Living Beyond Breast Cancer: Triple Negative Disease

Robert A. Somer, MD
Cooper Cancer Institute
July 10th, 2012
<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estimated New Cases</strong></td>
<td><strong>Estimated Deaths</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>Breast</td>
<td>Lung &amp; bronchus</td>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>240,890 (29%)</td>
<td>230,480 (30%)</td>
<td>85,600 (28%)</td>
<td>71,340 (26%)</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>Colon &amp; rectum</td>
<td>Prostate</td>
<td>Breast</td>
</tr>
<tr>
<td>115,060 (14%)</td>
<td>69,360 (9%)</td>
<td>33,720 (11%)</td>
<td>39,520 (15%)</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>Uterine corpus</td>
<td>Colon &amp; rectum</td>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td>71,850 (9%)</td>
<td>46,470 (6%)</td>
<td>25,250 (8%)</td>
<td>24,130 (9%)</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Thyroid</td>
<td>Pancreas</td>
<td>Pancreas</td>
</tr>
<tr>
<td>52,020 (6%)</td>
<td>36,550 (5%)</td>
<td>19,360 (6%)</td>
<td>18,300 (7%)</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>Non-Hodgkin lymphoma</td>
<td>Liver &amp; intrahepatic bile duct</td>
<td>Ovary</td>
</tr>
<tr>
<td>40,010 (5%)</td>
<td>30,300 (4%)</td>
<td>13,260 (4%)</td>
<td>15,460 (6%)</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>Melanoma of the skin</td>
<td>Leukemia</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>37,120 (5%)</td>
<td>30,220 (4%)</td>
<td>12,740 (4%)</td>
<td>9,570 (4%)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Kidney &amp; renal pelvis</td>
<td>Esophagus</td>
<td>Leukemia</td>
</tr>
<tr>
<td>36,060 (4%)</td>
<td>23,800 (3%)</td>
<td>11,910 (4%)</td>
<td>9,040 (3%)</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>Leukemia</td>
<td>Urinary bladder</td>
<td>Uterine corpus</td>
</tr>
<tr>
<td>27,710 (3%)</td>
<td>21,990 (3%)</td>
<td>10,670 (4%)</td>
<td>8,120 (3%)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Pancreas</td>
<td>Non-Hodgkin lymphoma</td>
<td>Liver &amp; intrahepatic bile duct</td>
</tr>
<tr>
<td>25,320 (3%)</td>
<td>21,980 (3%)</td>
<td>9,750 (3%)</td>
<td>6,330 (2%)</td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td>Kidney &amp; renal pelvis</td>
<td>Brain &amp; other nervous system</td>
</tr>
<tr>
<td>22,050 (3%)</td>
<td></td>
<td>8,270 (3%)</td>
<td>5,670 (2%)</td>
</tr>
<tr>
<td>All sites</td>
<td></td>
<td>All sites</td>
<td>All sites</td>
</tr>
<tr>
<td>822,300 (100%)</td>
<td>774,370 (100%)</td>
<td>300,430 (100%)</td>
<td>271,520 (100%)</td>
</tr>
</tbody>
</table>

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

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*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.


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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

Directed Therapy of Subtypes of Triple-Negative Breast Cancer

LISA A. CAREY

The University of North Carolina, Chapel Hill, North Carolina, USA

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 • HSL-201

Disclosures: Lisa A. Carey: Consultant/Advisory role: sanofi-aventis, HiPar, Wyeth, Pfizer, Genentech, Bristol-Myers Squibb,
Novartis (all uncompensated); Research funding/Contracted research: GalgoSmithKline, Boehringer-Ingelheim, Genentech, Wyeth,
Bristol-Myers Squibb (all uncompensated).

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from
commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer
reviewers.

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)-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-
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

<table>
<thead>
<tr>
<th>HER2</th>
<th>ER</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>ENDO</td>
<td>CHEMO</td>
</tr>
<tr>
<td></td>
<td>CHEMO</td>
<td>TRAZ</td>
</tr>
<tr>
<td>Negative</td>
<td>CHEMO</td>
<td>TRAZ</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>1980s</th>
<th>1990s: metastatic</th>
<th>2000s: adjuvant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>Als (metastatic)</td>
<td>Anastrozole</td>
</tr>
<tr>
<td>CMF</td>
<td>Zoladex</td>
<td>Letrozole</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Zoledronate</td>
<td>Exemestane</td>
</tr>
<tr>
<td></td>
<td>Taxanes (metastatic)</td>
<td>Fulvestrant</td>
</tr>
<tr>
<td></td>
<td>Epirubicin</td>
<td>Docetaxel</td>
</tr>
<tr>
<td></td>
<td>Vinorelbine</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine</td>
<td>Epirubicin</td>
</tr>
<tr>
<td></td>
<td>Liposomal doxorubicin</td>
<td>Nab paclitaxel</td>
</tr>
<tr>
<td></td>
<td>Capecitabine</td>
<td>Ixabepilone</td>
</tr>
<tr>
<td></td>
<td>Dexrazoxane (cardiac toxicity)</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lapatinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bevacizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pertuzumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Everolimus</td>
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</tbody>
</table>
A 50 year old woman is diagnosed with intermediate grade, 3.5 cm infiltrating ductal carcinoma, 3 involved axillary lymph nodes, no evidence of distant metastasis (stage II).

Baseline risk of recurrence ∼ 60%

- If ER or PR+
  - Chemotherapy + Endocrine therapy
  - Residual risk < 25%
- If HER2+
  - Chemotherapy + AntiHER2 therapy
  - Residual risk < 25%
- If triple negative
  - Chemotherapy…
  - Residual risk 30%–40%

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


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

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


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

<table>
<thead>
<tr>
<th>Sites involved</th>
<th>N</th>
<th>Bone</th>
<th>Soft Tissue</th>
<th>Viscera</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNBC</td>
<td>79</td>
<td>13%</td>
<td>13%</td>
<td>74%</td>
</tr>
<tr>
<td>ER+</td>
<td>123</td>
<td>39%</td>
<td>7%</td>
<td>54%</td>
</tr>
<tr>
<td>HER-2+</td>
<td>78</td>
<td>7%</td>
<td>12%</td>
<td>81%</td>
</tr>
</tbody>
</table>

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

**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.


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

<table>
<thead>
<tr>
<th></th>
<th>Gem/Carbo (n = 44)</th>
<th>BSJ-201 + Gem/Carbo (n = 42)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response, n (%)</strong></td>
<td>7 (16%)</td>
<td>20 (48%)</td>
<td>.002</td>
</tr>
<tr>
<td><strong>Clinical benefit rate, n (%)</strong></td>
<td>9 (21%)</td>
<td>26 (62%)</td>
<td>.0002</td>
</tr>
</tbody>
</table>

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

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")

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hereditary BRCA1</th>
<th>Triple Negative/Basal-Like(^1,2,3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER/PR/HER2 status</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>TP53 status</td>
<td>Mutant</td>
<td>Mutant</td>
</tr>
<tr>
<td>BRCA1 status</td>
<td>Mutational inactivation(^*)</td>
<td>Diminished expression(^*)</td>
</tr>
<tr>
<td>Gene-expression pattern</td>
<td>Basal-like</td>
<td>Basal-like</td>
</tr>
<tr>
<td>Tumor histology</td>
<td>Poorly differentiated (high grade)</td>
<td>Poorly differentiated (high grade)</td>
</tr>
<tr>
<td>Chemosensitivity to DNA-damaging agents</td>
<td>Highly sensitive</td>
<td>Highly sensitive</td>
</tr>
</tbody>
</table>

\(^*\)BRCA1 dysfunction due to germline mutations, promoter methylation, or overexpression of HMG or ID4

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

O’Shaughnessy J, et.al. NEJM 2011
A randomized phase III study of imiparib (BSI-201) in combination with gemcitabine/carboplatin - Windows Internet Explorer

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. Ruda, K. Miller, D. A. Yardley, R. W. Carlson, R. S. Finn, E. Chiriva-Interni, M. Freias, S. Gupta, A. Blackwood-Churchill, E. P. Minas, Baylor Sammons Cancer Center, Texas Oncology, University of Texas Southwestern Medical Center, Dallas, TX, The West Clinic, Memphis, TN; Virginia Oncology Associates, US Oncology, Annapolis, 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.

Abstract:
Background: A randomized phase II study in mTNBC suggested that imiparib (I), an anticancer agent with PARP inhibitory activity, added to GC improved overall survival (OS), without potentiating GC toxicity (O'Shaughnessy et al. J Clin Oncol 29: 2011). This confirmatory study evaluated the safety and efficacy of GC with or without I in a similar mTNBC patient 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 GC plus I (1000 mg/m²; IV) on days 1, 4, 8, and I (5.6 mg/kg; IV) on days 1, 4, 8, and I every 21 days. Upon central confirmation of disease progression on GC, crossover to GC 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 2009, 512 pts were randomized. Pts characteristics were balanced between the two arms. The study did not meet the criteria for significance for the 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. 102 of 259 GC pts (69%) crossed over to receive GC following disease progression. Most frequently occurring grade 3/4 adverse events included neutropenia (53% [GC] vs. 61% [GC+I]), 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, that of this phase II study, addition of I to GC did not meet the prespecified criteria for significance for the primary endpoints of OS and PFS in pts with mTNBC. Analyses aimed at further elucidating these findings are ongoing (clinicaltrials.gov: NCT00936552).

<table>
<thead>
<tr>
<th></th>
<th>GC (n = 259)</th>
<th>GCI (n = 201)</th>
<th>Hazard ratio (95% CI)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months</td>
<td>11.1</td>
<td>11.8</td>
<td>0.876 (0.687-1.116)</td>
<td>0.264</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>4.1</td>
<td>5.1</td>
<td>0.739 (0.546-0.976)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

* 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**: favors combination
- **TTP**: favors combination
- **Survival**: ?
- **Toxicity**: favors single agent
- **Quality of life**: ?

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 class³

**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

EMBRACE: Study Design

**Primary Endpoints**
- OS

**Secondary Endpoints**
- PFS
- ORR
- DoR
- Safety

**Trial Design**
- Open-label, multicenter study (N = 762)
- Locally recurrent or MBC
- 2-5 previous chemotherapies (≥ 2 for advanced disease)
- Previous anthracycline and taxane
- Refractory to most recent chemotherapy

**Treatment**
- Eribulin mesylate
  - 1.4 mg/m², 2-5 min IV bolus
  - Days 1 and 8 of 21-day cycle

**Possibilities**
- Physician’s choice
  - Any monotherapy
  - (cytotoxic, hormonal, biologic, radiotherapy, or supportive care only)

RND 2:1

Control Group Single Agent Treatment Received

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinorelbine</td>
<td>25%</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>19%</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>18%</td>
</tr>
<tr>
<td>Taxanes</td>
<td>15%</td>
</tr>
<tr>
<td>Other Chemotherapies</td>
<td>10%</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>10%</td>
</tr>
<tr>
<td>Hormonal Therapy</td>
<td>3%</td>
</tr>
</tbody>
</table>

Total patients = 247*

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

Updated Overall Survival Analysis

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

Patients with advanced breast cancer and bone metastases
(N = 2046)

- Zoledronic acid 4 mg IV* + Placebo SC every 4 wks
  (n = 1020)

- Denosumab 120 mg SC + Placebo IV every 4 wks
  (n = 1026)

*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).

Denosumab Reduced Time to First On-Study SRE

HR: 0.82 (95% CI: 0.71-0.95; \( P = .0096 \), superiority)

KM Estimate of Median Mos

- Denosumab: 32.4
- Zoledronic acid: 27.4

**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

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.

Understanding Biology: Gene Expression Microarray Approach

Normal Cells → mRNA → cDNA → ErbB2 → DNA microarray → Spot 1, Spot 2, Spot 3

<table>
<thead>
<tr>
<th>Spot</th>
<th>Green</th>
<th>Red</th>
<th>Red/\text{Green}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>200</td>
<td>10000</td>
<td>50.00</td>
</tr>
<tr>
<td>2</td>
<td>4800</td>
<td>4800</td>
<td>1.00</td>
</tr>
<tr>
<td>3</td>
<td>9000</td>
<td>300</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Thank god for computers
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.
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%