Breast Care at KP: The Pathway to Personalized Care
Find It, Treat It, Beat It

KPHC Beacon
Shining the Light on Chemotherapy

David Campen, MD NCAL
Chair – NCAL Regional Med Safety
Co-chair – KP National Beacon Steering

Kaiser Permanente
Background

- Chemotherapy risk
- KP Solutions, past and present
- Rapidly evolving field of medications
- Safety by standardization
Historical Milestones

- **1992** – Kaiser NW takes steps to standardize paper protocols
- **1994** – NCAL Permanente oncologist writes chemo software program in spare time; ultimately, 9 facilities use it
- **1994** – SCAL Pharmacy Director develops chemo management program following Dana-Farber tragedy
Chemotherapy

- Most risky drugs used in medicine
- Dose adjustments and timing are critical
- Requires coordinated effort between
  - Physician
  - Infusion Nurse
  - Oncology Pharmacist
THE DISTURBING CASE OF THE CURE THAT KILLED THE PATIENT

By CHRISTINE GORMAN; LAWRENCE MONDI AND ALICE PARK/NEW YORK AND ROD PAUL/BOSTON

Monday, Apr. 03, 1995

If anyone knew how to get the best medical treatment, it was Betsy Lehman. A health columnist who had worked at the Boston Globe since 1982, she had covered everything from leading-edge research to the finer points of a physician's bedside manner. When she learned she had an advanced case of breast cancer, she carefully studied her options and chose to undergo an experimental treatment offered at the Dana-Farber
New Oncology Drug Pipeline

<table>
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<th>Year</th>
<th># Onc Rx Approved</th>
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<td>2007</td>
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<td>9</td>
</tr>
<tr>
<td>2010</td>
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www.centerwatch.com/drug-information
Lack of standard dosing methods contributes to IV errors

From the August 23, 2007 issue

Key to Safe Medication Use:

Standardization
Standardization of Chemotherapy Protocols at KP

• Collaborative effort of Oncologists, Pharmacists, & Nurses
• Eliminated personal versions of protocols
• Supports patient individualization

<table>
<thead>
<tr>
<th>Protocol Type</th>
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<tr>
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<td>Other Beacon Protocols</td>
<td>28</td>
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</table>
KPHC Beacon

• Develop over 600 standardized protocols in use by five KP Regions
  ▪ New safety response tools, i.e., Mylotarg
  ▪ Implement Oncology Knowledge Database
  ▪ Develop standardized reports to aid in Quality, Safety, Drug Use, and Coding
Number of Patients Treated* via Beacon

- Oncology: 39,164
- Non-Oncology: 3,278

Number of Infusions given via Beacon

- Oncology: 365,888
- Non-Oncology: 27,018

*as of 5/4/2011
Vohs Award for Quality

- Advance care or service quality
- Showcase innovative techniques and knowledge that are transferrable throughout the Program
- Underscore the value of multidisciplinary teamwork
KPHC Beacon Oncology Module

2011 Vohs Award Multi-Region Winner

Video
Questions?
Breast Care at KP: The Pathway to Personalized Care
Find It, Treat It, Beat It

Beacon Oncology Module
Collaborative Build

Ann VonGehr, MD, NCal Region

Kaiser Permanente®
“Miracles will present themselves on the shoulders of research.”
Kaiser Permanente Thrive 2009 - The Medical Mind
http://insidekp.kp.org/insidekp/communicate/thrive/ads/radio.html

CCTAP - SCAL
Cancer Clinical Trials Access Program
Jonathan Polikoff, MD Director

KPOCT –NCAL
Kaiser Permanente Oncology Clinical Trials Program
Lou Fehrenbacher, MD Director
WHY DO RESEARCH AT KP?

- Offers patients **access** to cancer clinical trials and investigational therapies as treatment options.
- Maintains direct **control** of cancer patients’ care and improves patient satisfaction.
- Contributes towards KP’s reputation as an innovator in high-**quality** care delivery.
- Allows opportunities for oncologists to maintain and expand their present **knowledge** base.
WHY DO RESEARCH AT KP?

- Serves as a recruitment tool to attract the best oncology physicians

- **Aligns** southern and northern California Kaiser Permanente clinical trial access, creating potential for future opportunities

- Contributes to pharmaceutical **cost control**

- Satisfies **regulatory** demands
PROGRAM STRUCTURE

- Regionally coordinated and administered (San Diego/ Vallejo)

- Locally, each MSA has a research team comprised of a physician champion and dedicated research personnel, including a clinical research RN and a research assistant.

- The team has immediate access to all available clinical trials, eligibility criteria, and protocols to assist the local area medical oncologist in entering patients into clinical trials. BEACON protocols include the open studies.
PROGRAM STRUCTURE

- Senior manager works closely with local area administration to ensure compatibility with local needs and that issues are addressed as needed.
- Physician champions meet on a regular basis to discuss accrual/study updates and to vote on new trials.
- Sources of funding:
  - SCPMG (Dept. of Research and Evaluation)/TPMG (Department of Research)
  - Cooperative Groups (NCI) NSABP/SWOG/CTSU
  - Pharmaceutical Sponsors
Types of Studies

- Phase II
- Phase III
- Expanded Access
- Prevention
Accrual by Trial Type

Focus: A ratio of 65% Cooperative Trials to 35% Pharmaceutical & Expanded Access Trials

- Cooperative Group Trials are Phase II and Phase III studies funded primarily by the National Cancer Institute. CCTAP was a member of ECOG, CALGB and NSABP until Q4-2010 when SWOG replaced CALGB as a CCTAP affiliate. Included 1 Preventative Care Study (P5)

- Pharmaceutical trials are Phase II and Phase III studies that test novel therapeutics or attempt to establish new indications for FDA approved therapeutics.

- Expanded access programs bring active agents to our patients prior to their expected FDA approval.
Accrual CCTAP/ KPOCT / COLO

Year | CCTAP | KPOCT | COLO | TOTAL
--- | --- | --- | --- | ---
2008 | 237 | 389 | 48 | 674
2009 | 220 | 442 | 79 | 741
2010 | 164 | 295 | 49 | 508

Legend:
- **CCTAP**
- **KPOCT**
- **COLO**
- **TOTAL**
CCTAP 2010 – Drug Savings

Total YE Drug Savings – $2,509,587
Focus: All Study Drugs

- Sponsor funded study drugs are made available free of charge to the Permanente Medical Group and to our Oncology Patients

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<th>Qtr2</th>
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<th>Qtr3</th>
<th>Savings</th>
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Grand Total     | $540,182.00 | $699,143.00 | $628,269.00 | $641,993.00 | $     | -       | $2,509,587.00 |

E. Arredondo

Kaiser Permanente
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<td>NSABP B-30</td>
<td>P3 Adjuvant AC-T vs AT vs ATC in women with positive axillary nodes.</td>
<td>243 pts</td>
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<tr>
<td>NSABP B-31</td>
<td>P3 Adjuvant AC-WP followed by AC-WP plus Herceptin in node positive patients who overexpress Her2.</td>
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<td>NSABP B-44</td>
<td>(BETH) P3 Adjuvant TCH vs TCH + Avastin in women who overexpress Her2.</td>
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<td>P-2</td>
<td>P3 Study of Tamoxifen and Raloxifene (STAR) for Prevention of Breast Cancer</td>
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<td>PACCT-1</td>
<td>Program for the Assessment of Clinical Cancer Tests: Trial Assigning Individualized Options for Treatment: The TAILORx Trial</td>
<td>340 pts</td>
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Longer Therapy, Iatrogenic Amenorrhea, and Survival in Early Breast Cancer

Sandra M. Slawin, M.D., Jong-Hyeon Jeong, Ph.D., Charles E. Geyer, Jr., M.D., Joseph P. Costantino, Dr.P.H., Eduardo R. Pajon, M.D., Louis Fehrenbacher, M.D., James N. Atkins, M.D., Jonathan Polikoff, M.D., Victor G. Vogel, M.D., M.H.S., John K. Erban, M.D., Priya Rastogi, M.D., Robert B. Livingston, M.D., Edith A. Perez, M.D., Eleftherios P. Marmounas, M.D., M.P.H., Stephanie R. Land, Ph.D., Patricia A. Ganz, M.D., and Norman Wolmark, M.D.

ABSTRACT

BACKGROUND

Chemotherapy regimens that combine anthracyclines and taxanes result in improved disease-free and overall survival among women with operable lymph-node-positive breast cancer. The effectiveness of concurrent versus sequential regimens is not...
## Risk of Death: Sequential ACT vs. Concurrent ACT

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>No. of Events</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio with 95% CI</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Concurrent ACT</td>
<td>Sequential ACT</td>
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</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
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<td></td>
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<tr>
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<td>135</td>
<td>119</td>
<td>0.86</td>
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<td>≥50 yr</td>
<td>1933</td>
<td>143</td>
<td>121</td>
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<td><strong>No. of positive lymph nodes</strong></td>
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<tr>
<td>≥4</td>
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<tr>
<td>≤2 cm</td>
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<td>77</td>
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<td>200</td>
<td>165</td>
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<tr>
<td><strong>Hormone therapy</strong></td>
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<tr>
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## C. Risk of Death: Sequential ACT vs. Doxorubicin–Docetaxel

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<th>Subgroup</th>
<th>No. of Patients</th>
<th>No. of Events</th>
<th>Hazard Ratio</th>
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<td><strong>Age</strong></td>
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Sequential ACT Better

Doxorubicin–Docetaxel Better
### Risk of Death, According to Menstrual-History Subgroup

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<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>No. of Events</th>
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The New England Journal of Medicine
Downloaded from nejm.org at KAISER PERMANENTE on April 27, 2011. For personal use only. No other uses without permission. Copyright © 2010 Massachusetts Medical Society. All rights reserved.
Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer


ABSTRACT

BACKGROUND
We present the combined results of two trials that compared adjuvant chemotherapy with or without concurrent trastuzumab in women with surgically removed HER2-positive breast cancer.

METHODS

Updated B/31/N9831 Joint Analysis
Disease-Free Survival*

AC ⇒ T+ H
(n=1,989; 222 e)

AC ⇒ T
(n=1,979; 397 e)

Alive and disease-free (%)

N=619 events

HR*_{adj} = 0.48 (95% CI: 0.41-0.57)

*Nodes, receptor status, paclitaxel schedule, protocol

P < 0.000001

1,854 1,347 868 522 202 4
1,800 1,235 753 460 168 8

Number at risk
Effects of Tamoxifen vsRaloxifene on theRisk of DevelopingInvasive Breast Cancerand Other Disease Outcomes
The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial

Context. Tamoxifen is approved for the reduction of breast cancer risk, and raloxifene has demonstrated a reduced risk of breast cancer in trials of older women with osteoporosis.

Objective. To compare the relative effects and safety of raloxifene and tamoxifen on the risk of developing invasive breast cancer and other disease outcomes.

Design, Setting, and Patients. The National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene trial, a prospective, double-blind, randomized clinical trial conducted beginning July 1, 1990, in nearly 200 clinical centers throughout North America, with trial analysis initiated after at least 52% of accrued invasive breast cancers were diagnosed. Patients were 19747 postmenopausal women of mean age 58.5 years with increased 5-year breast cancer risk (mean risk, 4.03% [95% CI, 2.07%-6.17%]). Data reported are based on a cutoff date of December 31, 2005.

Intervention. Oral tamoxifen (20 mg/d) or raloxifene (60 mg/d) over 5 years.

Main Outcome Measures. Incidence of invasive breast cancer, uterine cancer, non-invasive breast cancer, bone fractures, thromboembolic events.

Results. There were 123 cases of invasive breast cancer in women assigned to tamoxifen and 168 in those assigned to raloxifene (incidence, 4.30 per 1000 vs 4.41 per 1000; risk ratio [RR], 1.02; 95% confidence interval [CI], 0.82-1.26). There were fewer cases of noninvasive breast cancer in the tamoxifen group (37 cases) than in the raloxifene group.
Study of Tamoxifen and Raloxifene (STAR): Initial Findings from the NSABP P-2 Breast Cancer Prevention Study

D.L. Wickerham, J.P. Costantino, V. Vogel, W.M. Cronin, R.S. Cecchini, J. Atkins, T. Bevers, L. Fehrenbacher, W. McCaskill-Stevens, N. Wolmark
Risk-Eligible Postmenopausal Women

STRATIFICATION
• Age
• Gail Model Risk
• Race
• History of LCIS

TAMOXIFEN
20 mg/day x 5 years

RALOXIFENE
60 mg/day x 5 years
P-2 STAR
Average Annual Rate and Number of Invasive Breast Cancers

- Gail Model Projection: 312*
- TAM: 163
- Raloxifene: 168

* # of events

*NSABP*
P-2 STAR
Average Annual Rate And Number Of Non-invasive (In Situ) Cancers

Relative risk = 1.40
95% Confidence Interval: 0.98 to 2.00

Av Ann Rate per 1000

57*

80

* # of events

TAM

Raloxifene
Eribulin monotherapy versus treatment of physician’s choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study

Javier Cortes, Joyce O'Shaughnessy, David Loesch, Joanne L Blum, Linda T Vahdat, Katarina Petrakova, Philippe Chollet, Alexey Manikas, Veronique Deras, Thierry Delozer, Vladimir Vladimirov, Fatima Cardoso, Han Koh, Philippe Bougnoux, Corina E Duccis, Seth Seegobin, Denis Mir, Nicole Meneses, Jantien Wanders, Chris Twelves, on behalf of the EMBRACE (Elsal Metastatic Breast Cancer Study Assessing Physician’s Choice Versus E7389) Investigators

Summary

Background Treatments with survival benefit are greatly needed for women with heavily pretreated metastatic breast cancer. Eribulin mesilate is a non-taxane microtubule dynamics inhibitor with a novel mode of action. We aimed to compare overall survival of heavily pretreated patients receiving eribulin versus currently available treatments.
Eribulin Results

Hazard ratio 0.81 (95% CI 0.66-0.99), p=0.041

Deaths: 274 (54%), eribulin; 148 (58%), TPC

Number at risk

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Erbulin (n=508)</th>
<th>TPC (n=254)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>508</td>
<td>254</td>
</tr>
<tr>
<td>2</td>
<td>491</td>
<td>237</td>
</tr>
<tr>
<td>4</td>
<td>451</td>
<td>206</td>
</tr>
<tr>
<td>6</td>
<td>401</td>
<td>176</td>
</tr>
<tr>
<td>8</td>
<td>320</td>
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<td>10</td>
<td>255</td>
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<td>12</td>
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<td>26</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>28</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Phase II Study of Bevacizumab Plus Temozolomide During and After Radiation Therapy for Patients With Newly Diagnosed Glioblastoma Multiforme


See accompanying editorial on page 124

Abstract

Purpose
This open-label, prospective, multicenter single-arm phase II study combined bevacizumab (BV) with radiation therapy (RT) and temozolomide (TMZ) for the treatment of newly diagnosed glioblastoma (GBM). The objectives were to determine the efficacy of this treatment combination and the associated toxicity.

Patients and Methods
Seventy patients with newly diagnosed GBM were enrolled between August 2006 and November 2008. Patients received standard RT starting within 3 to 6 weeks after surgery with concurrent administration of daily TMZ and biweekly BV. After completion of RT, patients resumed TMZ for 5 days every 4 weeks and continued biweekly BV. MGMT promoter methylation was assessed on patient tumor tissue. A University of California, Los Angeles/Kaiser Permanente Los Angeles
Negative Results Can Be Useful, Too

- **NSABP B-22**
  A Clinical Trial to Evaluate Dose Intensification and Increased Cumulative Dose on the Disease-Free Survival and Survival of Primary Breast Cancer Patients with Positive Axillary Nodes Receiving Postoperative Adriamycin-Cyclophosphamide Therapy

- **NSABP B-25**
  A Clinical Trial to Evaluate the Effect of Dose Intensification and Increased Cumulative Dose of Postoperative Adriamycin-Cyclophosphamide Therapy with G-CSF on the Disease-Free Survival and Overall Survival of Patients with Primary Breast Cancer and Positive Axillary Nodes
More Taste, Less Filling
The Future: More Specific, Less Toxic
Personalized Medicine

- Oncotype Dx – personalized risk assessment (ER+ patients only)
- PARP inhibition – Triple Negative Breast Cancer
- Her2 Blockade – multiple inhibitors
- Antibody drug conjugates (T-DM1)
- Anti-angiogenesis
- Genomic analysis (PI3K mutations etc.)
Breast Care at KP: The Pathway to Personalized Care
Find It, Treat It, Beat It

New Breast Cancer Trials
KPOCT 2011

Lou Fehrenbacher, MD Director, KPOCT–NCAL
Kaiser Permanente Oncology Clinical Trials: Breast Cancer

- KPOCT is a major contributor in many national breast cancer trials, NCI (NSABP, SWOG), and industry.
- Accrual is often in the top 3 U.S. institutions
- KPOCT trials are phases II and III
- KP involvement in trials, when recognized, greatly enhances KP’s reputation
- KPOCT has 85 oncologists who are investigators and enroll patients into these trials

Current major trials:
TDM-1
Trojan Horse for HER2+ Breast Cancer

- Trastuzumab (HER2 monoclonal Ab) and Maytansine (potent cytotoxic) conjugate
- Attaches to HER2+ surface antigen on HER2+ overexpressing breast cancer cell
- Cellular internalization
- Intracellular cleavage of T-M bond releases free maytansine
- In phase II trials, the most potent agent ever in HER2+ breast cancer
- Not FDA-approved, to date
DM1 is a highly potent antimicrotubule agent

T-DM1 undergoes receptor-mediated internalization

Free DM1 releases within cell

Source: Adapted with permission from Mackey JR. Discussant, ASCO 2009 Metastatic Breast Cancer Poster Discussion.
1st line metastatic breast cancer (MBC):
   - TDM1 vs. TDM1+pertuzumab vs. trastuzumab+taxane chemorx (standard arm)
     "Marianne" study

2nd, 3rd line MBC - open
   - TDM1 vs. Lapatinib+capecitabine (std arm)

4th, 5th line MBC (refractory) - to open
   - TDM1 vs. physician choice
Humans undergo millions of DNA mutations every day.

Multiple redundant DNA repair mechanisms fix these mutations to prevent consequences.

Chemotherapy induces innumerable DNA defects.

These are overwhelmingly rapidly repaired.
Inherited defects in DNA repair lead to high rates of cancer, including triple negative breast cancer (BRCA 1 + 2).

Most cancers have acquired defects in DNA repair mechanisms in addition to critical pathway defects.

Parp (poly ADP ribose polymerase) is a major DNA repair pathway.

BRCA 1,2 defects are in a separate repair pathway from Parp.
Phase II Randomized Trial in Triple Negative Breast Cancer (TNBC)

Eligibility

mTNBC with measurable disease
0-2 prior chemotherapy regimens for mBC

R

BSI-201 (5.6 mg/kg IV D1, 4, 8, 11)
Gemcitabine (1000 mg/m² IV d1,8) +
Carboplatin (AUC 2 IV d 1, 8) q21 days

Gemcitabine (1000 mg/m² IV d1,8) +
Carboplatin (AUC 2 IV d 1, 8) q21 days

# Phase II Randomized Trial of Parp Inhibitor BSI-201 in TNBC

## Results: Efficacy (N = 116)

<table>
<thead>
<tr>
<th></th>
<th>GC</th>
<th>GC + BS-201</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response rate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 44, 42)</td>
<td>16%</td>
<td>48%</td>
<td>—</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Clinical benefit rate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CR + PR + SD ≥ 6 mos)</td>
<td>21%</td>
<td>62%</td>
<td>—</td>
<td>0.0002</td>
</tr>
<tr>
<td>(n = 44, 42)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median progression-free survival</strong></td>
<td>3.3 mos</td>
<td>6.9 mos</td>
<td>0.342 (0.20-0.58)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(n = 59, 57)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median overall survival</strong></td>
<td>5.7 mos</td>
<td>9.2 mos</td>
<td>0.348 (0.19-0.65)</td>
<td>0.0005</td>
</tr>
<tr>
<td>(n = 59, 57)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Parp Inhibitor Studies in Breast Cancer

- Iniparib (BSI 201) is a potent IV Parp inhibitor
- Numerous other Parp inhibitors in development, many oral
- Triple negative breast cancer: highly aggressive, poorly responsive CA
  - High Parp activity, defects in other repair pathways

- Bipar 20091123- Phase III, TNBC Carbo/Gem +/- BSI 201, Results: ASCO 2011
- Bipar Expanded Access- NonRand: TNBC 2nd-4th line, BSI 201 with Carbo/Gem KPNC >30 patients
Future Studies with Parp Inhibitors

- **B-48: NSABP NeoAdjuvant Study in Palpable Breast Cancer.** Chemorx +/- BSI 201. Fall 2011?

- **Ongoing Squamous Cell Lung Cancer:** Phase III randomized Carbo/Gem +/- BSI 201

- **Proposed Ovarian Cancer Phase III**

- **Other Breast Cancer settings**
Multi-Gene Expression Determines Prognosis and Response

?? In All Stages of Breast Cancer:

- Many genes are up and down regulated in cancers, including breast cancer (BC)

- Gene expressions differ in BC subtypes:
  - Luminal A, ER+, low prolif
  - Luminal B, ER+ high prolif
  - Normal
  - HER2 positive
  - Basal, Triple Negative, (ER,PR,HER2 negative)

- Gene expression scores have been able to predict outcome and chemotherapy sensitivity
Oncotype DX 21 Gene Recurrence Score Assay

16 Cancer and 5 Reference Genes From 3 Studies

**PROLIFERATION**
- Ki-67
- STK15
- Survivin
- Cyclin B1
- MYBL2

**ESTROGEN**
- ER
- PR
- Bcl2
- SCUBE2

**INVASION**
- Stromolysin 3
- Cathepsin L2

**GSTM1**  **BAG1**  **CD68**

**REFERENCE**
- Beta-actin
- GAPDH
- RPLPO
- GUS
- TFRC

\[ RS = +0.47 \times \text{HER2 Group Score} \]

\[-0.34 \times \text{ER Group Score} \]

\[+1.04 \times \text{Proliferation Group Score} \]

\[+0.10 \times \text{Invasion Group Score} \]

\[+0.05 \times \text{CD68} \]

\[-0.08 \times \text{GSTM1} \]

\[-0.07 \times \text{BAG1} \]

**Category**  **RS (0 – 100)**

- **Low risk**  **RS < 18**
- **Int risk**  **RS \geq 18 \text{ and } < 31**
- **High risk**  **RS \geq 31**
NSABP B-20: Node Negative ER+ Breast Cancer

Tam vs. Tam + Chemo – All 651 Pts

Small advantage to CMF chemorx

```
N       Events
424        33
227        31
```

$p = 0.02$
B-20: Absolute % Increase in DRFS at 10 Years

Benefit of Chemo Depends on RS

- Low RS < 18, n = 353
- Intermediate RS 18-30, n = 134
- High RS ≥ 31, n = 164

Total of 651 Patients

% Increase in DRFS at 10 Yrs (mean ± SE)

p-value (interaction chemo x RS) = 0.04
KPOCT Studies Evaluating a Gene Expression Tool Prospectively

PACCT 1: Node Negative ER+ Patients

- Divided into High, Intermediate, Low Recurrence Score (RS).
- Intermediate group randomized to chemoRx or No chemorx. Thousands of pts randomized.
- Finished Accrual: end 2010  KPOCT >50 Pts
- Results may reduce adjuvant chemorx more than 50%
**SWOG 1007: Node Positive ER+ Patients**

- Opening Summer 2011
- Patients divided into High, Intermediate, Low RS
- Intermediate group randomized to Chemorx or No chemorx.
- Based on SWOG 8816 node positive trial with same outcome as B20 re: RS predicting chemorx benefit
Operable Breast Cancer
HER-2 Positive Tumor
Path-Positive Axillary Nodes

Randomization

AC x 4* 

↓

Taxol x 4

AC x 4*

↓

Taxol x 4 + Herceptin

* Tamoxifen for ER+ or PgR+, optional for ≥50 yrs.
  Optional for ER− and PgR− patients ≥50 yrs.

Accrual 2000 to 2005, KP highest in US, 105
Combined Analysis Disease-Free Survival

**B-31**

- **AC→T**: 872, 171 events
- **AC→T+H**: 864, 83 events
- HR = 0.45, 2P = 1x10^{-9}

**N9831**

- **AC→T**: 807, 90 events
- **AC→T+H**: 808, 51 events
- HR = 0.55, 2P = 0.0005
OS of All Participants in NSABP B-31
2009 Update

Figure 2. Overall Survival (as of 09/30/2009)

NSABP Protocol B-31

40% Reduction in Death
At 8-year follow-up

<table>
<thead>
<tr>
<th>Trt</th>
<th>N</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC-&gt;T</td>
<td>1024</td>
<td>187</td>
</tr>
<tr>
<td>AC-&gt;TH</td>
<td>1030</td>
<td>119</td>
</tr>
</tbody>
</table>

RR=0.60  p<0.0001
<table>
<thead>
<tr>
<th>Central HER2 Assay</th>
<th>ACT #events/total</th>
<th>ACTH #events/total</th>
<th>RR (95% CI)</th>
<th>P-value</th>
<th>Interaction p-value</th>
</tr>
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<tbody>
<tr>
<td><strong>DFS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pos</td>
<td>163/875</td>
<td>85/804</td>
<td><strong>0.47</strong> (0.37-0.62)</td>
<td>&lt;0.0001</td>
<td>0.47</td>
</tr>
<tr>
<td>Neg</td>
<td>20/92</td>
<td>7/82</td>
<td><strong>0.34</strong> (0.14-0.80)</td>
<td>0.014</td>
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<tr>
<td><strong>RFI</strong></td>
<td></td>
<td></td>
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<tr>
<td>Pos</td>
<td>145/875</td>
<td>77/804</td>
<td><strong>0.49</strong> (0.37-0.65)</td>
<td>&lt;0.0001</td>
<td>0.58</td>
</tr>
<tr>
<td>Neg</td>
<td>16/92</td>
<td>6/82</td>
<td><strong>0.36</strong> (0.14-0.92)</td>
<td>0.034</td>
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<td><strong>OS</strong></td>
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<tr>
<td>Pos</td>
<td>55/875</td>
<td>38/804</td>
<td><strong>0.66</strong> (0.43-0.99)</td>
<td>0.047</td>
<td>0.08</td>
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<tr>
<td>Neg</td>
<td>10/92</td>
<td>1/82</td>
<td><strong>0.08</strong> (0.01-0.64)</td>
<td>0.017</td>
<td></td>
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</table>
NSABP B-31: FISH Negative, IHC 0,1+,2+

Disease-Free Survival

HR=0.64, p=0.16

Time from Randomization vs. % Disease-Free
DFS for IHC 0-2 and FISH ratio < 2.0 in NCCTG 9831

Fig. 1

Disease-Free Survival (%)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC→T</td>
<td>44</td>
<td>14</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>AC→T+H</td>
<td>59</td>
<td>9</td>
<td>0.51 (0.21 to 1.23)</td>
<td>.14</td>
</tr>
</tbody>
</table>

doxorubicin, cyclophosphamide and paclitaxel

HR = 0.51

doxorubicin, cyclophosphamide, paclitaxel and trastuzumab

B-47 Adjuvant Trastuzumab in Patients with Normal HER2 Expression Breast Cancer

High Risk Primary Breast Cancer
IHC 1+ or 2+ for HER2
FISH Negative

Randomization

Docetaxel 75mg/m^2 + CTX 600mg/m^2 Q3wk x 6
Or (MD Choice)
ACx4, + Paclitaxel Qwk x 12
Std or DD AC

Docetaxel 75mg/m^2 + CTX 600mg/m^2 Q3wk x 6
Or (MD Choice)
ACx4, Paclitaxel Qwk x 12
Std or DD AC
+ Trastuzumab x 1 yr
beginning with TC or WP
**KP NorCal Population-based cohort of All Consecutive BC patients 1/2000 to 1/2006**

<table>
<thead>
<tr>
<th>IHC</th>
<th>0 %total</th>
<th>1+ 32%</th>
<th>2+/FISH- 15%</th>
<th>3+/FISH+ 13.6%</th>
<th>Total# 16,975</th>
</tr>
</thead>
</table>

47%

**3.5X as many patients with IHC 1+, 2+ and FISH-negative THAN FISH+/3+**
Participate in KP Clinical Trials

- **All of our current best therapies were:**
  - The experimental arm of a clinical trial
  - Compared to a prior standard best therapy
  - The winner of that comparison

- **George Sledge MD ex-ASCO president:**
  “No one is smarter than a Phase III trial.”

- **Give our patients a chance to receive next year’s best therapy**
Questions?