# Living Beyond Breast Cancer: Triple Negative Disease

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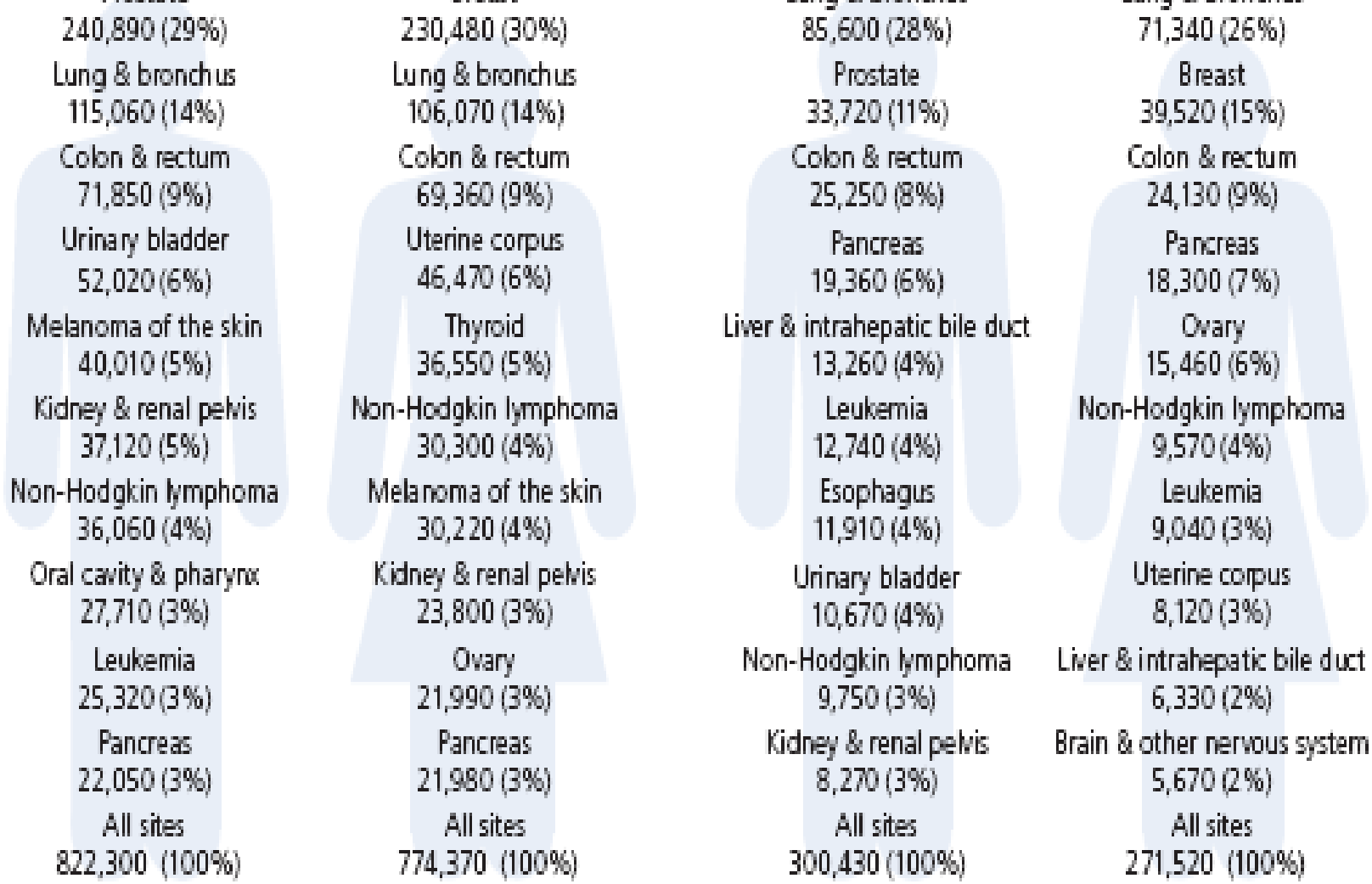
Cooper Cancer Institute
July 10th, 2012

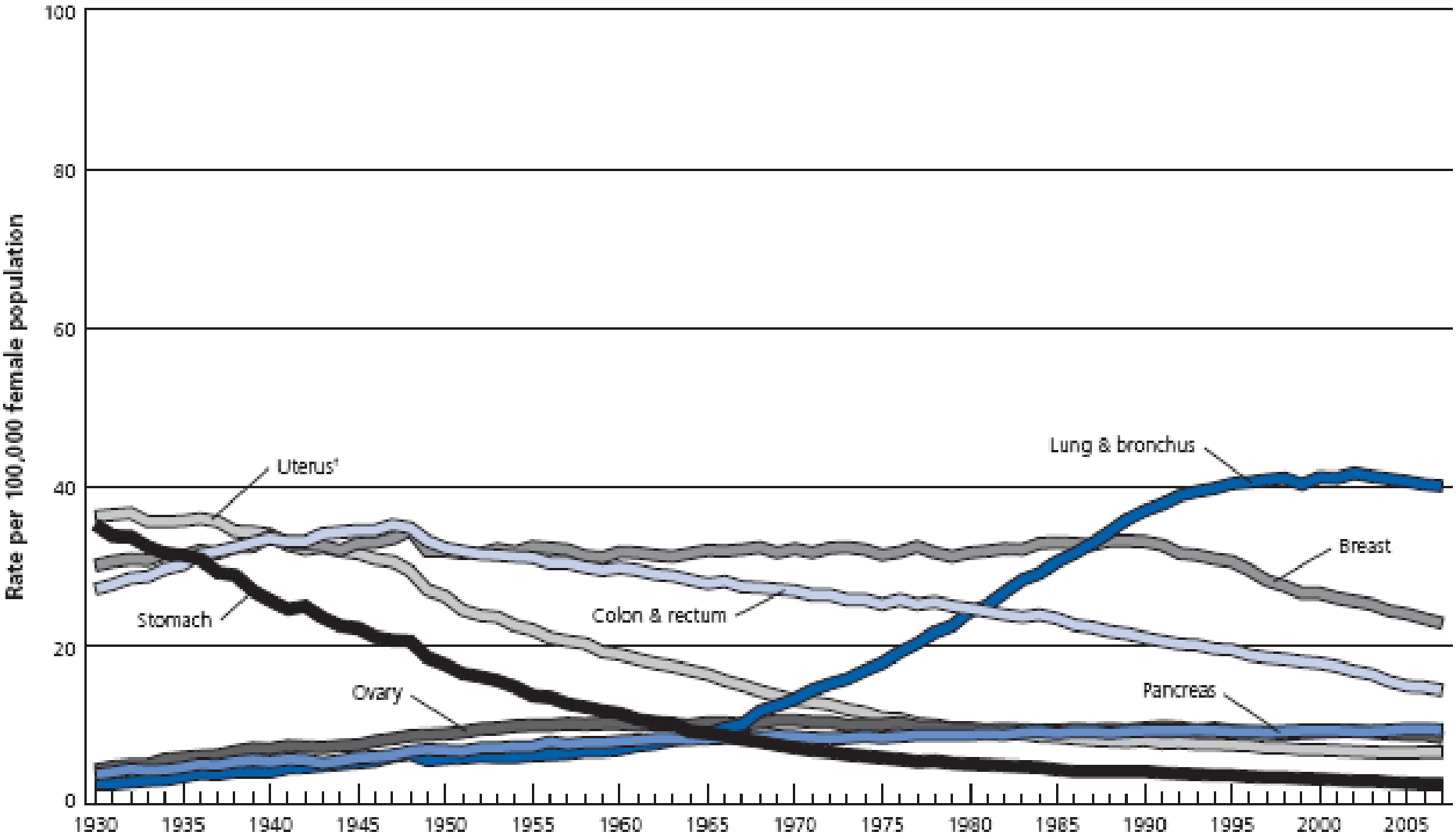
# Leading Sites of New Cancer Cases and Deaths – 2011 Estimates



| Estimated New Cases* | | Estimated Deaths | |
|---|---|---|---|
| Male | Female | Male | Female |
| Prostate<br>240,890 (29%) | Breast<br>230,480 (30%) | Lung & bronchus<br>85,600 (28%) | Lung & bronchus<br>71,340 (26%) |
| Lung & bronchus<br>115,060 (14%) | Lung & bronchus<br>106,070 (14%) | Prostate<br>33,720 (11%) | Breast<br>39,520 (15%) |
| Colon & rectum<br>71,850 (9%) | Colon & rectum<br>69,360 (9%) | Colon & rectum<br>25,250 (8%) | Colon & rectum<br>24,130 (9%) |
| Urinary bladder<br>52,020 (6%) | Uterine corpus<br>46,470 (6%) | Pancreas<br>19,360 (6%) | Pancreas<br>18,300 (7%) |
| Melanoma of the skin<br>40,010 (5%) | Thyroid<br>36,550 (5%) | Liver & intrahepatic bile duct<br>13,260 (4%) | Ovary<br>15,460 (6%) |
| Kidney & renal pelvis<br>37,120 (5%) | Non-Hodgkin lymphoma<br>30,300 (4%) | Leukemia<br>12,740 (4%) | Non-Hodgkin lymphoma<br>9,570 (4%) |
| Non-Hodgkin lymphoma<br>36,060 (4%) | Melanoma of the skin<br>30,220 (4%) | Esophagus<br>11,910 (4%) | Leukemia<br>9,040 (3%) |
| Oral cavity & pharynx<br>27,710 (3%) | Kidney & renal pelvis<br>23,800 (3%) | Urinary bladder<br>10,670 (4%) | Uterine corpus<br>8,120 (3%) |
| Leukemia<br>25,320 (3%) | Ovary<br>21,990 (3%) | Non-Hodgkin lymphoma<br>9,750 (3%) | Liver & intrahepatic bile duct<br>6,330 (2%) |
| Pancreas<br>22,050 (3%) | Pancreas<br>21,980 (3%) | Kidney & renal pelvis<br>8,270 (3%) | Brain & other nervous system<br>5,670 (2%) |
| All sites<br>822,300 (100%) | All sites<br>774,370 (100%) | All sites<br>300,430 (100%) | All sites<br>271,520 (100%) |

*Excludes basal and squamous cell skin cancers and in situ carcinoma except urinary bladder.

# Age-adjusted Cancer Death Rates,* Females by Site, US, 1930-2007



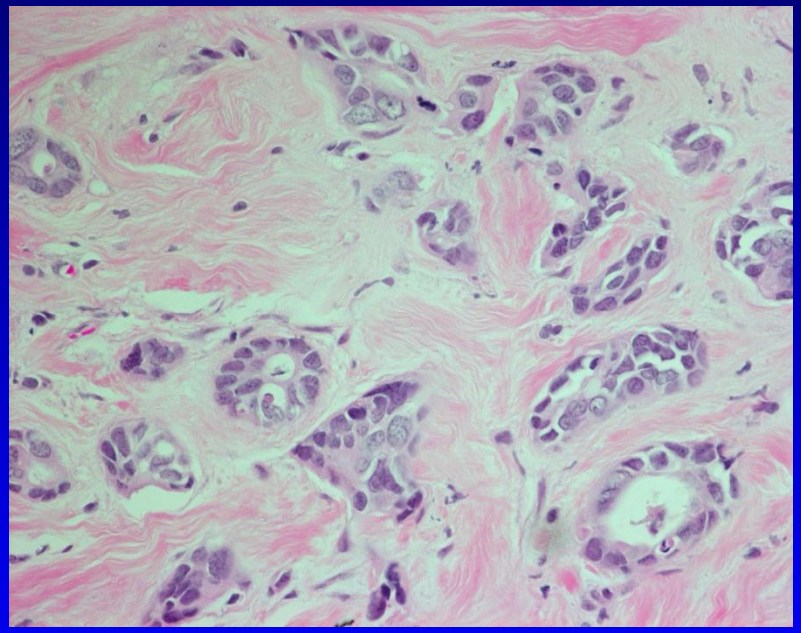

*Per 100,000, age adjusted to the 2000 US standard population.

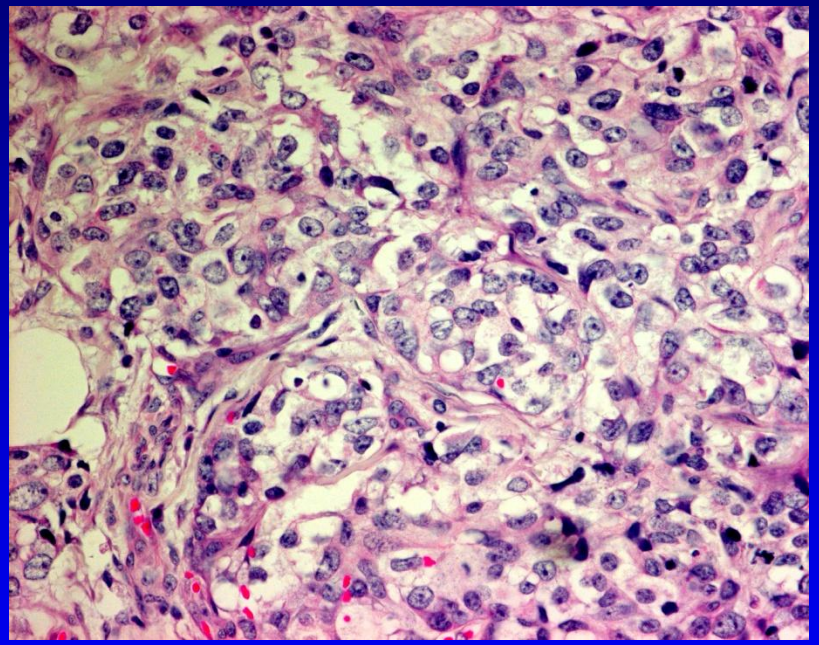
**Note:** Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the liver, lung and bronchus, and colon and rectum are affected by these changes.

**Source:** US Mortality Data, 1960 to 2007, US Mortality Volumes, 1930 to 1959, National Center for Health Statistics, Centers for Disease Control and Prevention.

**Breast cancers can look like this…**

**....or like this**





***Low grade, more benign appearing***

***High grade, aggressive appearing***

*Courtesy A. Harden, L. Dressler*

# Triple Negative Breast Cancer (TNBC)

- 'Triple negative': ER-negative, PR-negative, HER2-negative
  - Depending on thresholds used to define ER and PR positivity and methods for HER2 testing
- TNBC accounts for 10–17% of all breast carcinomas
- Significantly more aggressive than other molecular subtype tumors
- Higher relapse rate than other subtypes
- No specific targeted therapy

Reis-Filho JS, et al. *Histopathology* 2008;52:108-118.

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# Directed Therapy of Subtypes of Triple-Negative Breast Cancer

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**Key Words.** Triple-negative breast cancer • Chemotherapy • Epidermal growth factor receptor Vascular endothelial growth factor receptor • Antiangiogenesis • BRCA1 • Poly(ADP-ribose) polymerase Cetuximab • Bevacizumab • Olaparib • BSI-201

**Disclosures: Lisa A. Carey:** *Consultant/advisory role:* sanofi-aventis, BiPar, Wyeth, Pfizer, Genentech, Bristol-Myers Squibb, Novartis (all uncompensated); *Research funding/contracted research:* GlaxoSmithKline, Boehringer-Ingelheim, Genentech, Wyeth, Bristol-Myers Squibb (all uncompensated).

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## ABSTRACT

**In developed countries, there has been a remarkable improvement in mortality from breast cancer, but almost all of that benefit has occurred in the estrogen receptor $(ER)^+$ and human epidermal growth factor receptor $(HER)\text{-}2^+$ subsets. Triple-negative breast cancer, defined as tumors that are negative for ER, progesterone receptor, and HER-2, represent a minority of breast cancers. However, because of the poor prognosis in this particular subtype, triple-negative disease accounts for a disproportionate number of metastatic cases and breast cancer deaths. While chemotherapy is effective in triple-negative disease, research continues to better target therapies and predict prognosis. Recent studies have suggested a link between *BRCA* mutations and triple-negative disease, but the nature of this link remains opaque. Antiangiogenic agents such as bevacizumab have demonstrated efficacy across subtypes. More recently, poly(ADP-ribose) polymerase inhibitors appear to take advantage of the concept of synthetic lethality, or dual pathway inhibition, in attacking triple-negative and *BRCA*-associated tumors. These and other studies in triple-negative disease will help us to better identify effective treatment options and improve outcomes in these patients. This article addresses the nature of, and therapeutic strategies for, triple-negative breast cancer.**
***The Oncologist*** 2011;16(suppl 1):71–78

## INTRODUCTION

Triple-negative breast cancer, defined as tumors that are negative for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER)-2, represent a minority of breast cancers. However, because of the poor prognosis in this particular subtype, triple-negative disease accounts for a disproportionate number of metastatic cases and breast cancer deaths.

Like any other subtype of breast cancer, triple-negative disease generally presents as early breast cancer. A classic case is shown in Figure 1 of a stage II breast cancer patient with a baseline risk for recurrence of approximately 60%, based on tumor size and nodal status. In a hormone recep-

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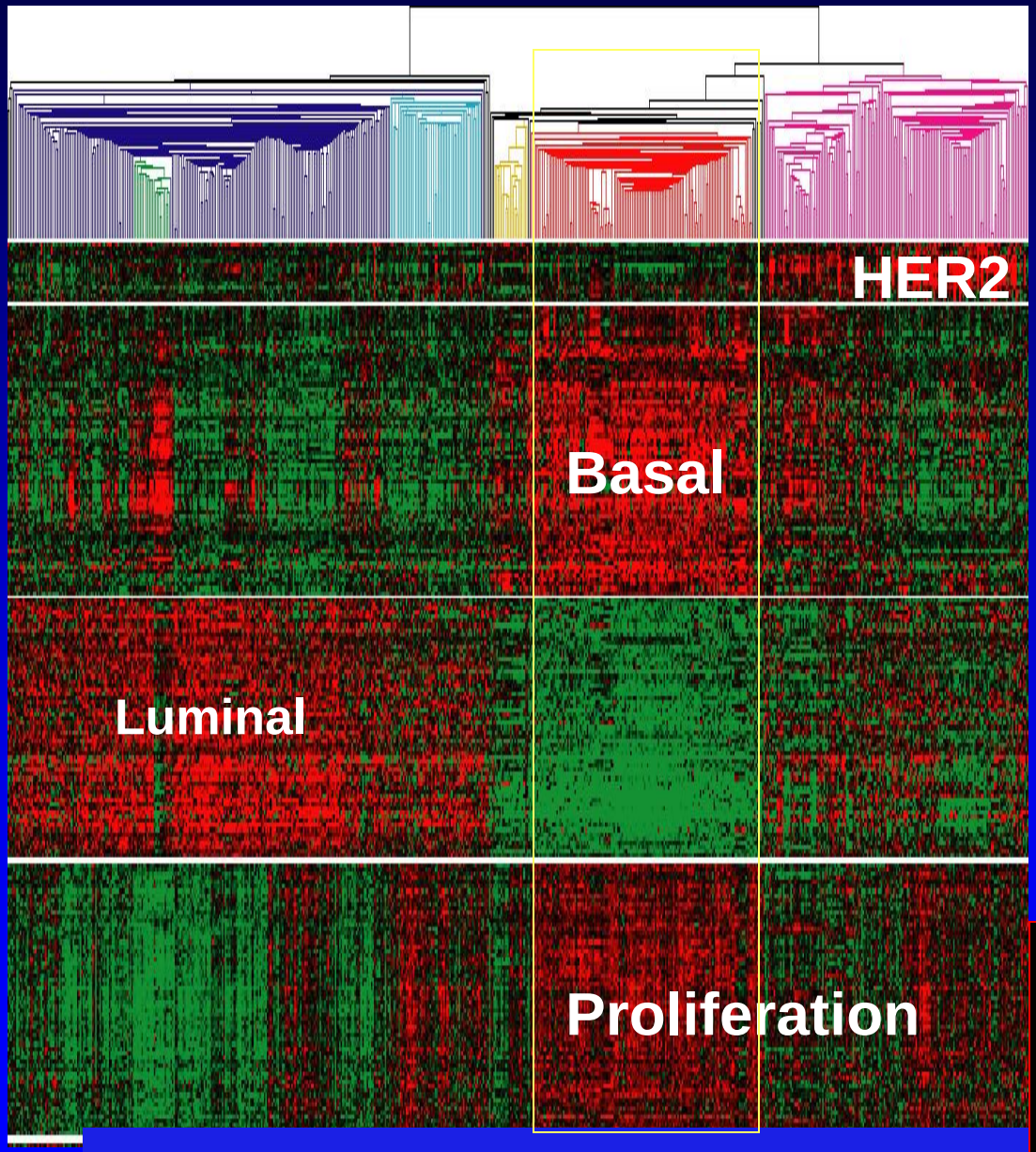
Reprinted from ***The Oncologist*** 2010;15(suppl 5):49–56.  1083-7159/2010/$30.00/0 doi: 10.1634/theoncologist.2011-S1-71

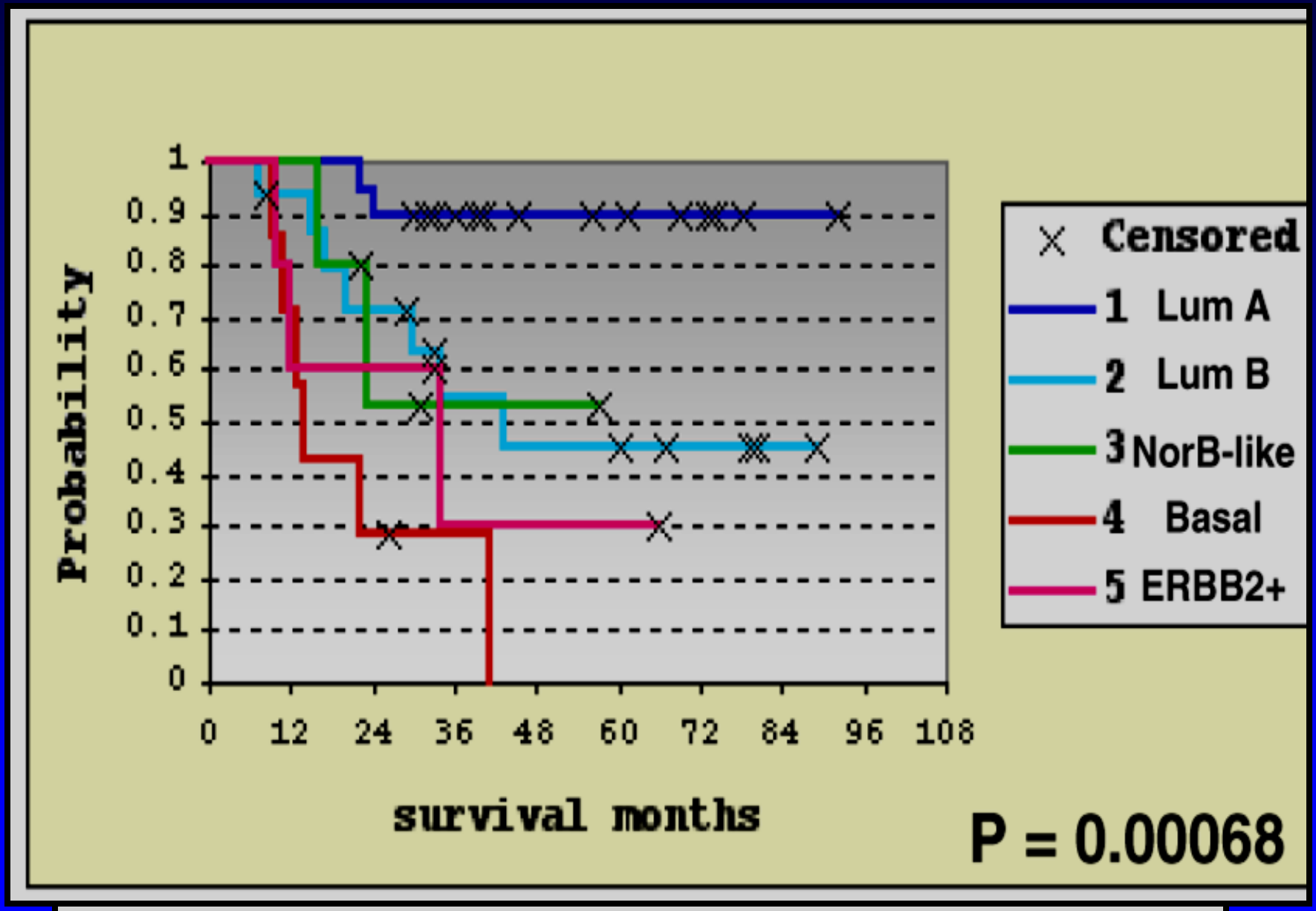
# Subtype Example: Basal-like Breast Cancer:




- Low HER2 cluster expression
- High basal cluster
  - EGFR
  - basal cytokeratins
  - others…
- Low ER (and related genes) cluster expression
- Very proliferative
- High degree of genomic instability

***Insensitive to conventional targeted therapies***

# Subtypes and Prognosis




*Sorlie T et al, PNAS 2001*

# Breast Cancer Biology in 2012: A Pragmatic View

| HER2 | ER: Positive | ER: Negative |
|---|---|---|
| Negative | **ENDO**<br>CHEMO | **CHEMO** |
| Positive | **CHEMO**<br>**TRAZ**<br>ENDO | **CHEMO**<br>**TRAZ** |

# Issues in Adjuvant Therapy: Side Effects of Long Term Therapy

- Herceptin for HER2+ (infusional x1 year)
  - LVEF decline ~ 10%, symptomatic in <5%
  - Unlike anthracyclines, probably partly reversible
  - Implications later (aging, other cardiac RF) unknown
- Tamoxifen for ER+ (5 years)
  - Hot flashes, uterine Ca (1/2000 overall, ~0.5-1% in selected pts), DVT/PE (4x baseline risk)
  - BUT improved bone health
- Aromatase inhibitors for ER+ postmenopausal (5 years)
  - Myalgia/arthralgias (most common reason to discontinue)
  - Osteoporosis acceleration
- Bisphosphonates – on trial (for now) 3-5 years
  - ONJ 0.7% maximum. May be ameliorated by oral Abx and washes.

# New drugs for breast cancer

**1980s**

- Anthracyclines
- CMF
- Tamoxifen

**1990s: metastatic**

- AIs (metastatic)
- Zoladex
- Zoledronate
- Taxanes (metastatic)
- Epirubicin
- Vinorelbine
- Gemcitabine
- Liposomal doxorubicin
- Capecitabine
- Dexrazoxane (cardiac toxicity)

**2000s: adjuvant**

- Anastrozole
- Letrozole
- Exemestane
- Fulvestrant
- Docetaxel
- Paclitaxel
- Epirubicin
- Nab paclitaxel
- Ixabepilone
- Trastuzumab
- Lapatinib
- Bevacizumab
- Pertuzumab
- Everolimus

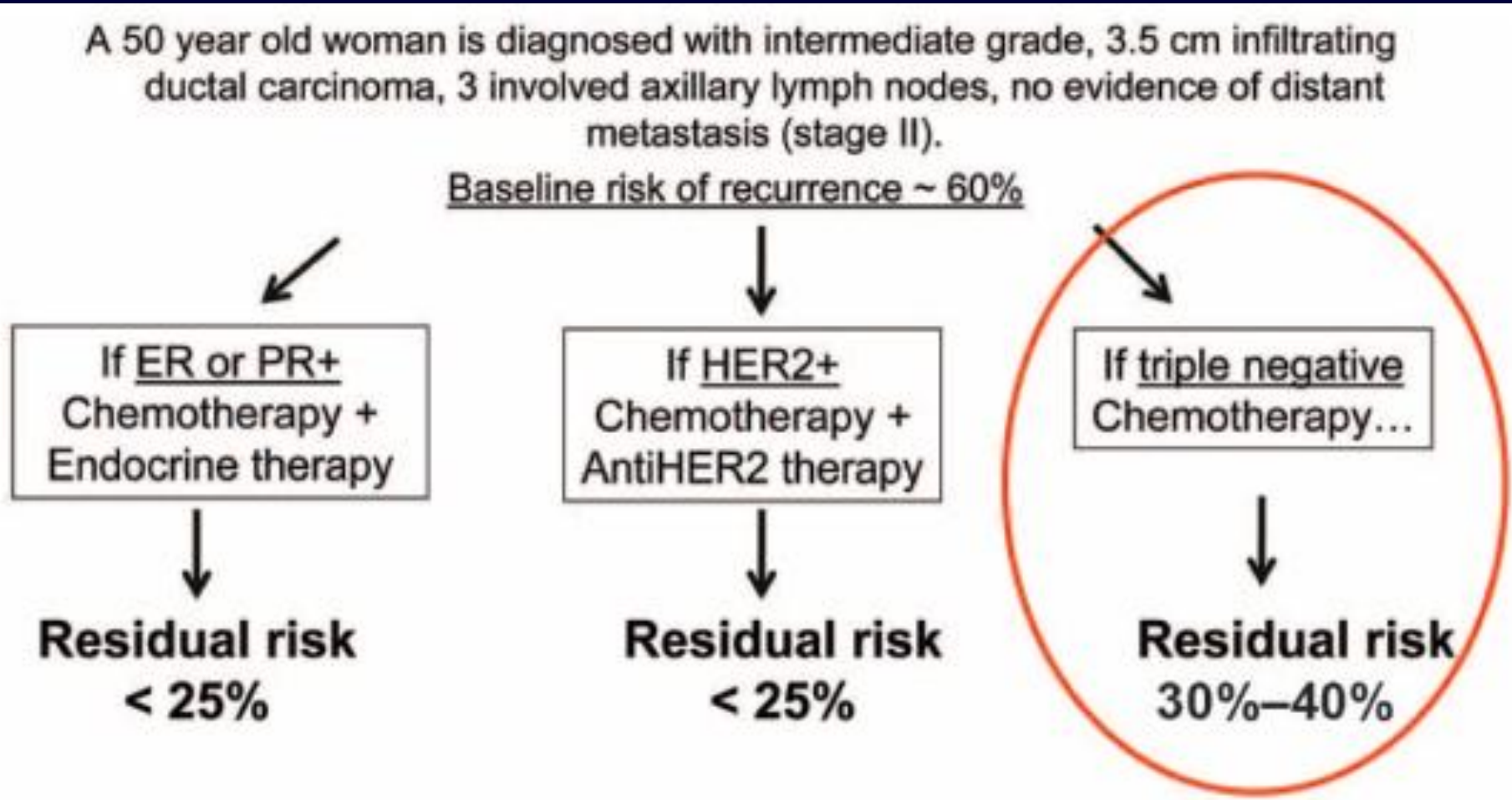



**Figure 1.** Adjuvant therapy for early breast cancer (90% are early at diagnosis).

Abbreviations: ER, estrogen receptor; HER-2, human epidermal growth factor receptor; PR, progesterone receptor.

Risk of relapse over time

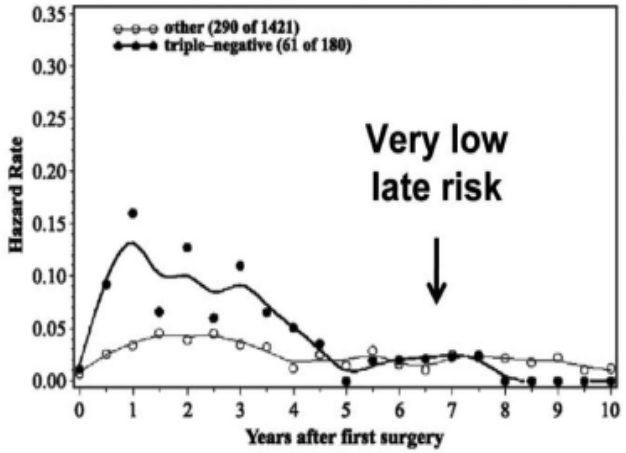



**Figure 6.** Triple-negative breast cancer behavior.

Adapted and reprinted by permission from the American Association for Cancer Research: Dent R, Trudeau M, Pritchard KI et al. Triple-negative breast cancer: Clinical features and patterns of recurrence. Clin Cancer Res 2007;13:4429–4434.

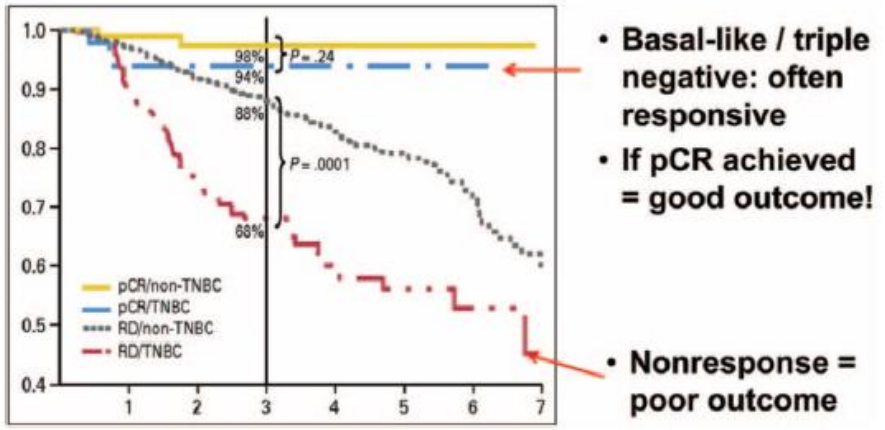



**Figure 7.** Responsiveness to conventional chemotherapy.

Abbreviations: pCR, pathologic complete response; RD, residual disease; TNBC, triple-negative breast cancer.

From Liedtke C, Mazouni C, Hess KR et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 2008;26: 1275–1281. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved.

**Table 2.** Heterogeneity in relapse site by subtype

| Sites involved | N | Bone | Soft Tissue | Viscera |
|---|---|---|---|---|
| TNBC | 79 | 13% | 13% | 74% |
| $ER^+$ | 123 | 39% | 7% | 54% |
| $HER\text{-}2^+$ | 78 | 7% | 12% | 81% |

Abbreviations: ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

Based on Liedtke C, Mazouni C, Hess KR et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 2008;26: 1275–1281. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved.

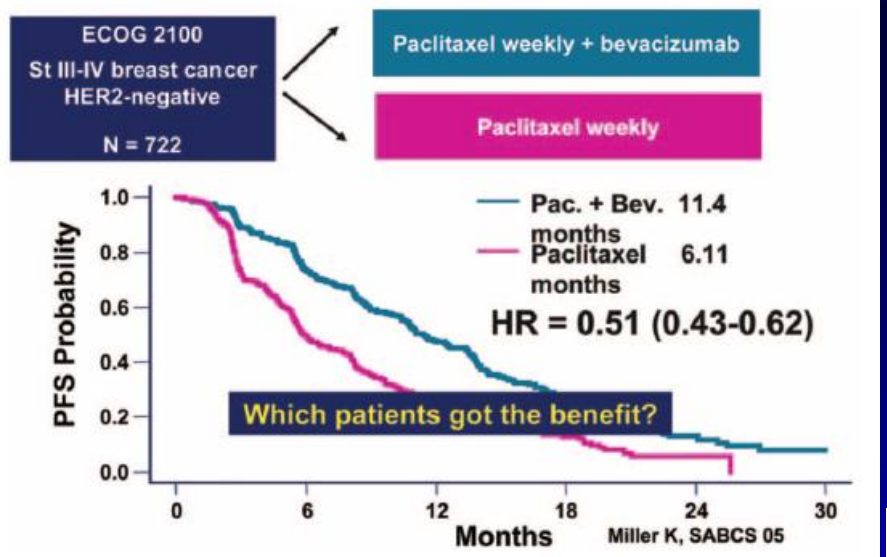



**Figure 8.** ECOG 2100: Randomized phase III trial of bevacizumab added to paclitaxel in stage IV breast cancer.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER-2, human epidermal growth factor receptor; HR, hazard ratio; PFS, progression-free survival.

From Miller K, Wang M, Gralow J et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007;357:2666–2676. Copyright © 2007 Massachusetts Medical Society. All rights reserved.

**Table 6.** Gemcitabine and carboplatin with or without BSI-201: results

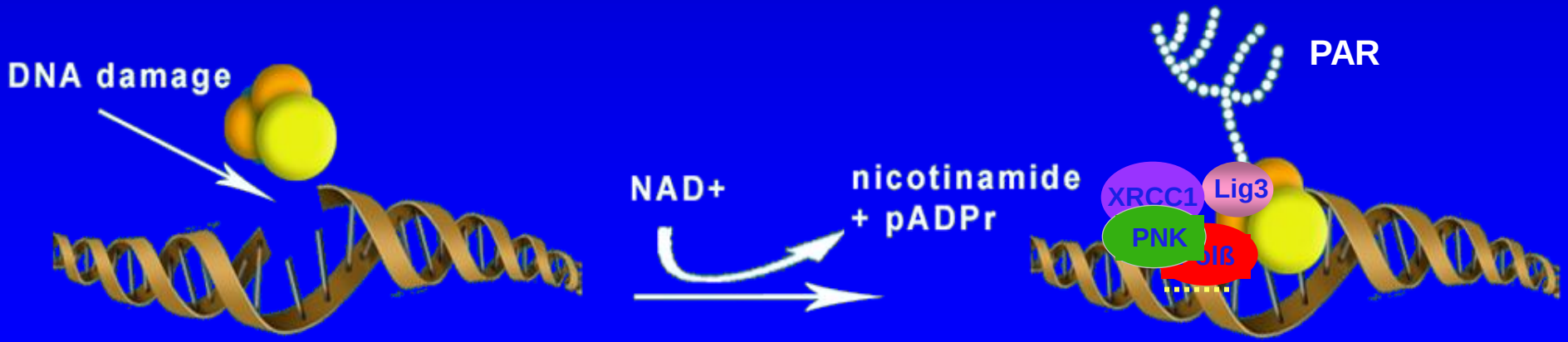
| | Gem/Carbo ($n$ = 44) | BSI-201 + Gem/Carbo ($n$ = 42) | $p$-Value |
|---|---|---|---|
| Objective response, $n$ (%) | 7 (16%) | 20 (48%) | .002 |
| Clinical benefit rate | 9 (21%) | 26 (62%) | .0002 |

Safety: no differences in hematologic or nonhematologic toxicities; no differences in gemcitabine/carboplatin dose reductions between study arms.

From O'Shaughnessy J, Osborne C, Pippen J et al. Final results of a randomized phase II study demonstrating efficacy and safety of BSI-201, a poly(ADP-ribose) polymerase (PARP) inhibitor, in combination with gemcitabine/carboplatin (G/C) in metastatic triple negative breast cancer (TNBC) [abstract 3122]. Presented at the 2009 San Antonio Breast Cancer Symposium, San Antonio, Texas, December 2009.

# Poly(ADP-Ribose) Polymerase (PARP)

- **A key role in the repair of DNA single-strand breaks**
- **Through the base excision repair pathway (BER)**
- **Binds directly to sites of DNA damage**
- **Once activated, it uses NAD as a substrate, and generates large, branched chains of poly (ADP-ribose) polymers on multiple target proteins**
- **Recruits other DNA repair enzymes**



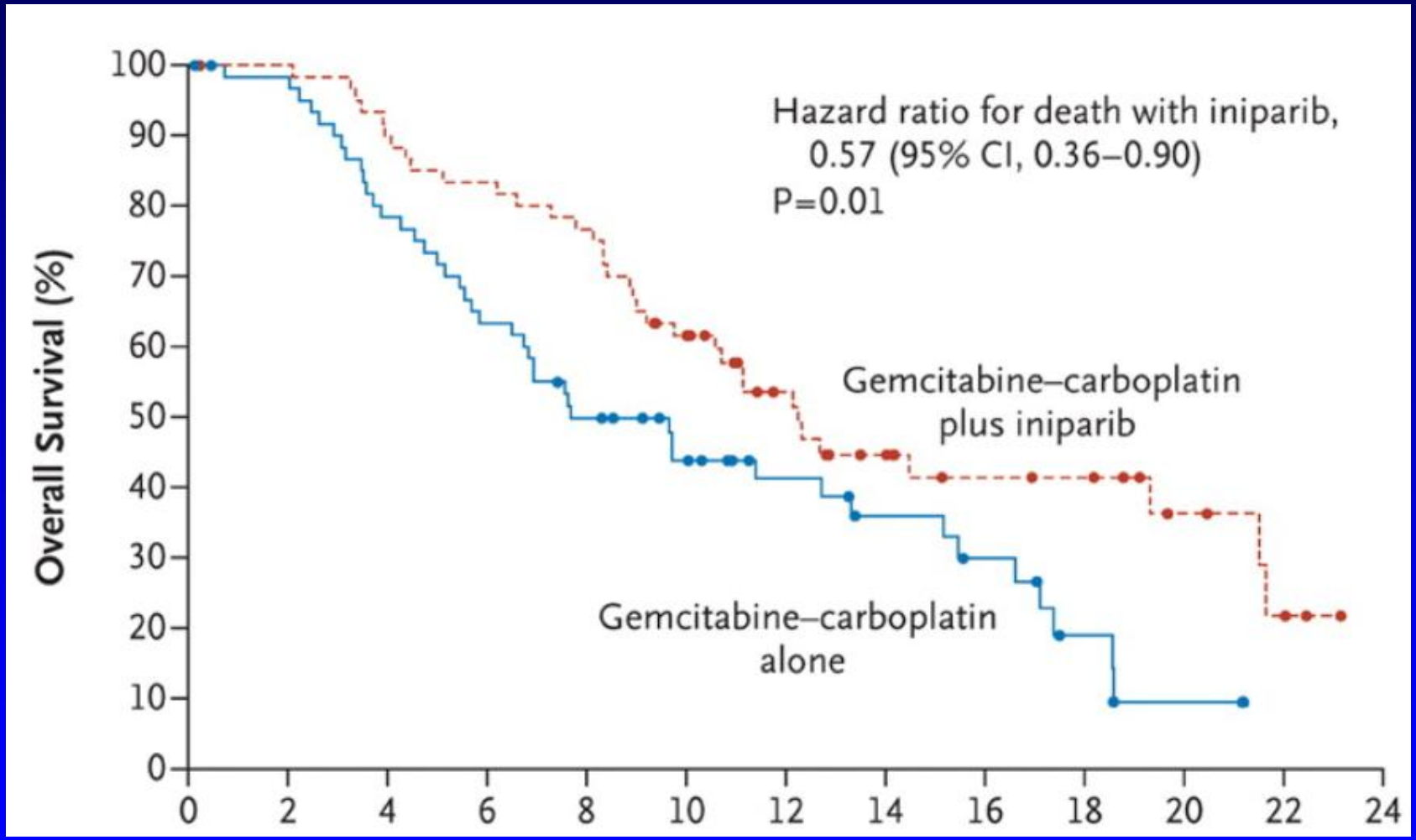
# TNBC Shares Clinical and Pathologic Features with BRCA-1-Related Breast Cancers ("BRCAness")

| Characteristics | Hereditary *BRCA1* | Triple Negative/Basal-Like[1,2,3] |
|---|---|---|
| **ER/PR/HER2 status** | Negative | Negative |
| **TP53 status** | Mutant | Mutant |
| **BRCA1 status** | Mutational inactivation* | Diminished expression* |
| **Gene-expression pattern** | Basal-like | Basal-like |
| **Tumor histology** | Poorly differentiated (high grade) | Poorly differentiated (high grade) |
| **Chemosensitivity to DNA-damaging agents** | Highly sensitive | Highly sensitive |

*BRCA1 dysfunction due to germline mutations, promoter methylation, or overexpression of HMG or ID4[4]

[1]Perou et al. Nature. 2000; 406:747-752
[2]Cleator et al.Lancet Oncol 2007;8:235-44
[3]Sorlie et al. Proc Natl Acad Sci U S A 2001;98:10869-74
[4] Miyoshi et al. Int J Clin Oncol 2008;13:395-400

# Final Results:
# Phase II Gem Carbo +/- Iniparib in TNBC




O'Shaughnessy J, et.al. NEJM 2011

2011 ASCO Annual Meeting

**Session Type and Session Title:**
Oral Abstract Session, Breast Cancer - Triple-negative/Cytotoxics/Local Therapy

**Abstract No:**
1007

**Citation:**
J Clin Oncol 29: 2011 (suppl; abstr 1007)

**Author(s):**
J. O'Shaughnessy, L. S. Schwartzberg, M. A. Danso, H. S. Rugo, K. Miller, D. A. Yardley, R. W. Carlson, R. S. Finn, E. Charpentier, M. Freese, S. Gupta, A. Blackwood-Chirchir, E. P. Winer; Baylor Sammons Cancer Center, Texas Oncology, US Oncology, Dallas, TX; The West Clinic, Memphis, TN; Virginia Oncology Associates, US Oncology, Norfolk, VA; University of California San Francisco, San Francisco, CA; Indiana University Simon Cancer Center, Indianapolis, IN; Sarah Cannon Research Institute, Nashville, TN; Stanford University, Stanford, CA; University of California, Los Angeles, Los Angeles, CA; sanofi-aventis, Malvern, PA; BiPar Sciences, South San Francisco, CA; Dana-Farber Cancer Institute, Boston, MA

Abstracts that were granted an exception in accordance with ASCO's Conflict of Interest Policy are designated with a caret symbol (^) here and in the printed Proceedings.

**Abstract Disclosures**

**Abstract:**

**Background:** A randomized phase II study in mTNBC suggested that iniparib (I), an anticancer agent with PARP inhibitory activity, added to GC improved overall survival (OS), without potentiating GC toxicity (O'Shaughnessy et al. NEJM 2011). This confirmatory study evaluated the safety and efficacy of GC with or without I in a similar mTNBC pt population. **Methods:** This randomized, open-label phase III study enrolled pts ≥18 years with mTNBC, measurable disease, and ≤2 prior cytotoxic regimens for metastatic TNBC. Pts were stratified based on having 0 vs. 1–2 prior metastatic therapies. Pts were randomized (1:1) to GC alone or GCI. G (1000 mg/m$^2$; IV) and C (AUC 2; IV) were given on days 1 and 8, and I (5.6 mg/kg; IV) on days 1, 4, 8, and 11 every 21 days. Upon central confirmation of disease progression on GC, crossover to GCI was permitted. Primary endpoints were OS and progression-free survival (PFS); secondary endpoints were objective response rate and safety. **Results:** Between July 2009 and March 2010, 519 pts were randomized. Pt characteristics were balanced between the two arms. The study did not meet the criteria for significance for co-primary endpoints of OS and PFS. Efficacy results in pts stratified by line of therapy (57% in 1st line; 43% in 2nd or 3rd line) will be presented. 152 of 258 GC pts (59%) crossed over to receive GCI following disease progression. Most frequently occurring grade 3/4 adverse events included neutropenia (53% [GC] vs. 61% [GCI]), anemia (22% vs. 18%), thrombocytopenia (24% vs. 28%), and leukopenia (15% vs. 16%). Overall, addition of I did not significantly add to the toxicity profile of GC alone. **Conclusions:** Although this study demonstrated a consistent safety profile to that of the phase II study, addition of I to GC did not meet the pre-specified criteria for significance for co-primary endpoints of OS and PFS in pts with mTNBC. Analyses aimed at further elucidating these findings are ongoing (clinicaltrials.gov: NCT00938652).

| | GC (n = 258 ) | GCI (n = 261) | Hazard ratio (95% CI) | P value* |
|---|---|---|---|---|
| **Median OS, months** | 11.1 | 11.8 | 0.876 (0.687-1.116) | 0.284 |
| **Median PFS, months** | 4.1 | 5.1 | 0.794 (0.646-0.976) | 0.027 |

*Based on 2-sided log-rank test.

# Case

- 53-yr-old woman diagnosed with stage I (11-mm; ER-, PgR-, and HER2-negative) breast cancer
  - Initial therapy: lumpectomy, AC x 4, RT
- Persistent cough developed 18 mos later
  - Imaging found a pleural effusion and multiple lung nodules
  - Cytology confirms original diagnosis
  - Treated with docetaxel + capecitabine but disease progresses after 2 cycles
  - Currently PS = 1

Which of the following treatment options would you recommend for this patient?

A. Ixabepilone
B. Cisplatin + gemcitabine
C. Eribulin
D. Liposomal doxorubicin
E. Vinorelbine

# Expert Insight: 5 Breast Cancer Experts' Choice of Therapy for This Patient

- Expert 1: eribulin
- Expert 2: eribulin
- Expert 3: eribulin
- Expert 4: cisplatin + gemcitabine
- Expert 5: cisplatin + gemcitabine

# Single-Agent vs Combination Chemotherapy for MBC

- Response rate $\Rightarrow$ favors combination
- TTP $\Rightarrow$ favors combination
- Survival $\Rightarrow$ ?
- Toxicity $\Rightarrow$ favors single agent
- Quality of life $\Rightarrow$ ?

Few combination trials using investigational drugs truly tested the hypothesis of combination vs sequential single-agent therapy

# Description and Indication

## *Description*[1]

- A non-taxane microtubule dynamics inhibitor
- Synthetic analogue of halichondrin B, a product isolated from the marine sponge *Halichondria okadai*
- First agent in the halichondrin class[3]

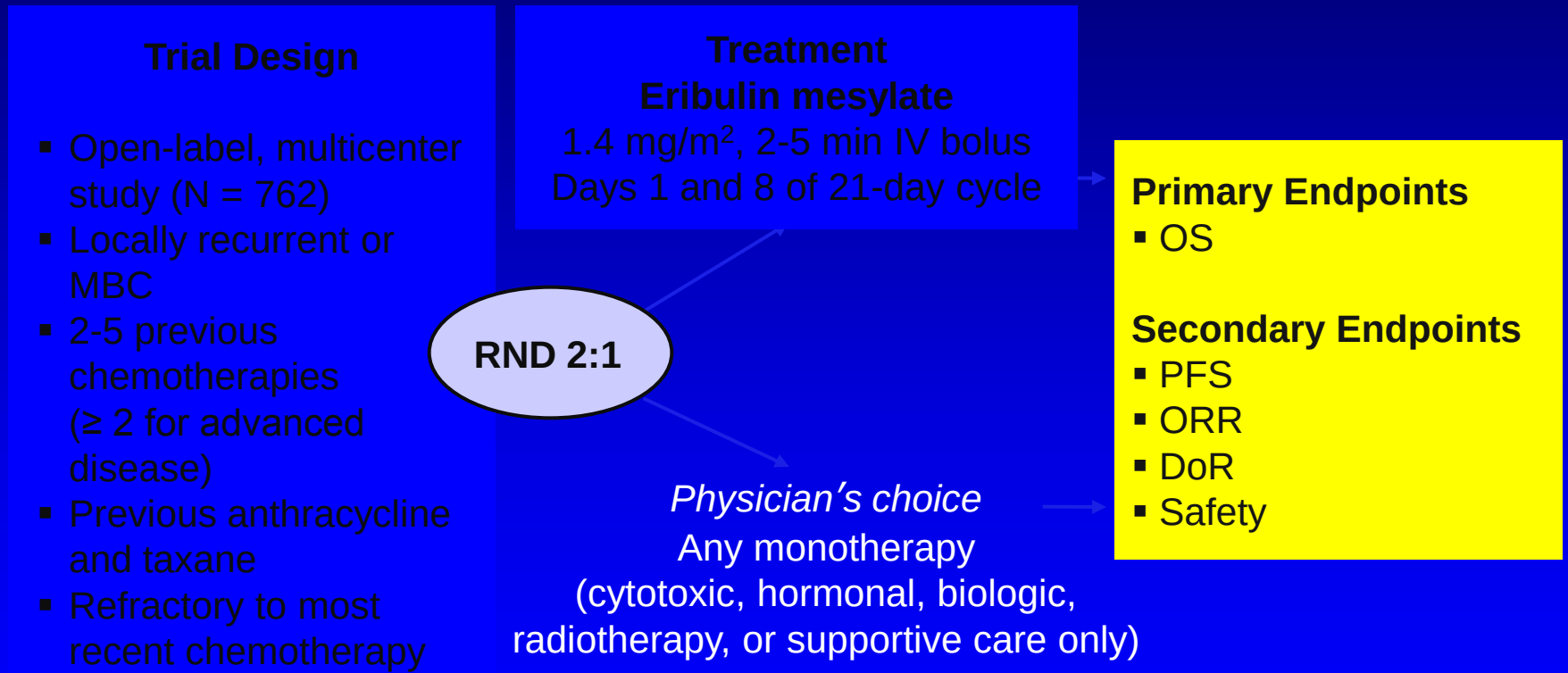
*Halichondria okadai*[2]
*(Photo by Saito)*

## *Indication*[1]

- Indicated for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease
- Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting

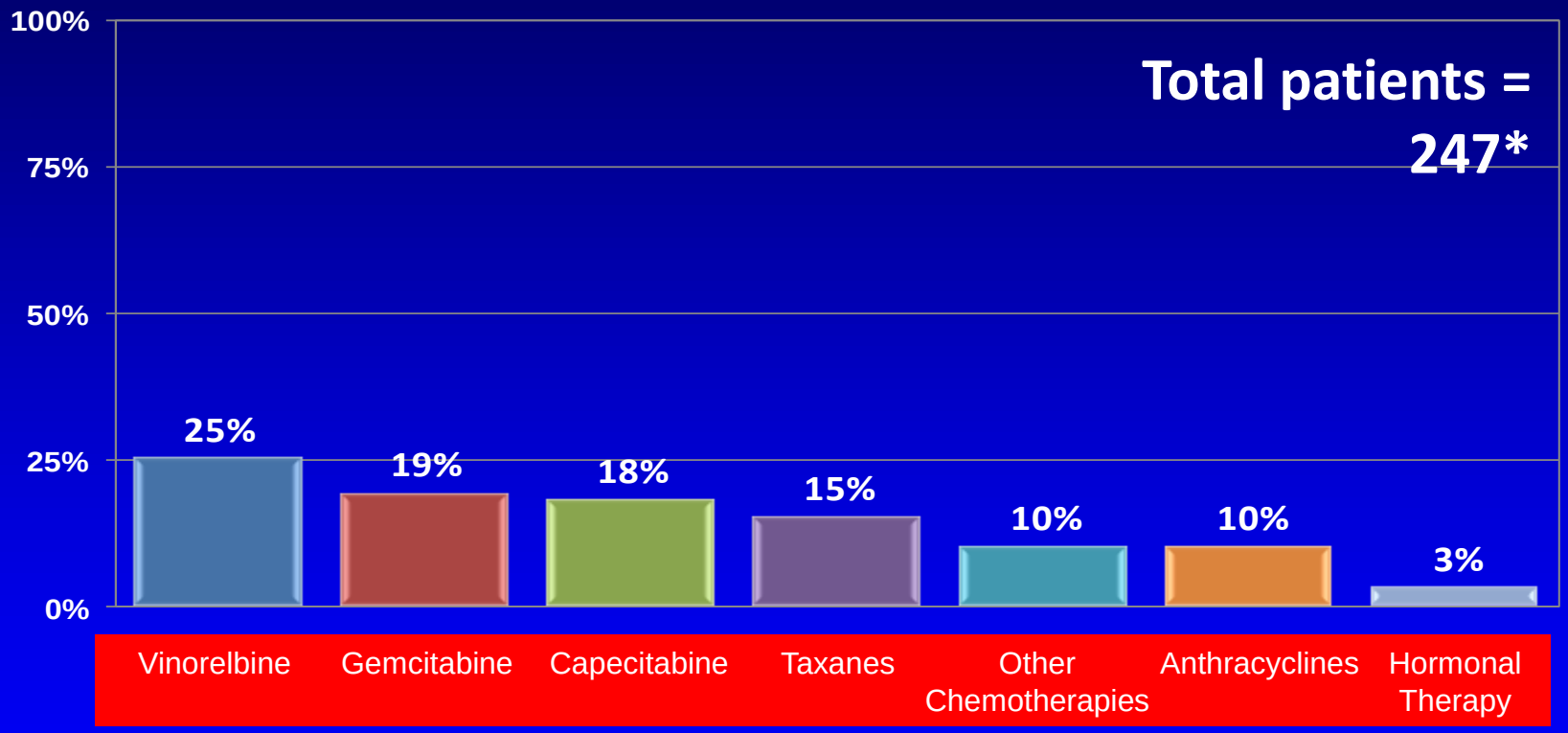
[1] Halaven [package insert]. Woodcliff Lake, NJ: Eisai Inc.; 2010.
[2] Image available at http://www.shimoda.tsukuba.ac.jp/~hassei/images/H.%20okadaiS.jpg.
[3] Kingston DG. *J Nat Prod*. 2009;72:507-515.

# EMBRACE: Study Design




Cortes J, et al. Lancet. 2011;377:914-923.

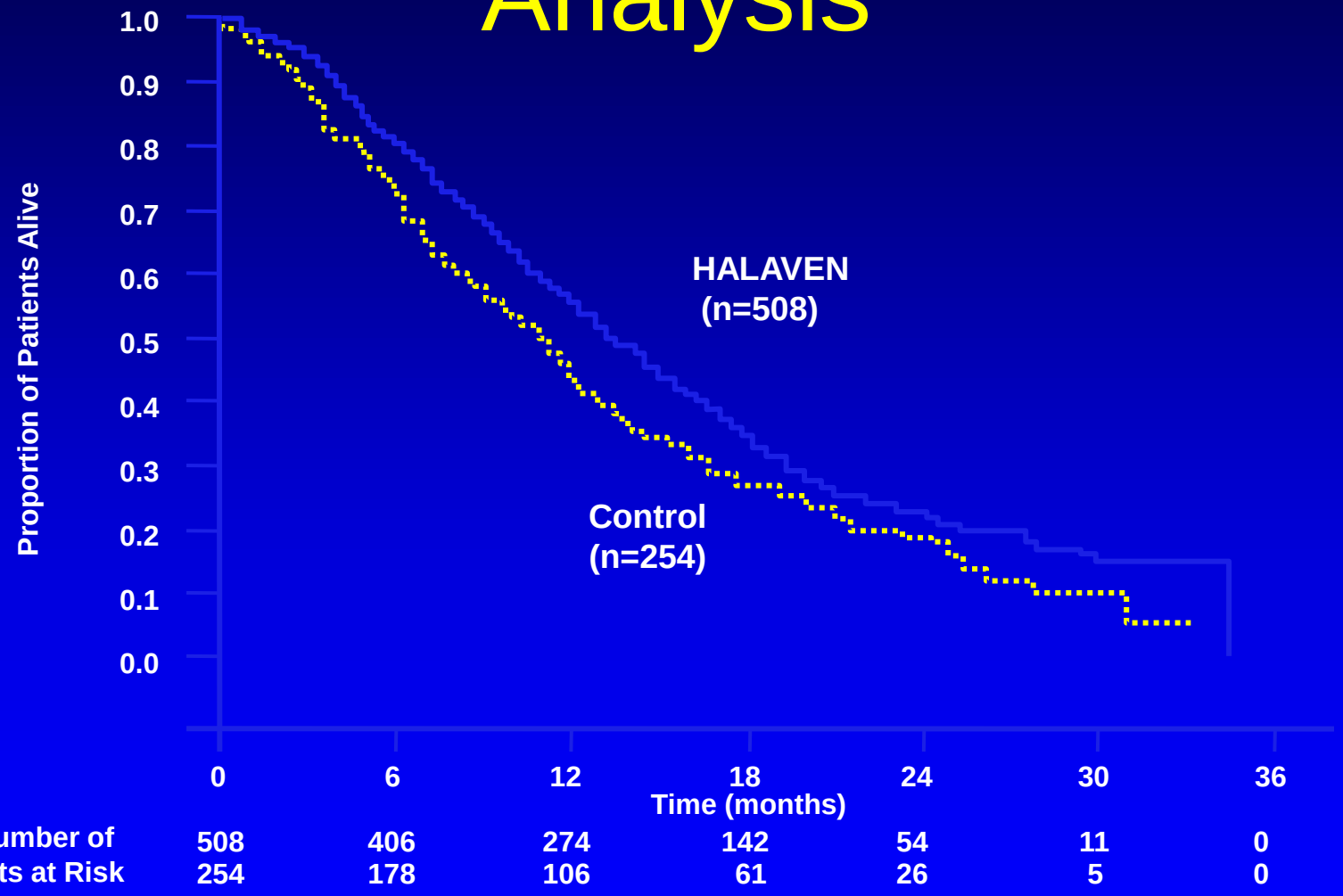
# Control Group Single Agent Treatment Received




*Number of patients who actually received the drug vs ITT population (n =254).

Halaven [package insert]. Woodcliff Lake, NJ: Eisai Inc.; 2010.

# Updated Overall Survival Analysis

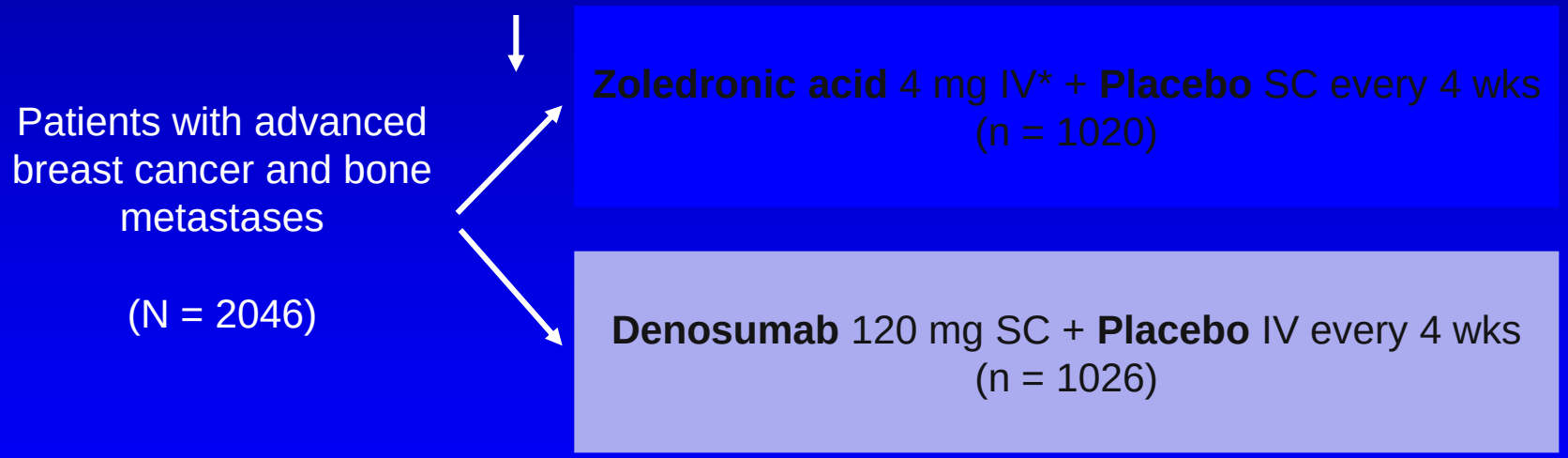



Halaven [package insert]. Woodcliff Lake, NJ: Eisai Inc.; 2010.

# Denosumab vs Zoledronic Acid: Study Design

- Extended analysis of randomized, double-blind, phase III trial
  - Primary endpoint: time to first on-study SRE

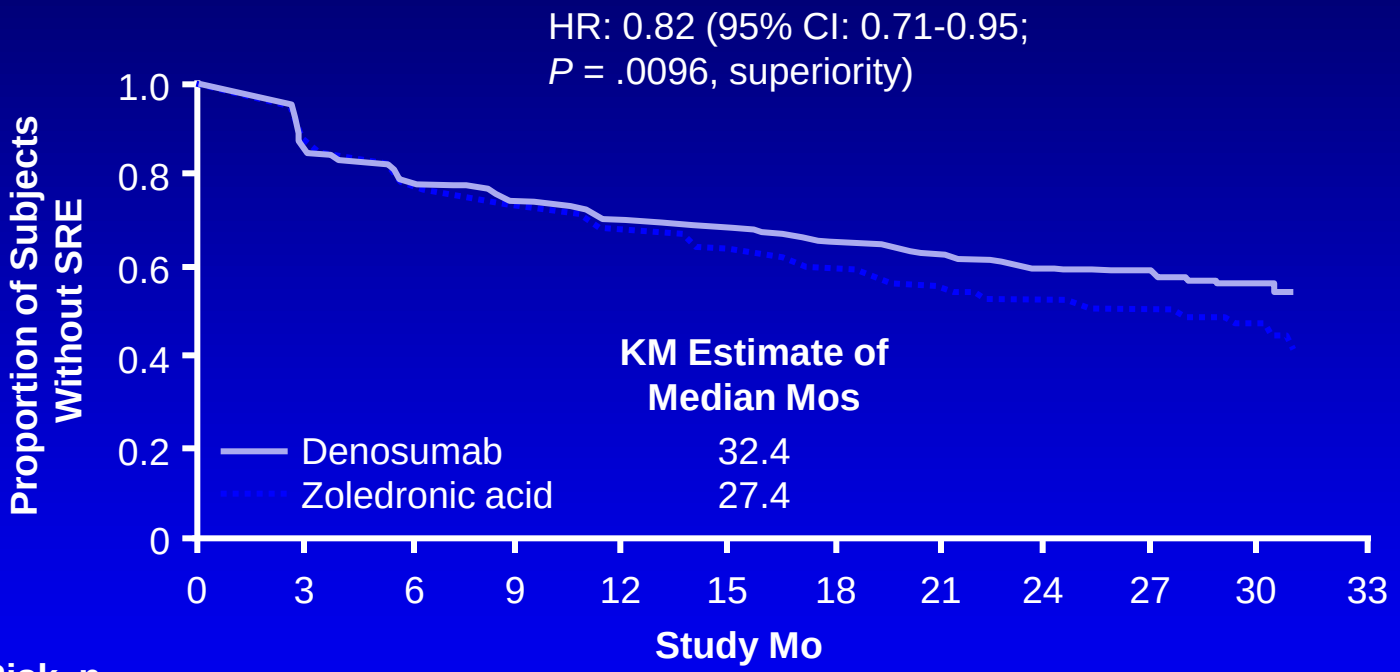
*Stratified by previous SREs, previous oral bisphosphonate, current chemotherapy, geographic region*




*Dose adjusted for baseline creatinine clearance and subsequent dose intervals determined by serum creatinine according to product label. All patients encouraged to take supplemental calcium (≥ 500 mg/day) and vitamin D (≥ 400 IU/day).

Stopeck A, et al. SABCS 2010. Abstract P6-14-01.

# Denosumab Reduced Time to First On-Study SRE




**Pts at Risk, n**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zoledronic Acid | 1020 | 831 | 675 | 584 | 498 | 429 | 356 | 265 | 186 | 111 | 38 | 4 |
| Denosumab | 1026 | 834 | 692 | 597 | 510 | 444 | 384 | 280 | 193 | 101 | 38 | 9 |

- Other endpoints: no difference in OS or time to overall disease progression between denosumab and zoledronic acid arms

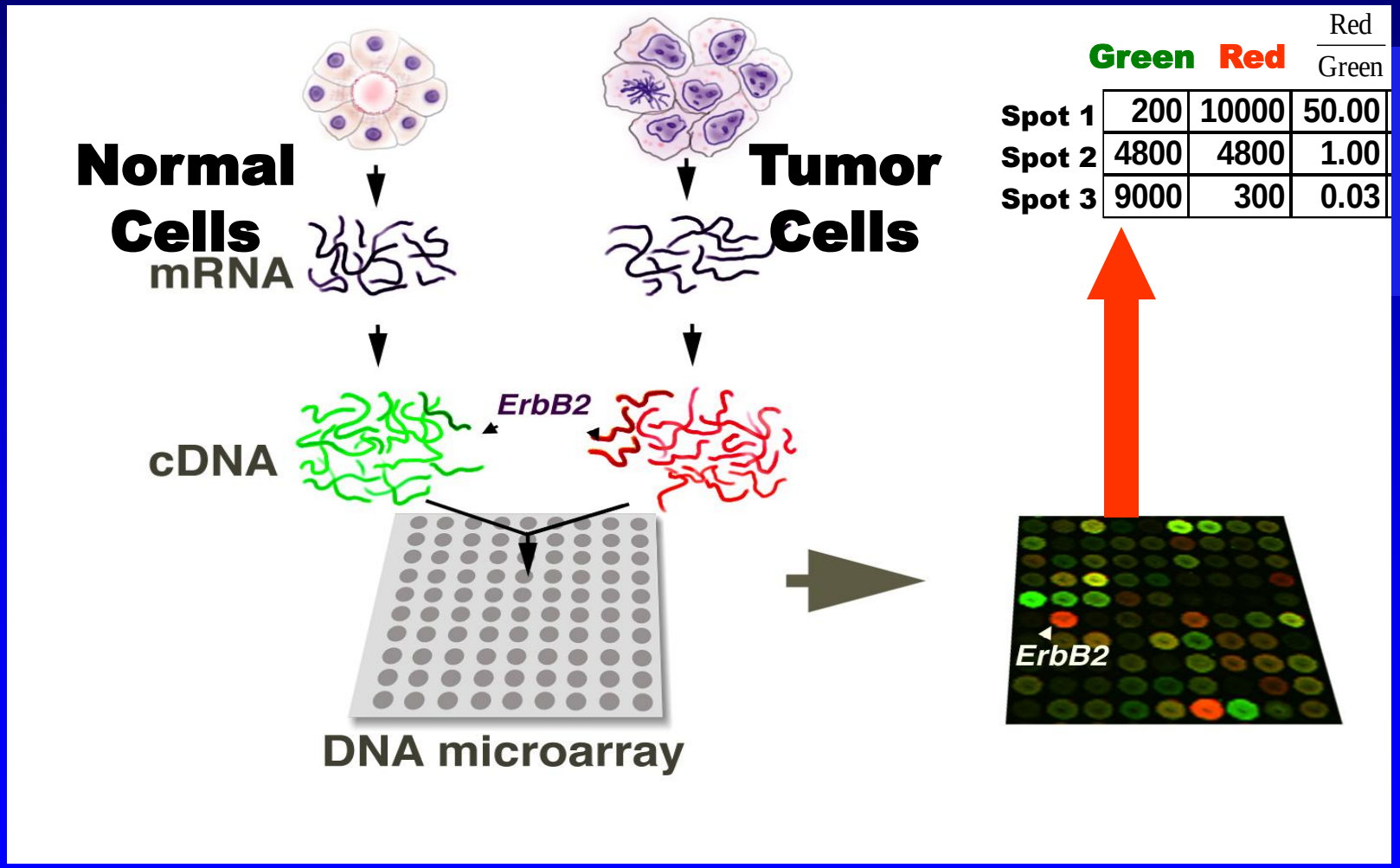
Stopeck A, et al. SABCS 2010. Abstract P6-14-01.

# Hellenic Cooperative Oncology Group: 403 women

- Overall, 16 percent of the women with triple-negative breast cancer (TNBC) had a deleterious *BRCA1* mutation.
- For the women who were diagnosed with TNBC at age 40 or younger, 36 percent were found to have a mutation
- For the women diagnosed with TNBC at age 50 or younger, 27 percent were found to have a mutation
- For the women with TNBC and a family history of breast or ovarian cancer in a 1st- or 2nd-degree relative, 48 percent were found to have a mutation

Fostira F, Tsitlaidou M, Papadimitriou C, *et al.* Prevalence of *BRCA1* mutations among 403 women with triple-negative breast cancer: implications for genetic screening selection criteria: a Hellenic Cooperative Oncology Group Study. *Breast Cancer Research and Treatment* 2012 (published online before print Mar 21 2012)

# Understanding Biology: Gene Expression Microarray Approach

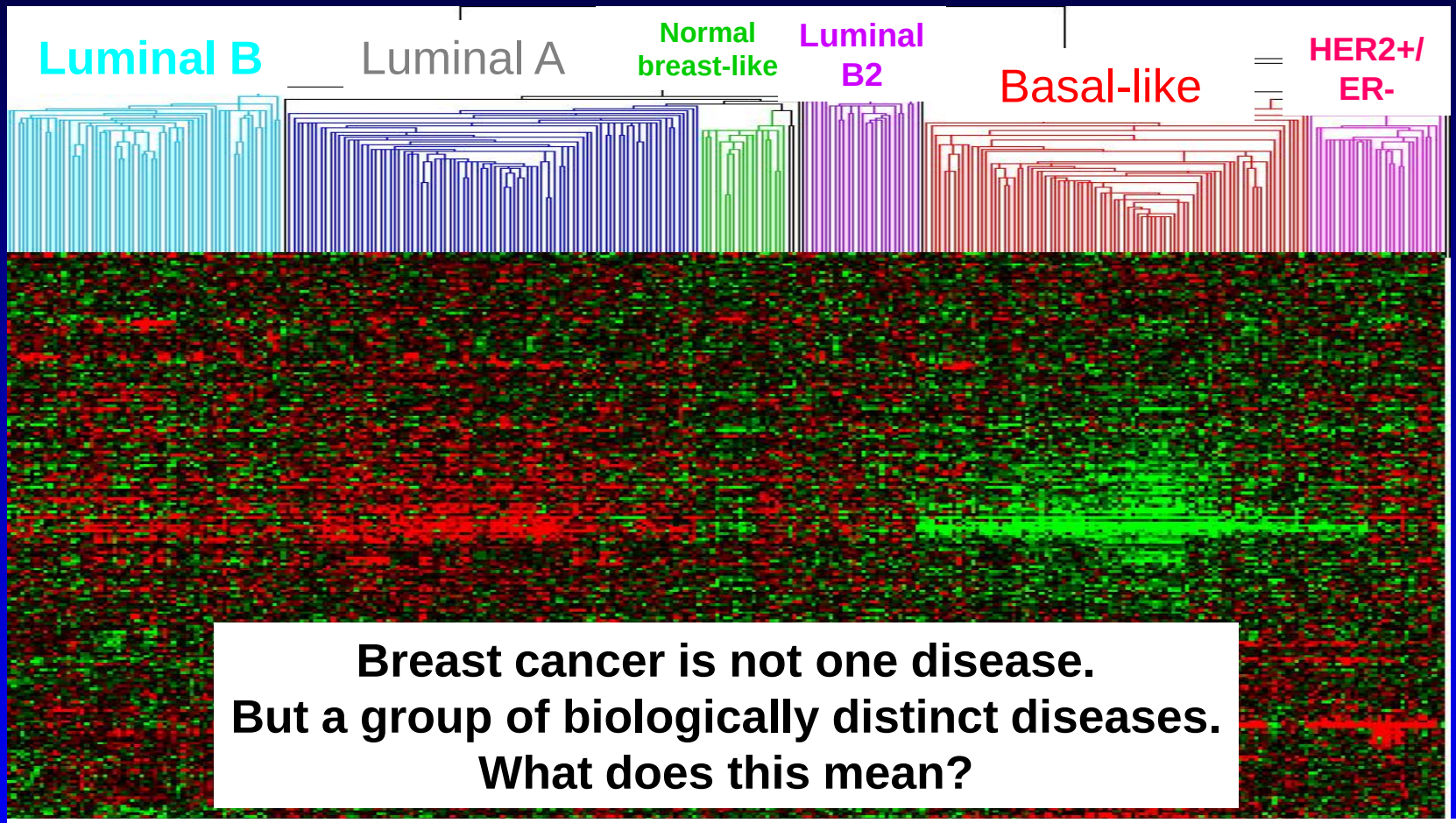



| | Green | Red | Red / Green |
|---|---|---|---|
| Spot 1 | 200 | 10000 | 50.00 |
| Spot 2 | 4800 | 4800 | 1.00 |
| Spot 3 | 9000 | 300 | 0.03 |

| NAME | BC/FUMI0 | BC/FUMI4 | BC/FUMI4 | BC601B-A | BC601A-B | BC/FUMI1 | BC/FUMI2 | BC/FUMI2 | BC/FUMI1 | BC/FUMI1 | BC102B-B | BC/FUMI2 | BC/FUMI3 | BC/FUMI3 | BC/FUMI1 | BC/FUMI1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| adipose differentiation-related prote | 0.242 | 1.21 | -0.253 | -0.841 | -0.423 | -0.363 | -0.852 | -1.383 | | -2.642 | 0.501 | -0.25 | -0.605 | -0.636 | 0.229 | -0.626 |
| plasminogen activator, urokinase re | 0.908 | 0.485 | -0.397 | -0.767 | -0.886 | -0.251 | -0.683 | 0.057 | -0.317 | -1.2 | 0.125 | | -0.536 | -0.248 | | -0.365 |
| plasminogen activator, urokinase re | 0.4635 | 0.3545 | -0.8975 | -1.23 | -0.8335 | 0.0175 | -1.002 | 0.1555 | -0.4325 | -1.008 | -0.1785 | | -0.7445 | -0.1485 | 0.0555 | 0.2055 |
| coronin, actin binding protein, 1C A | 0.551 | 0.151 | -0.422 | 0.007 | -0.638 | 0.087 | | -0.689 | -0.91 | -0.853 | 0.052 | -0.492 | -0.201 | -0.152 | -0.368 | -0.741 |
| **coatomer protein complex, subun | -1.061 | -0.8655 | -0.1235 | -0.9895 | 0.3815 | -0.4955 | -0.2775 | -0.1465 | -1.109 | -0.8635 | 0.2615 | -0.0905 | -0.3225 | -0.6035 | 0.0195 | -0.9345 |
| coactosin-like protein R78490 | -0.8835 | -0.4545 | 0.2375 | -1.177 | 0.2155 | -0.2975 | -0.9385 | -0.2815 | -1.494 | -0.5985 | 0.4095 | -0.3465 | 0.2185 | -0.1345 | -0.2895 | -0.5525 |
| folylpolyglutamate synthase R4486 | 0.686 | 1.583 | 1.313 | 0.048 | -0.272 | -0.143 | -0.394 | 0.423 | -0.445 | -0.854 | 0.322 | -0.03 | -0.412 | 0.214 | -1.098 | -0.175 |
| lysozyme (renal amyloidosis) N639 | -0.18 | 1.155 | 1.575 | -1.635 | 0.355 | 0.295 | -0.805 | 0.135 | -2.145 | -0.955 | 0.575 | 0.735 | -0.435 | -0.855 | -0.8 | -1.705 |
| chemokine (C-C motif) receptor 1 AA036881 | 0.524 | 1.233 | -1.459 | -0.095 | -0.122 | -0.196 | 0.101 | | | -0.942 | -0.2 | -0.133 | -0.549 | -0.763 | | -0.059 |
| interferon, gamma-inducible protei | -0.181 | -0.062 | 0.37 | 0.064 | 0.418 | -0.33 | -0.098 | -0.289 | -1.042 | -0.332 | 0.907 | 1.056 | -0.8 | -0.193 | -0.789 | -1.25 |
| cystatin B (stefin B) H22919 | -0.188 | -0.489 | -0.603 | 0.074 | -0.212 | -0.295 | -0.54 | -0.535 | -0.453 | -0.479 | -0.021 | 0.291 | -0.651 | -0.536 | -0.401 | -0.511 |
| cathepsin S AA236164 | -0.791 | | 0.334 | -0.316 | 0.723 | -0.46 | 0.39 | -0.452 | | -0.413 | | 1.063 | -0.849 | -1.088 | -0.94 | -1.291 |
| small inducible cytokine A2 (monoc | 0.2665 | 0.2955 | 0.5315 | -0.1285 | 0.4255 | -1.099 | -0.7265 | -0.6035 | -1.052 | -1.438 | 0.1355 | 0.0365 | -0.4335 | 0.0875 | -1.218 | -0.7785 |
| natural killer cell transcript 4 AA458 | 0.483 | 0.348 | 0.575 | -0.685 | 0.971 | -0.335 | -0.222 | -0.116 | -1.644 | -0.66 | -0.322 | 0.885 | -0.08 | -0.02 | -0.441 | -0.51 |
| superoxide dismutase 2, mitochond | 0.431 | 0.301 | -0.836 | 0.519 | | -0.492 | -0.834 | -0.86 | | 0.781 | 0.005 | -1.163 | -1.283 | -0.969 | | -0.586 |
| superoxide dismutase 2, mitochondrial AA487 | 0.3185 | -0.6835 | 0.4865 | 0.6925 | -0.7895 | -0.6005 | -0.5815 | 0.4995 | 0.0165 | 0.3755 | -0.1225 | -1.129 | -1.137 | | | -0.6935 |
| transforming growth factor, beta-in | 0.0235 | 0.6525 | -0.3785 | -0.5505 | -0.3675 | -0.4755 | -0.1105 | 0.3435 | 0.0785 | -0.4735 | 0.7925 | 1.532 | -0.3355 | -0.0885 | 0.2495 | -0.1985 |
| glycine dehydrogenase (decarboxy | -1.122 | -1.412 | -1.275 | -1.764 | -0.611 | 1.259 | -1.25 | -0.76 | -2.159 | -1.72 | -1.017 | -0.972 | -0.715 | -0.543 | -0.658 | -0.818 |
| syndecan 2 (heparan sulfate protec | -1.828 | -1.7 | -1.409 | -1.964 | -0.975 | 1.516 | -1.24 | -1.75 | -2.219 | -2.477 | -1.08 | 0.29 | -1.641 | -2.045 | -0.315 | -1.356 |
| glutathione S-transferase pi R3364 | -1.726 | -1.892 | -1.568 | | | 1.528 | -1.346 | -2.157 | -3.114 | -3.146 | -0.943 | 0.236 | -1.349 | -1.674 | -0.416 | -1.557 |
| chitinase 3-like 2 AA668821 | | | | -0.771 | -1.436 | -1.454 | -0.813 | -1.578 | 0.312 | -0.167 | 0 | -0.469 | 0.129 | -0.566 | | -0.489 |
| nuclear factor I/B W87528 | 0.464 | -1.314 | -0.187 | | | | | | | | -1.825 | | -0.441 | -0.928 | 0.316 | -1.188 |
| ras homolog gene family, member | -1.382 | -0.471 | -0.421 | | | | | | | | -0.713 | -0.167 | 0.09 | 1.074 | | -0.393 |
| ras homolog gene family, member | -1.311 | -0.763 | -0.61 | | | | | | | | -0.486 | -0.778 | -0.579 | 0.812 | 0.348 | -0.222 |
| **zinc finger, DHHC domain containing 5 AA4 | -0.965 | -0.571 | | | | | | | | | -0.926 | -1.153 | -0.462 | -0.683 | 0.828 | 0.347 |
| keratin 5 (epidermolysis bullosa sin | -0.309 | -0.485 | -0.748 | -0.909 | -0.403 | -0.127 | -0.371 | -0.778 | -1.596 | -1.787 | -0.782 | 0.242 | -0.559 | -0.804 | 0.79 | 0.374 |
| keratin 5 (epidermolysis bullosa simplex, Dowl | | -0.655 | -2.421 | 0.301 | 0.689 | -0.38 | -0.131 | -1.647 | | -1.396 | 0.248 | -1.118 | -0.389 | -1.423 | 1.963 | -0.068 |
| keratin 17 AA026100 | | -0.593 | -2.294 | 0.181 | -0.45 | 0.457 | -1.132 | -0.754 | | -2.708 | -0.641 | -0.148 | -0.201 | 0.161 | 2.264 | 1.758 |
| tripartite motif-containing 29 AA055 | -0.523 | -0.763 | | -0.726 | -0.155 | -0.401 | | -1.8 | -1.591 | -1.789 | -1.076 | -0.929 | -1.132 | -1.051 | | -0.24 |
| pleiomorphic adenoma gene-like 1 AA463204 | -0.7035 | -0.5595 | -0.7765 | -0.2835 | | | -0.1885 | | -1.466 | -2.035 | -0.1475 | -0.7075 | -0.4025 | -1.054 | 0.3535 | -0.5835 |
| secreted frizzled-related protein 1 AA002080 | -1.951 | -2.022 | -1.982 | 0.069 | -0.117 | -1.543 | -2.996 | | | -2.657 | -0.275 | -1.187 | -0.262 | -0.688 | 3.135 | 0.295 |
| Homo sapiens cDNA FLJ11796 fis, clone HEM | -1.425 | | -0.74 | -0.798 | 0.243 | -0.225 | -0.061 | | | -0.957 | -0.001 | | -0.491 | -0.28 | 0.595 | -0.721 |
| ESTs AA074677 | | -0.411 | -0.412 | -0.879 | -0.78 | -0.401 | -0.135 | -0.508 | | -2.237 | 0.077 | | -0.72 | -1.057 | | -1.301 |
| pellino homolog 1 (Drosophila) W8 | -0.3805 | -1.159 | -0.6945 | -0.3935 | -0.1785 | -0.3665 | -0.3835 | -0.2825 | 0.1245 | 0.3185 | 0.2735 | -1.329 | -0.9455 | -1.313 | | -0.4235 |
| matrix metalloproteinase 7 (matrilys | -0.887 | | | -2.32 | 0.16 | -1.65 | | -1.54 | | -1.065 | 1.453 | | -1.55 | -2.859 | | -0.04 |
| moesin R22977 | 0.452 | -0.759 | -0.433 | -0.691 | 0.148 | -0.538 | -0.28 | -0.478 | -0.477 | 0.019 | 0.062 | | -0.001 | 0.259 | -0.24 | -0.314 |
| prion protein (p27-30) (Creutzfeld-J | -0.8095 | -1.302 | -0.5695 | -1.843 | -0.8355 | -0.3325 | -0.7305 | 0.2015 | -0.3825 | -0.2335 | -0.4605 | -1.181 | -0.6875 | -0.3315 | 0.2825 | -0.0605 |
| chitinase 3-like 1 (cartilage glycoprotein-39) A | 1.474 | 1.071 | 0.678 | 0.987 | -1.357 | | | -2.185 | | -1.619 | 3.517 | -0.465 | -1.549 | -1.699 | | -1.262 |
| annexin A8 AA235002 | | -0.55 | | -0.832 | 0.209 | 0 | -0.576 | -0.199 | | -1.046 | -0.454 | -0.221 | 0.134 | -0.015 | 0.619 | 0.519 |
| hypothetical protein FLJ20481 N32 | -0.078 | -0.939 | -1.002 | 0.058 | -0.058 | -0.158 | -1.65 | -0.794 | | -1.612 | 0.17 | 1.318 | 0.404 | -0.312 | | -0.039 |
| ADP-ribosylation factor-like 7 N353 | -0.9415 | -0.0585 | -0.3685 | -0.9365 | -0.2155 | 0.0715 | -0.2825 | -0.5505 | | -1.107 | -0.5855 | 0.2285 | -0.2475 | 0.1635 | | -0.1405 |
| cystatin A (stefin A) W72207 | | -0.532 | -0.941 | 0.909 | 1.783 | 0.164 | -0.106 | -0.577 | | -1.496 | 0.588 | 3.351 | -0.73 | | | -0.855 |
| inhibitor of DNA binding 3, dominar | -0.46 | -0.587 | -0.421 | -0.358 | 0.326 | | 0.638 | | -0.642 | | -0.224 | -0.143 | -0.445 | -0.58 | 0.377 | |
| complement component 1, r subcor | 0.116 | | 0.475 | -1.506 | 0.089 | -0.624 | 0.876 | -1.115 | | -1.773 | -0.505 | -0.276 | -0.204 | -1.308 | 0.584 | -0.431 |
| nicotinamide N-methyltransferase T | 0.675 | -0.083 | 0.035 | -0.244 | 0.053 | -0.021 | -0.365 | -1.174 | -1.235 | -1.789 | -0.688 | 0.972 | -0.261 | -0.532 | 0.606 | 0 |
| myosin IE AA029956 | -0.6075 | | -0.5465 | -0.8195 | -0.3755 | -0.3535 | -0.5545 | -0.6505 | | -1.089 | 0.0005 | -0.0205 | 0.1535 | -0.1775 | | -0.0005 |
| major histocompatibility complex, c | -0.494 | -0.582 | -1.091 | -0.32 | 0.305 | -0.098 | -0.085 | 0.262 | -1.668 | -1.457 | -0.039 | -0.362 | -0.218 | -0.838 | -0.197 | -0.537 |
| fatty acid binding protein 7, brain W72051 | | | -1.595 | -2.086 | -1.717 | -0.387 | -2.433 | -0.184 | | | -1.441 | | -0.603 | 0.446 | | 0.728 |
| kynureninase (L-kynurenine hydrolase) H874 | -0.342 | -0.591 | 1.233 | 0.358 | -0.954 | -1.687 | -1.194 | -1.515 | -2.291 | -0.198 | 0.075 | -0.657 | -1.675 | -0.58 | -1.138 | |
| cytochrome P450, subfamily I (dio | 1.065 | -0.579 | 0 | -0.767 | 0.392 | -0.386 | -0.479 | -0.752 | -0.401 | -0.549 | 0.165 | 0.11 | -0.605 | -0.779 | 0.499 | -0.131 |
| cytochrome P450, subfamily I (dio | 2.202 | -0.047 | -0.231 | -0.604 | -0.234 | -0.713 | -0.836 | -1.99 | -1.558 | -1.474 | 0.425 | 0.622 | -0.872 | -1.706 | | -0.579 |
| S100 calcium binding protein A8 (c | -1.641 | 0.014 | -1.05 | 4.29 | -0.162 | -0.899 | -1.625 | -1.818 | | -2.268 | -1.165 | -1.2 | -1.797 | -1.329 | | -1.087 |
| signal transducer and activator of transcription | -0.2855 | -0.6135 | 2.59 | -0.0555 | -0.4895 | -0.3215 | -1.224 | -1.718 | -1.387 | -0.4765 | -0.7565 | -1.143 | -0.8755 | | | -0.9545 |
| gamma-aminobutyric acid (GABA) A receptor | 3.044 | | -1.498 | 0.076 | 0.153 | -0.766 | -0.789 | | | -1.485 | -0.69 | | -0.823 | -0.104 | | -0.235 |
| EphB6 AA609284 | | 0.6365 | -1.062 | -0.5295 | -0.1345 | | -0.6565 | | | | | -0.0415 | -0.0885 | 0.0535 | | -0.3235 |
| secretory leukocyte protease inhibi | -2.088 | -1.806 | -1.596 | 0.434 | -1.378 | -1.269 | -0.849 | -1.961 | -2.645 | -3.187 | -1.637 | | -0.996 | -1.568 | 0.538 | -1.344 |
| aldo-keto reductase family 1, member C1 (dih | 0.83 | 0.835 | -0.435 | 1.743 | 1.173 | -0.558 | -1.21 | | | -1.547 | | -0.834 | 0.712 | 0.104 | | -0.296 |
| latrophilin W74533 | -1.28 | 0.216 | -0.322 | -0.467 | -0.563 | 0.111 | 0.383 | -0.648 | -0.95 | -1.333 | -0.903 | | 0.469 | 0 | | 0.274 |
| echinoderm microtubule associated | -0.0045 | -0.1755 | -0.1055 | 0.1595 | -0.2585 | -0.5155 | -1.05 | -0.3895 | -0.1395 | -0.8335 | -0.0445 | -0.4845 | 0.0045 | -0.7135 | 0.1435 | -0.2125 |
| epidermal growth factor receptor (erythroblast | -0.676 | -1.527 | -0.203 | -1.07 | -1.157 | -0.979 | -1.085 | | | -2.181 | -1.547 | -0.782 | -0.768 | | | 0.432 |
| ERO1-like (S. cerevisiae) AA1868( | 0.3395 | 0.4075 | -0.6115 | -0.3415 | | -0.4095 | -0.8285 | -0.4075 | -0.4405 | -0.4075 | -1.335 | -0.2325 | -0.7075 | -0.7125 | | -0.3035 |
| **hypothetical protein FLJ20624 R9 | -0.232 | -0.341 | | -0.153 | -0.446 | 0.838 | -1.658 | 0.466 | -0.553 | -0.909 | -0.199 | -0.662 | -0.334 | 0.371 | -0.029 | 0.617 |
| forkhead box D1 AA069132 | -1.192 | -0.07 | -0.666 | -0.596 | 0.02 | 0.388 | -0.54 | 0.11 | | -1.016 | -1.28 | -1.077 | -0.051 | -0.477 | -0.561 | 0.796 |
| met proto-oncogene (hepatocyte growth factor receptor) AA410591 | | | | -1.151 | -0.373 | 0.228 | | 0.322 | | -0.654 | -0.23 | 0.176 | 0.74 | 0.446 | | 0.177 |
| ESTs, Weakly similar to TRHY_HUMAN TRICH | -0.137 | -0.378 | -0.339 | 0.263 | 0.618 | 0.02 | 0.518 | | | -1.656 | 1.242 | 0.885 | 0.19 | 0.389 | | -0.164 |
| ESTs AA149250 | | | 1.847 | -0.295 | 0.293 | | -0.215 | | | -1.641 | -0.868 | -0.33 | -0.395 | 0.21 | | -0.185 |
| Homo sapiens mRNA; cDNA DKFZp564O2364 | 3.135 | 0.0215 | 0.3145 | 0.7915 | -0.2245 | 1.343 | -0.0505 | | | -0.1155 | 1.125 | | -0.1125 | -0.5255 | | -0.3445 |
| hypothetical protein FLJ10337 AA1 | -0.6325 | 0.8375 | 0.2155 | -0.7935 | -0.1815 | -0.3315 | -0.4795 | -0.6435 | -0.6095 | -0.4435 | 0.2225 | 0.0585 | -0.3355 | 0.2375 | | 0.1205 |
| integral membrane protein 3 AA034 | -0.998 | -0.313 | 0.52 | -1.106 | -0.005 | -0.618 | -0.901 | -0.847 | -2.533 | -2.828 | -1.247 | -0.647 | -1.005 | -1.651 | -0.119 | -0.465 |

**Thank god for computers**

# Breast Cancer Molecular Subtypes




**Breast cancer is not one disease.**
**But a group of biologically distinct diseases.**
**What does this mean?**

**It means that it does not make sense to ask "what causes breast cancer?"**
**It also means that individualized medicine is not just desirable, it is crucial.**

Courtesy Chuck Perou

# July 1, 2021

Dear Dr. Mackey:

Ultigenomics has determined your patient's T2N1 primary breast cancer has the following phenotype, and intervention is recommended:

- Tumor
  - PI3K-activating mutation: PiKtrimicin
  - HER2 pathway activation: T-DM1
  - Telomerase activation: Tipglu
- Stroma
  - VEGFR pathway activation: ramucirumab
  - Bone tropism: denosumab

This will reduce your pt's estimated 10-yr risk of recurrence from 63% to 4%