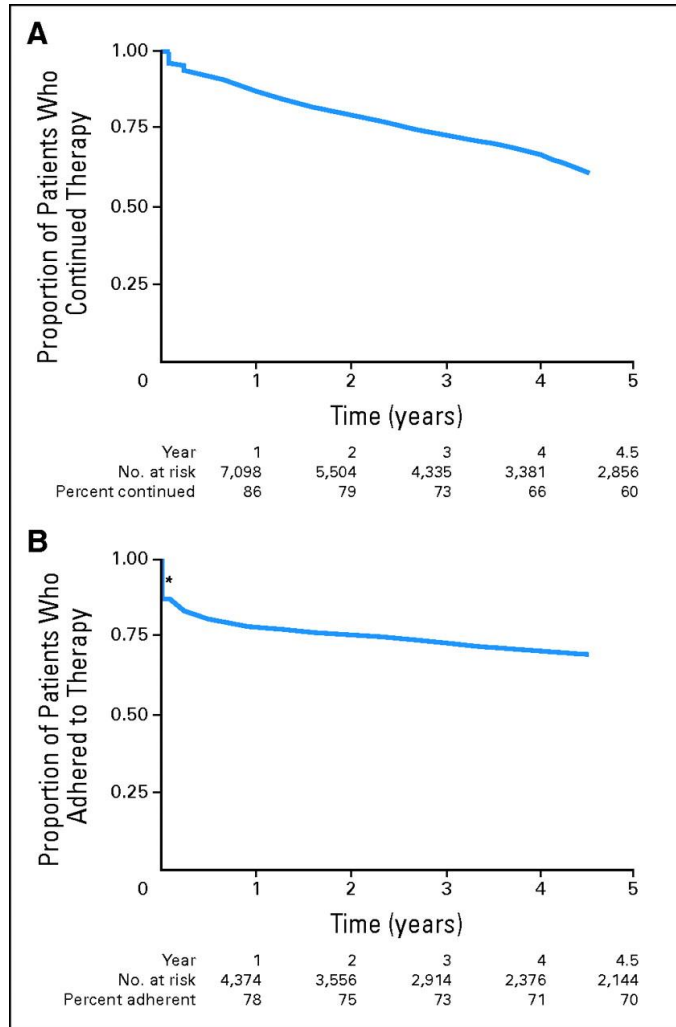
- **Selection, duration and sequence**
- **Predictive markers beyond ER, PR—Ki67?**
- **Reversal or prevention of endocrine resistance**
- **Compliance of patient and doctor**
- **Dissemination of endocrine prevention strategies for high risk women**



Use of BCI, Oncotype RS or IHC4 to Predict Early and Late Recurrence in TransATAC



Kaplan-Meier Curve for Continuation of Hormonal Therapy among 8,769 Patients

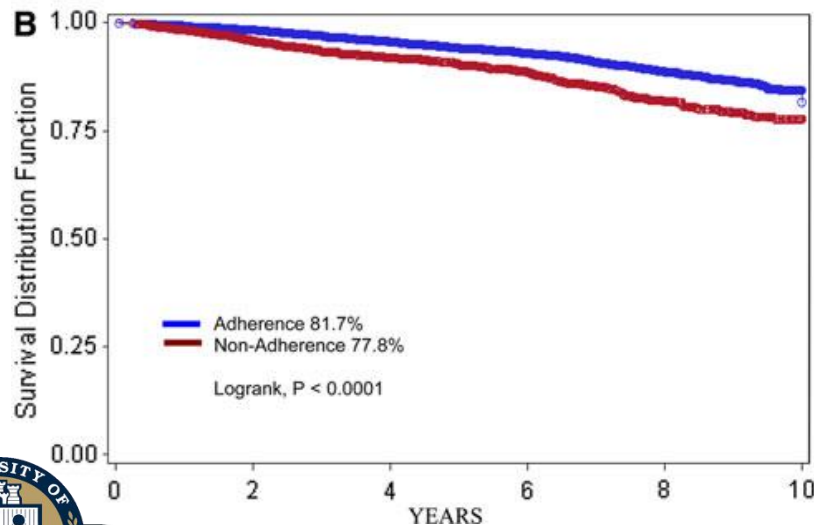
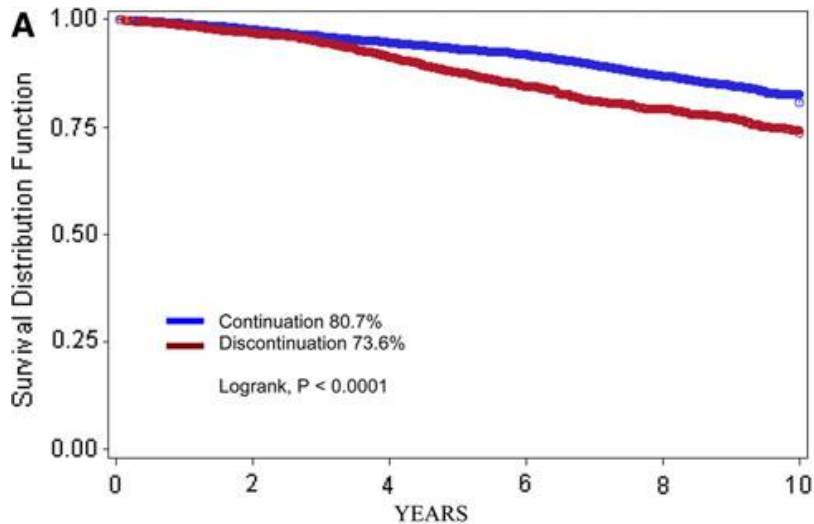


Over 4.5 years:

- 32% discontinued**
- 28% of those who continued were non-adherent**
- 49% took therapy for full duration at optimal schedule**



Increased Mortality with Early Endocrine Therapy Non-adherence and Discontinuation



Pt No	Adherence	HR
3214	<90%	1.04
1684	<80%	1.49*
659	<70%	1.84*
196	<60%	3.71*



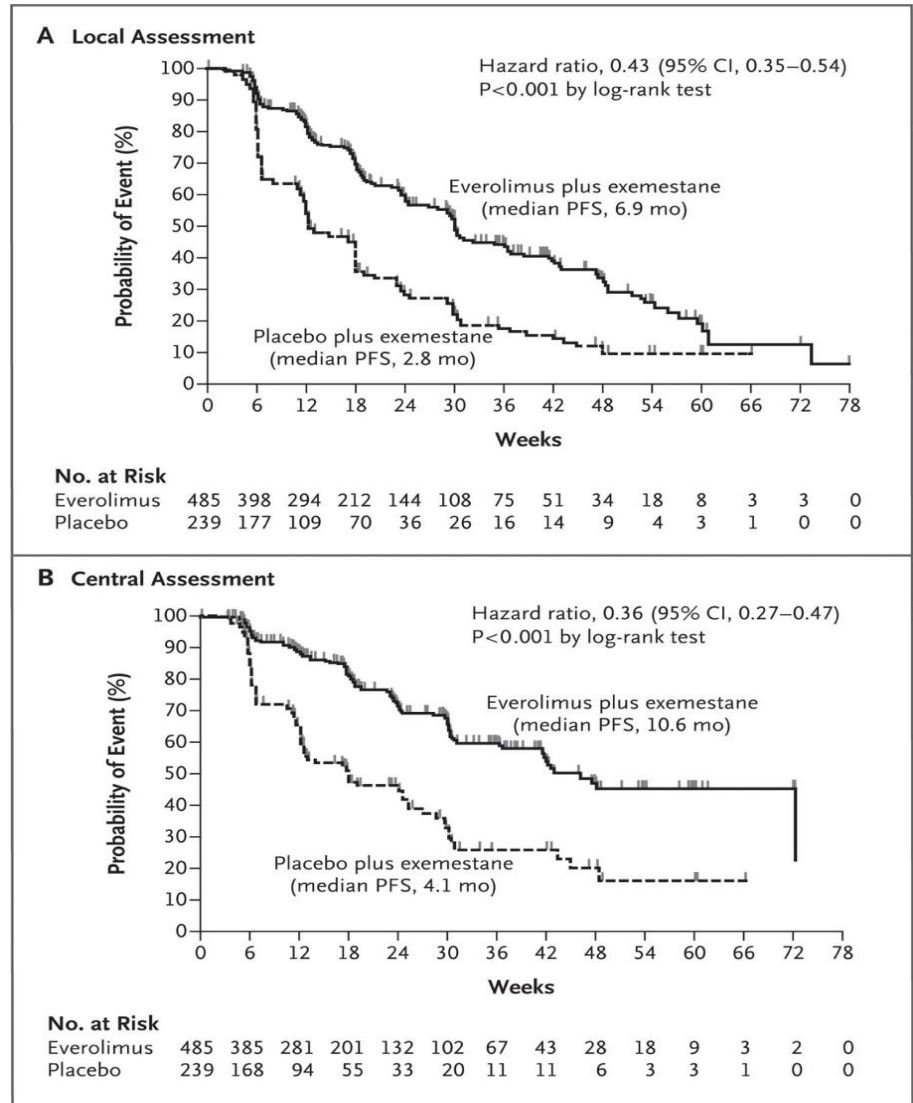
Hershman et al, BCRT, 2010

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Everolimus in Postmenopausal Hormone-Receptor-Positive Advanced Breast Cancer

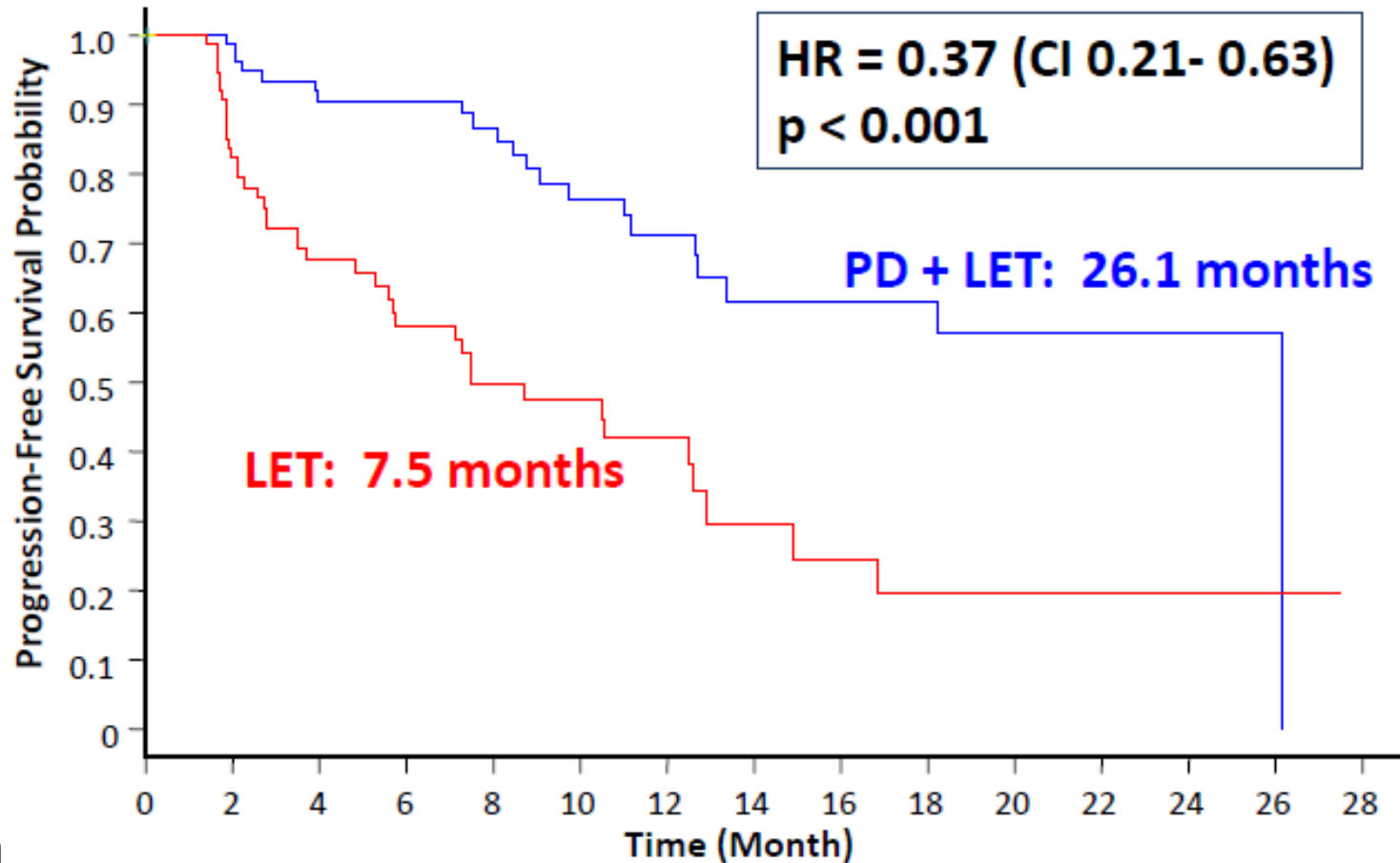
- Postmenopausal
- Advanced breast cancer
- ER+ HER2 -
- Refractory to letrozole or anastrozole
- End point=PFS
- 2:1 randomization

Baselga et al, N Engl J Med, 2012



Use of a CDK4/6 Inhibitor

PD 0332991 + Letrozole Progression Free Survival

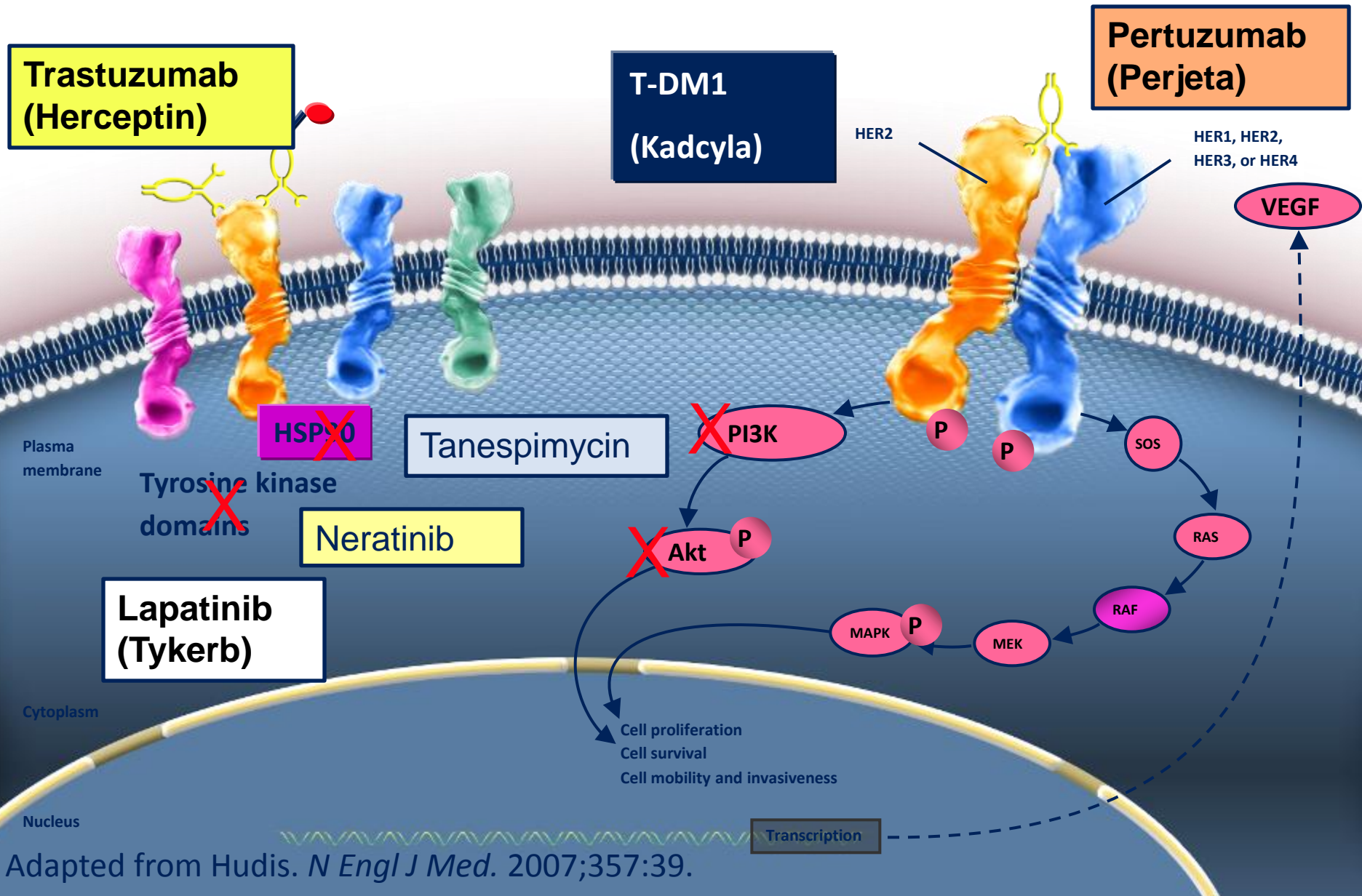


Topics for Today

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- **Other systemic approaches**



Strategies for Targeting HER2



Adapted from Hudis. *N Engl J Med.* 2007;357:39.

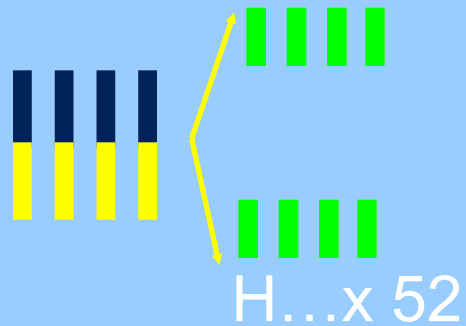
Rationale for Adjuvant Trastuzumab Trials

- **Some breast cancers overexpress HER2**
- **Trastuzumab alone or with chemotherapy provides effective palliation in metastatic disease with HER2-overexpression**
- **Cardiac toxicity is seen with trastuzumab, especially with anthracycline**

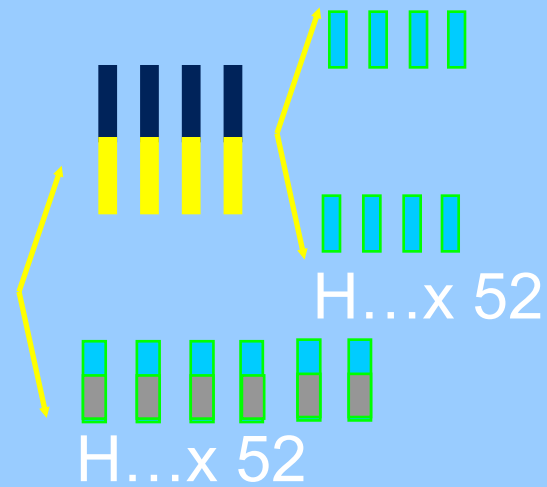


Adjuvant Trastuzumab Trials

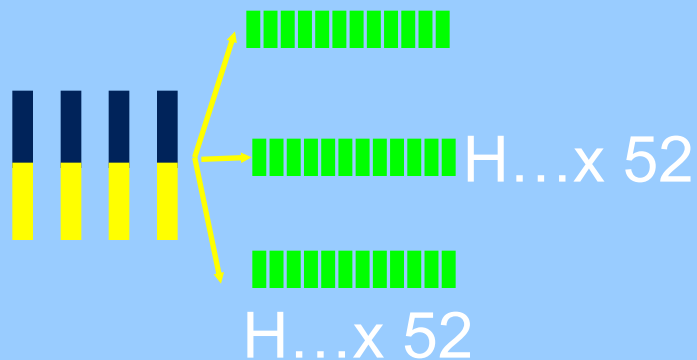
NSABP B-31



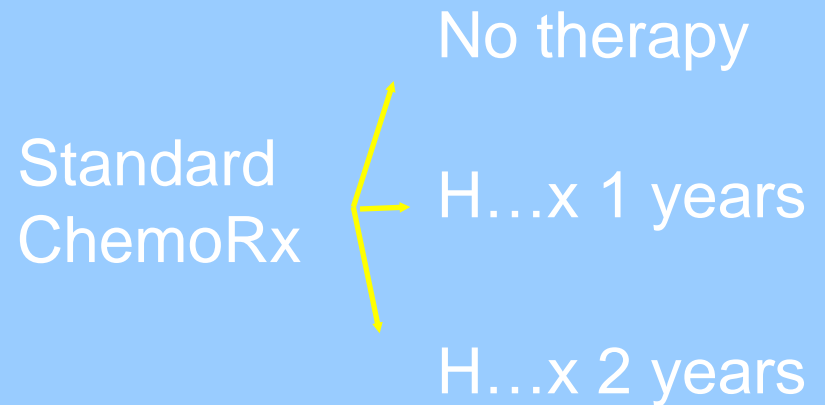
BCIRG 006



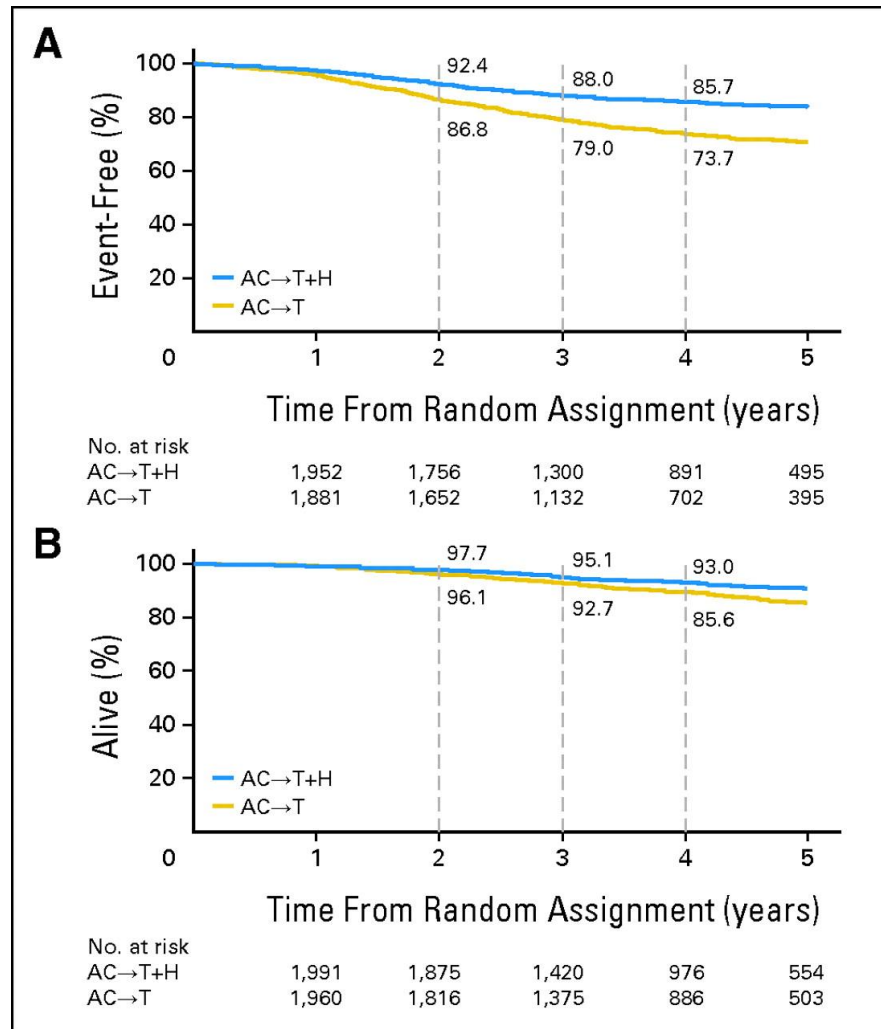
NCCTG 9831



HERA



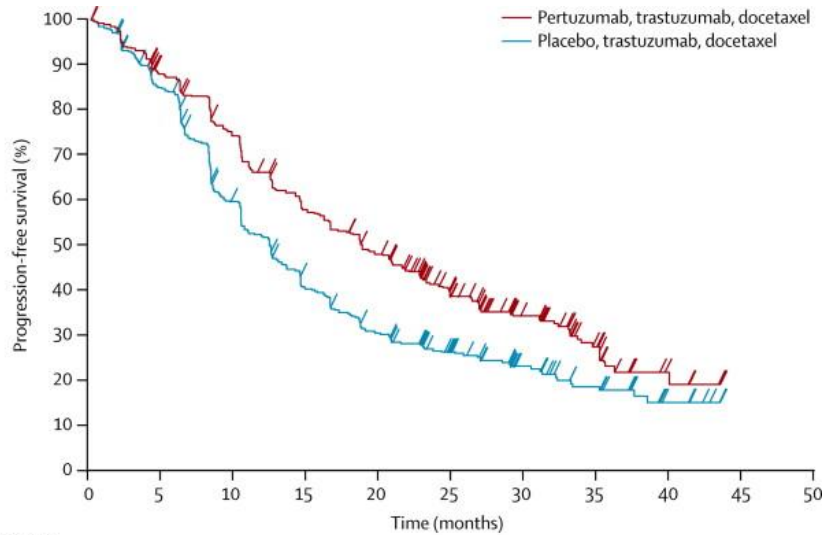
Adjuvant Trastuzumab Therapy--N9831 and B-31



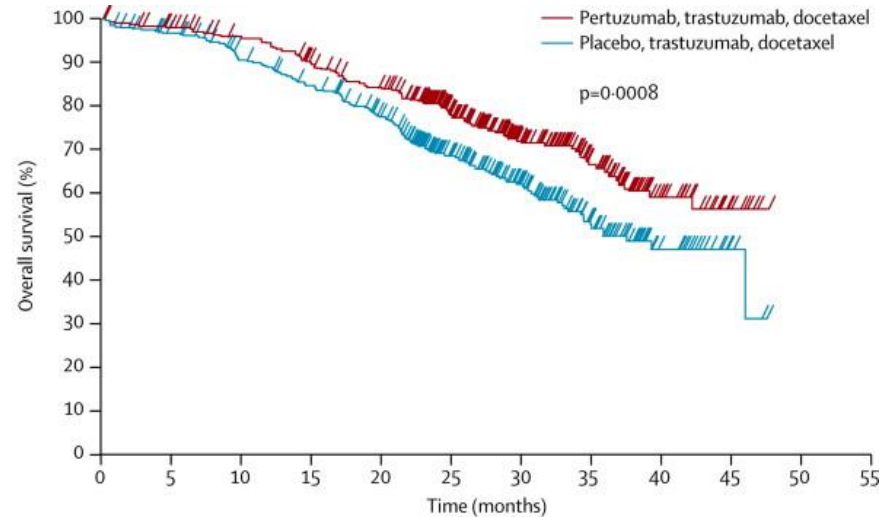
- Improved EFS and overall survival
- No clear markers of response
- Acceptable toxicity



Improved PFS and Overall Survival with Addition of Pertuzumab to Trastuzumab for Stage IV Breast Cancer—Cleopatra Trial



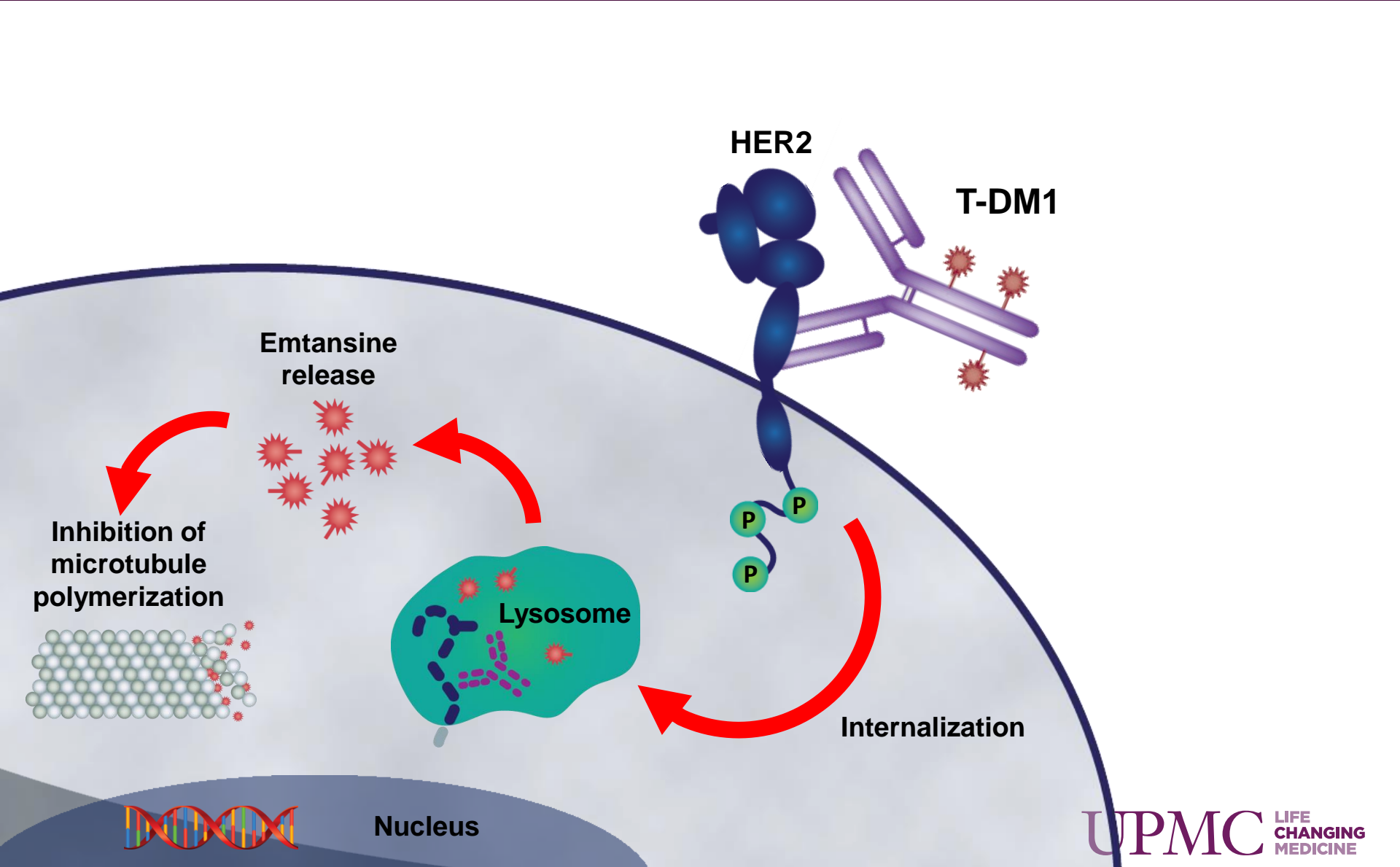
Number at risk	0	5	10	15	20	25	30	35	40	45	50
Pertuzumab	402	341	284	218	178	108	67	34	8	0	0
Placebo	406	329	223	148	110	72	42	26	8	0	0



Number at risk	0	5	10	15	20	25	30	35	40	45	50	55
Pertuzumab	402	387	371	342	317	230	143	84	33	9	0	0
Placebo	406	383	350	324	285	198	128	67	22	4	0	0

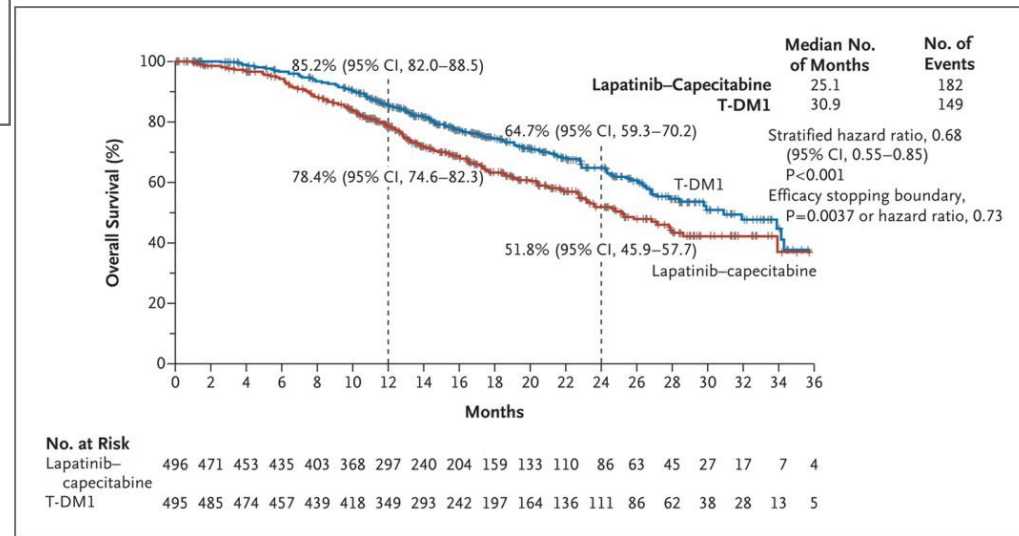
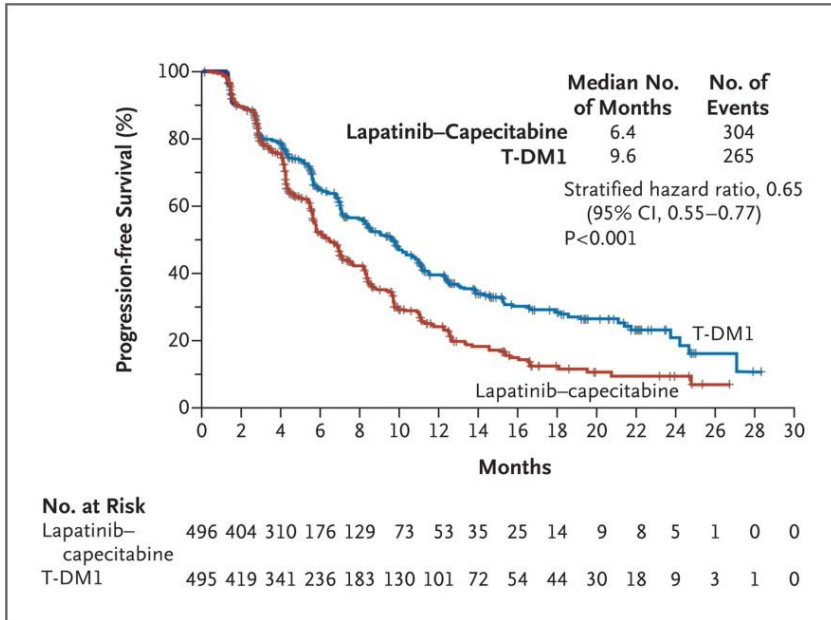
Swain et al, Lancet Oncol, 2013

Mechanism of Action of T-DM1



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

Improved PFS and OS for Stage IV with T-DM1



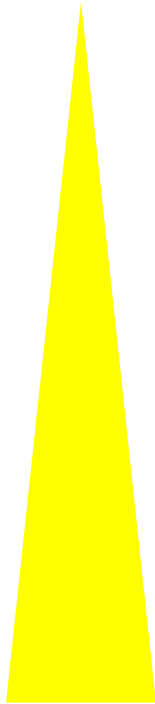
Verma et al, N Engl J Med, 2013



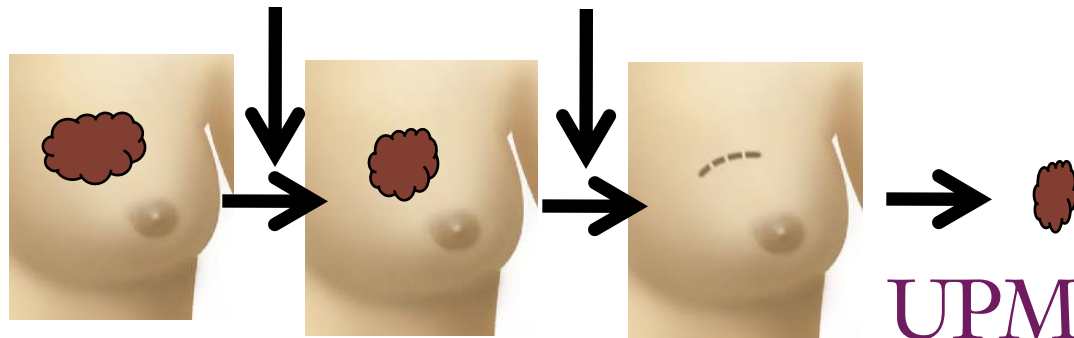
Neoadjuvant Therapy with Anti HER Agents

- Using pCR as endpoint:
- Lapatinib
- Pertuzumab
- Trastuzumab
- Lapatinib + trastuzumab
- Trastuzumab + pertuzumab

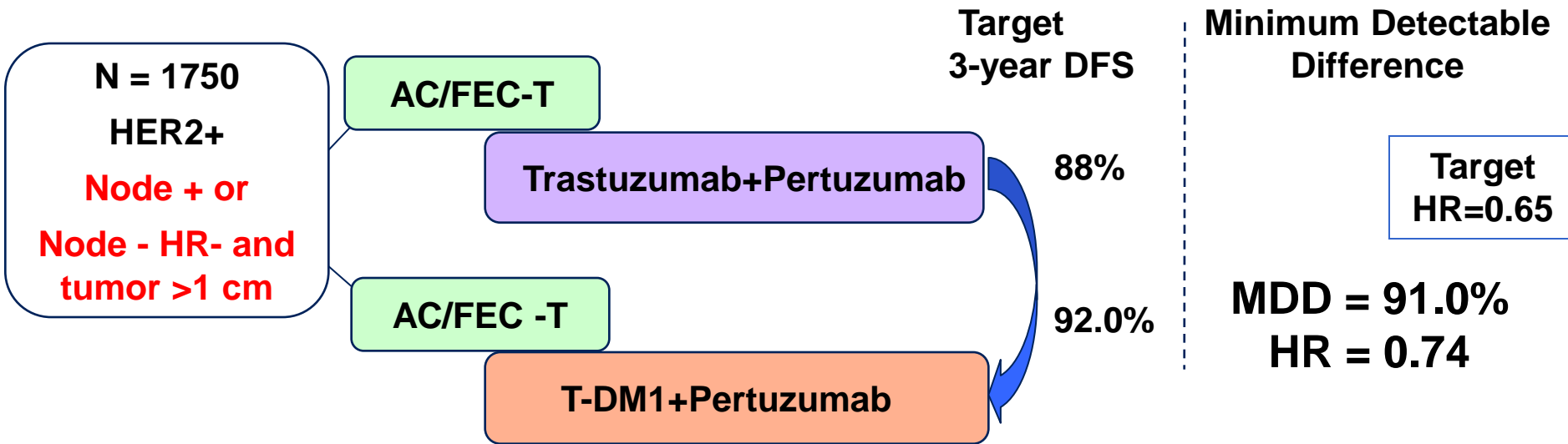
Lowest pCR



Highest pCR



Anticipated Result of Adjuvant anti-HER-2 Trials



**Stratify by Region,
Nodal status, HR status**

Primary endpoint: IDFS

Secondary endpoints: DFS, DRFI, OS

17 months to enroll; 54 months to data

Alpha = 0.05; 80% power; 171 events

400 sites; 14 months ramp up to 190 pt/m peak; average 0.26 p/s/m

AC: adriamycin/cyclophosphamide; FEC: 5FU/epirubicin/cyclophosphamide; T: docetaxel Q3W or paclitaxel QW;
MDD: Minimal Detectable Difference

Challenges in Optimal HER-2 Therapy

- **Needed for all patients with HER-2 expressing tumors?**
- **Value in breast cancer with normal HER-2 expression**
- **Selection, duration and sequence of anti-HER agents**
- **Predictive markers beyond HER-2**
- **Combinations with other therapies—need for chemotherapy?**
- **Brain as a sanctuary site**



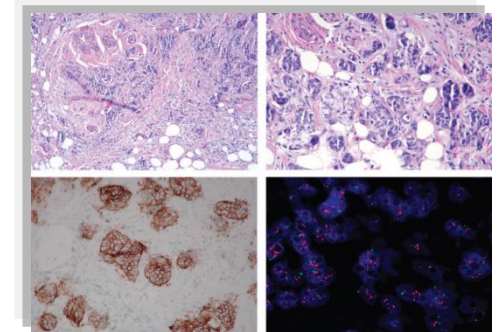
Importance of Accurate Testing ASCO-CAP Guidelines

ER and PR testing

- Up to 20% inaccuracy
- Determine on all invasive and recurrent cancers
- Positive if at least 1% positive tumor nuclei

HER-2 testing

- Up to 20% inaccuracy
- Determine on all invasive cancers
- Positive if 3+ IHC or positive FISH



Wolff et al, J Clin Oncol, 2007

Hammond et al, J Clin Oncol, 2010



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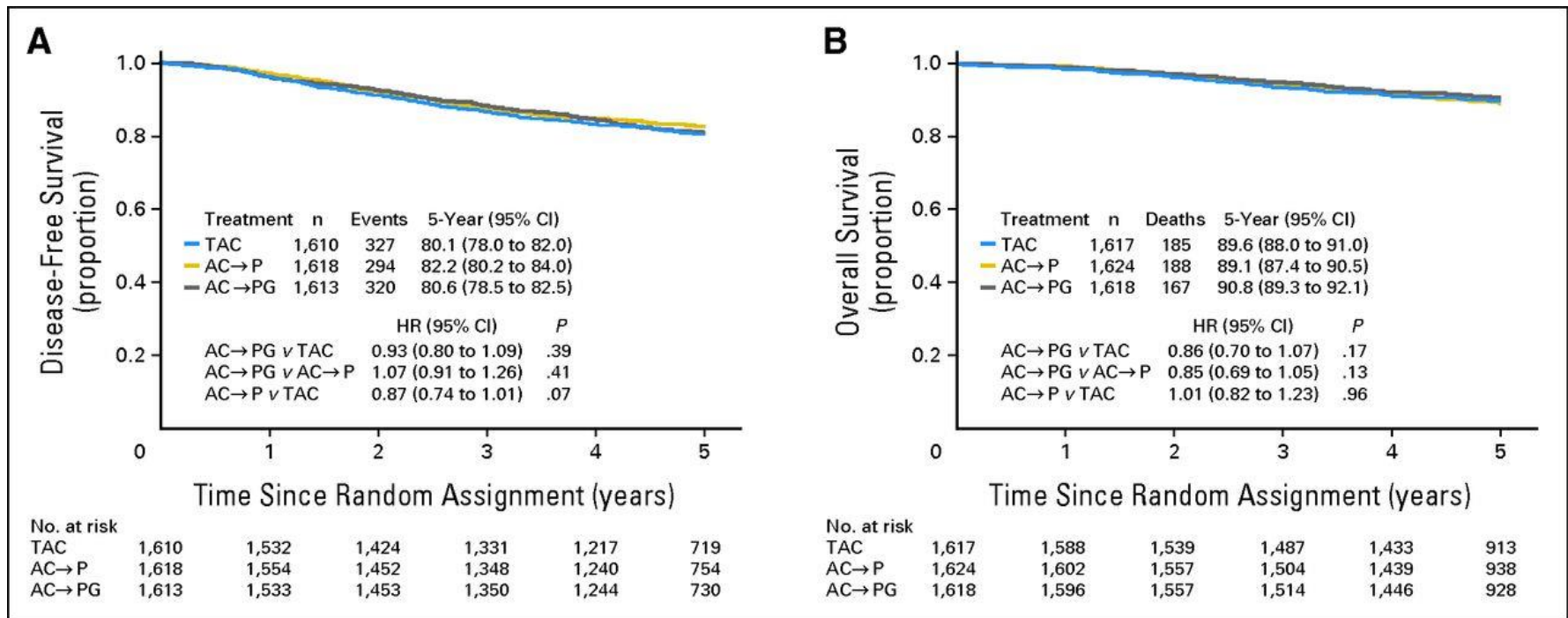
Many Active Chemotherapy Agents

- **Cyclophosphamide**
- **Doxorubicin**
- **Epirubicin**
- **Liposomal doxorubicin**
- **5-fluorouracil**
- **Methotrexate**
- **Paclitaxel**
- **Albumin-bound paclitaxel**
- **Docetaxel**
- **Navelbine**
- **Vinblastine**
- **Eribulin**
- **Ixabepilone**
- **Mitoxantrone**
- **Capecitabine**
- **Gemcitabine**
- **Carboplatin**
- **And more coming...**



NSABP B38—Last of the Large Adjuvant Chemotherapy Trials?

4800 women—5 years—No difference!



Swain et al, J Clin Oncol, 2013



Potential Approaches to Micrometastatic Disease

Molecular Target

- Osteoclasts
- Metastasis suppressor genes
- VEGF/angiogenesis
- NFkB/inflammation
- T cells/immunity
- Cancer stem cells

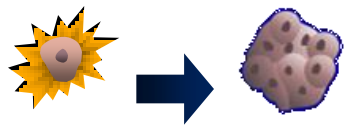
Antimetastatic Drugs

- Bisphosphonates, RANKLi
- Medroxyprogesterone acetate (MPA)
- Bevacizumab
- NFkB inhibitors
- Anti-T_{reg} Rx, CTLA-4 blockade, anti-PD1
- Hedgehog, Wnt, Notch inhibitors

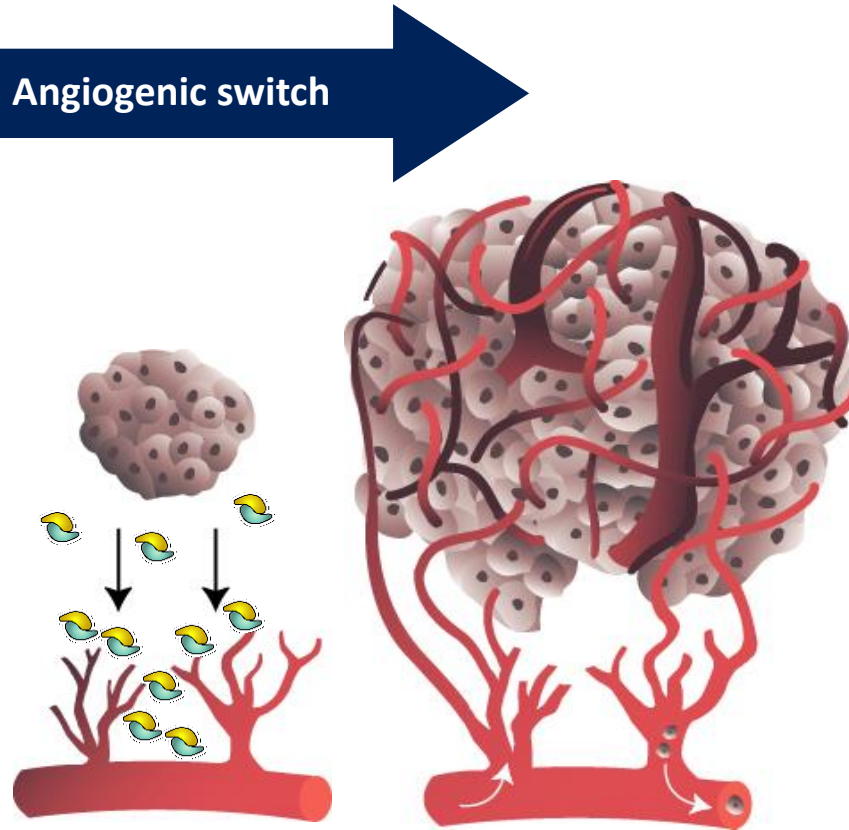
The Angiogenic Switch Is Necessary for Tumor Growth and Metastasis

Tumor is dormant

Angiogenic switch



Small avascular tumor



Tumor secretion of angiogenic factors stimulates angiogenesis

Rapid tumor growth and metastasis

Initiation

Proliferation

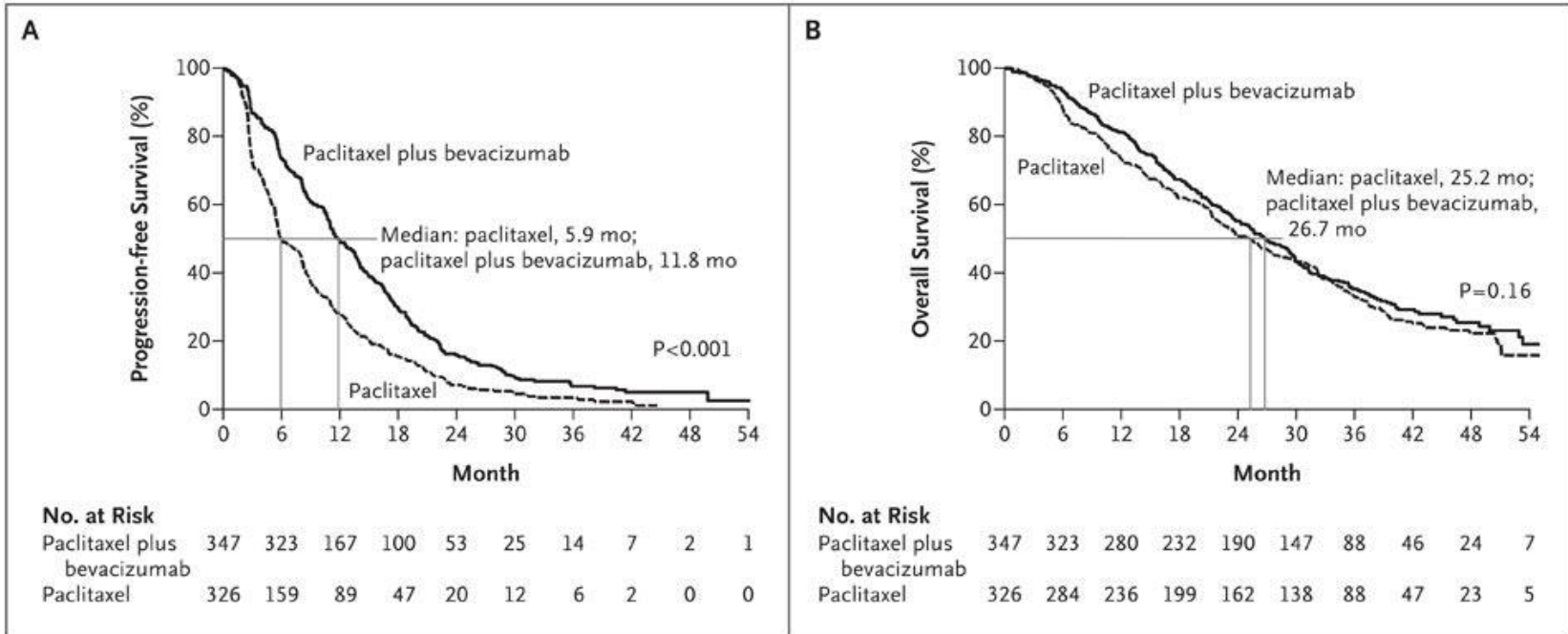
Maturation

Neovascularization

- Makes rapid tumor growth possible by supplying oxygen and nutrients and removing waste
- Facilitates metastasis

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Pivotal Trial of Chemotherapy +/- Bevacizumab for Advanced Breast Cancer



PFS

Survival

Miller et al, N Engl J Med, 2007



The Paradox of Bevacizumab

- Prolongs PFS but not overall survival in stage IV disease
- Improves pCR with neoadjuvant chemo
- Seeking evidence of efficacy in adjuvant setting (one negative trial in triple negative breast cancer so far)
- No identified tumor or host markers of response to date
- Clear activity in other types of cancer
- Value of other anti-angiogenesis inhibitors?
- A focal point for dialogue about meaningful endpoints and cost



Rationale for Adjuvant Bisphosphonate Trials

- **Bone is a common site of breast cancer recurrence**
- **Bisphosphonate use with standard chemotherapy or endocrine therapy reduces skeletal morbidity in advanced breast cancer (ASCO Guidelines)**
- **Preclinical studies suggest potential direct antitumor effects**



Some Adjuvant Bisphosphonate Trials

•(BIG 1-04)

•AZURE

•N = 3349

Zoledronate x 5y
vs nil
Stage II

Clodronate x 3y
vs placebo
Stage I/II

NSABP
-B34

•N = 3323

Other important
first generation
bisphosphonate
trials
in early BC
(any HR,
any menop status)

•GAIN

•N = 3000

Ibandronate PO
x 2y vs nil
Stage II

Zoledronate x 5y
vs nil
Stage II

NaTan

N = 543



•From M Piccart

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Some Adjuvant Bisphosphonate Trials

•(BIG 1-04)

•AZURE

•N = 3349



Other important first generation bisphosphonate

NSABP
-B34

•N = 3323

•Hypothesis--Useful in an environment of estrogen deprivation?

•GA

•N = 3000

Stage II

Stage II

Tan

543



•From M Piccart

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- **A plea for prevention**
- **Tailoring local therapy**
- **Hormone-responsive breast cancer**
- **HER-2 positive breast cancer**
- **Other systemic approaches**



Potential Approaches to Micrometastatic Disease

Molecular Target

- Osteoclasts
- Metastasis suppressor genes
- VEGF/angiogenesis
- NFkB/inflammation
- T cells/immunity
- Cancer stem cells

Antimetastatic Drugs

- Bisphosphonates, RANKLi
- Medroxyprogesterone acetate (MPA)
- Bevacizumab
- NFkB inhibitors
- Anti-T_{reg} Rx, CTLA-4 blockade, anti-PD1
- Hedgehog, Wnt, Notch inhibitors

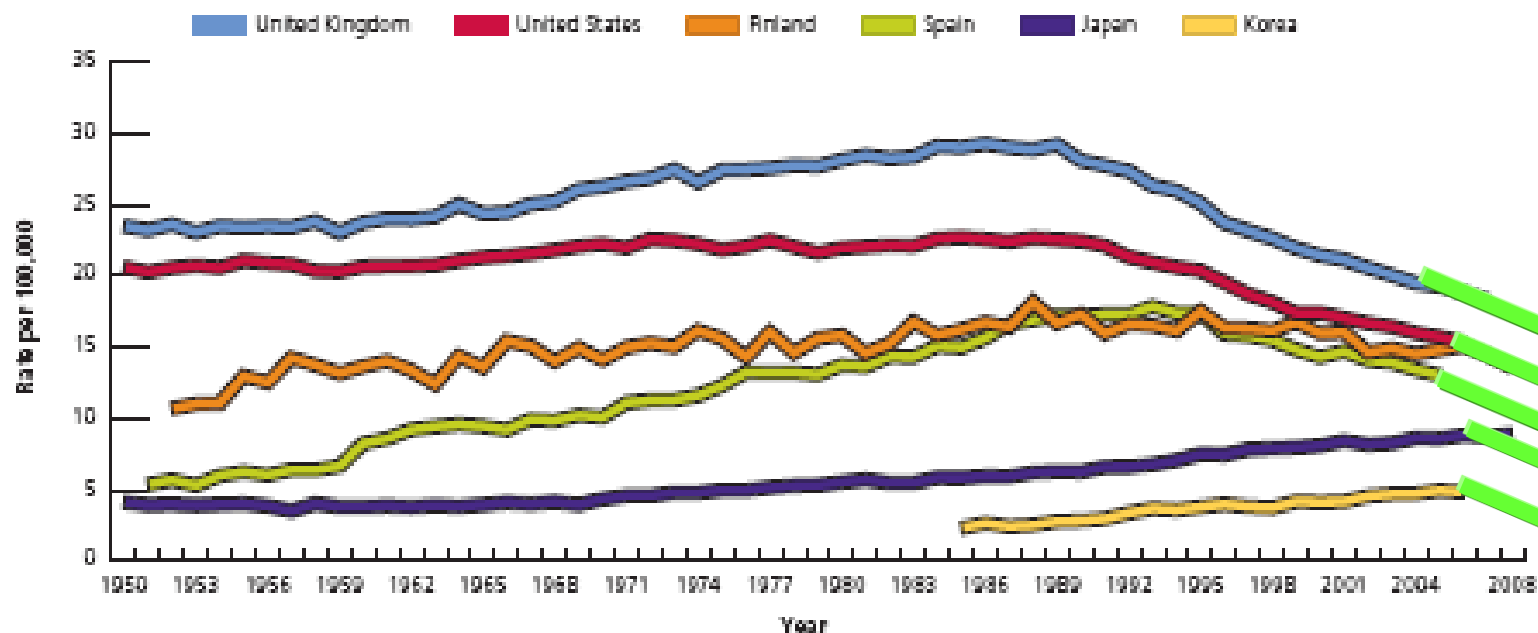


Challenges for the Development of Biologics

- **How to make trials faster, smaller, and less expensive**
 - **Novel trial designs**
 - **How to define success--endpoints**
 - **Refined regulatory environment—
FDA's acceptance of pCR as
endpoint for accelerated approval in
breast cancer**
 - **Enrichment for the target population
(if you really know the target!)**

Changing Landscape of Breast Cancer

Figure 5. Trends in Age-standardized Female Breast Cancer Death Rates in Select Countries



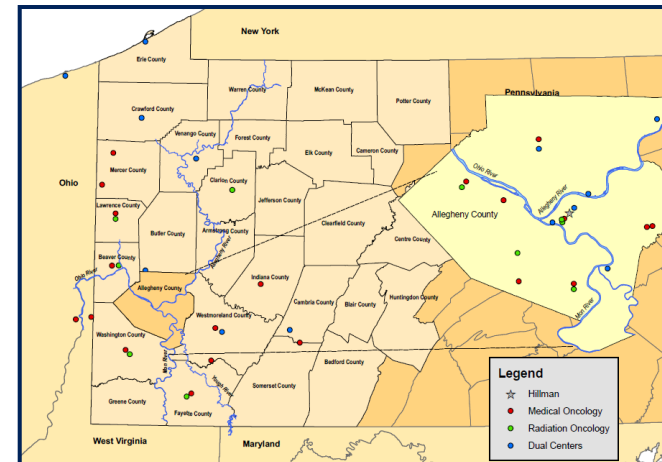
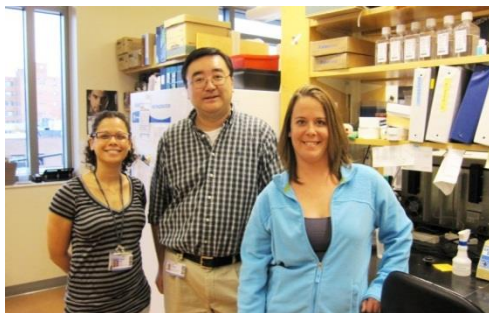
Source: WHO Mortality Database.



www.cancer.org

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Thanks to So Many....



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