Hormone-Independent Metastatic Breast Cancer

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Discussion Points

• Heterogeneity of hormone resistant breast cancers
  – Triple negative
  – HR positive disease resistant to hormonal therapies

• Goals of treatment
  – To prolong life
  – Maintain QOL
  – Palliate symptoms

• Optimally balance the benefits and toxicities of therapy
Improvements in OS in MBC

-Population based study from British Columbia
-Compared survival in pts with first diagnosis of MBC in 4 time cohort

<table>
<thead>
<tr>
<th>Year of Diagnosis</th>
<th>OS (days)</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991-1992</td>
<td>438</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>1994-1995</td>
<td>450</td>
<td>0.97</td>
<td>.65</td>
</tr>
<tr>
<td>1997-1998</td>
<td>564</td>
<td>0.84</td>
<td>.011</td>
</tr>
<tr>
<td>1999-2001</td>
<td>667</td>
<td>0.72</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Ref: Chia et al. Cancer 2007;110:973-979
- 11 ECOG adjuvant chemotherapy trials from 1978-2002
- 13,785 patients, of whom 3447 (25%) had distant recurrence
- Median OS after recurrence was 20 months
- Improvement in OS seen only in those pts with short DRFI (trastuzumab effect)
- Shorter DRFI, ER neg, # positive LNs, and black race associated with inferior survival after relapse —NOT year of recurrence

Patterns of Recurrence in ESBC

- 1/90 thru 3/11
- 53 RCTs and > 86,000 pts
- Proportion of Loco-regional recurrences has decreased from 30% to 15% (P<0.001)
- Only use of adjuvant chemotherapy was statistically correlated
- Improvements in DFS are more weighted towards a reduction in LR rather distant met recurrences

Caveats of Data

• Perils of Phase II studies
  – Do not necessarily translate into positive phase III trials

• Choice of endpoints
  – PFS vs OS
  – Obtain FDA approval
God speaks to oncologists with large, randomized phase III trials

The devil speaks with small single institution phase II trials

Paraphrasing George W. Sledge, M.D.
Surrogate Endpoints for Overall Survival in Metastatic Breast Cancer

- Excellent correlation between RR and PFS
- Poor correlation between PFS and OS

Determinants of Therapy

• Understand the drivers of the tumor
• Great targets
  – Estrogen Receptor
  – Her 2 Receptor
• Triple Negative
  – No proven target
  – Heterogeneity
Changes in ER, PgR, and HER2 between the original primary and metastasis

- Heterogeneity within the original tumor and metastatic sites

Breast cancer recurrence (N = 117)

- Receptors concordant with primary (62.4%)
- Receptors discordant with primary (37.6%)

ER discordance (16.0%)
Gain 4/25 (16.0%)
Loss 11/69 (15.9%)

PgR discordance (40.4%)
Gain 4/48 (8.3%)
Loss 34/36 (73.9%)

HER2 discordance (9.6%)
Gain 6/73 (8.2%)
Loss 2/10 (20.0%)

Amir E et al. JCO 2012;30:587-592
Survival By Discordance

- No compromise in outcome
- No discordance in TN
- Loss of PR associated with worse TTP with HT
- Re-analysis primary tumors, discordance rates (ER 6%, PR 12%, HER2 4%)
- Avoid Bone Bx (lowest yield at 64%)
- Lead to changes in Rx in 14% (1 in 7)

Amir E et al. JCO 2012;30:587-592
Intrinsic Subtypes (Perou and Sorlie)

Luminal A  Luminal B  ERBB2+  Basal  Normal

BL1  BL2  IM  M  MSL  LAR

Triple Negative Tumors

BL1 = basal-like 1
BL2 = basal-like 2
IM = immunomodulatory
M = mesenchymal
MSL = mesenchymal stem-like
LAR = luminal androgen receptor

Ref: Sorlie et al. PNAS 2001; 98;10869
## Triple Negative Subtype as a Determinant of Therapy

<table>
<thead>
<tr>
<th>TN Subtype</th>
<th>Characteristics</th>
<th>Targeted Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal like-1</td>
<td>BRCA, HRD High pCR rates</td>
<td>Platinums, PARP inhibitors</td>
</tr>
<tr>
<td>Basal like-2</td>
<td>~BL1, but EGF, MET, IGFR1</td>
<td>EGFR inhibitors</td>
</tr>
<tr>
<td>Immunomodulatory (IM)</td>
<td>immune cell signaling, NFKB, JAK/STAT, TNF Medullary</td>
<td>Anti-PD-1, PD-L1, CTLA-4 antibodies, JAK 2 inhibitors</td>
</tr>
<tr>
<td>Mesenchymal (M)</td>
<td>EMT, TGF-B, Src Metaplastic cancer</td>
<td>Dasatinib, Sarcoma regimens (Doxil, Temsirolimus, Bev 42% RR in 12 pts)¹</td>
</tr>
<tr>
<td>Mesenchymal stem-like (MSL)</td>
<td>Angiogenesis: VEGFR2, PDGF, EGFR</td>
<td>Anti-angiogenics</td>
</tr>
<tr>
<td>Luminal androgen receptor (LAR)</td>
<td>Androgen receptor and other hormone pathways</td>
<td>Bicalutamide, abiraterone, enzalutamide, mTOR i</td>
</tr>
</tbody>
</table>

(Ref: Moroney et al. CCR 2012: 18:5796)
# PARP Inhibitors in BRCA Associated Breast Cancer

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>ORR</th>
<th>PFS (mo)</th>
<th>Germline BRCA</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>400mg BID 100mg BID</td>
<td>11/27 (41%) 6/22 (22%)</td>
<td>5.7 mo (4.6 – 7.4 )</td>
<td>100%</td>
<td>Fatigue, nausea, vomiting, anemia</td>
</tr>
<tr>
<td>Veliparib</td>
<td>40mg BID + TMZ Expansion</td>
<td>17% (all) 37.5% (BRCA +)</td>
<td>1.9 mo 5.5 mo</td>
<td>23 TN + 8 BRCA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.5 mo</td>
<td>21 BRCA</td>
<td>Myelo-suppression</td>
</tr>
</tbody>
</table>

PARP Inhibitors and BRCA Disease

- Olaparib 400mg BID
- No responses in TN without BRCA germline mutations
- SD in 38% of BRCA carriers of which ~50% were TN
- Major toxicities: Fatigue, nausea, vomiting, decreased appetite

Targeting EGFR

• EGFR overexpressed in TNBC
• Correlate with BL subtype
• BL subtype often have defects in DNA repair genes and thus may be particularly sensitive to DNA damaging agents such as platinums
Cetuximab in TN MBC

Stage IV TNBC ≤ 1 prior Rx for MBC 2:1

- Cisplatin 75mg/m² D1 q 3 weeks + Cetuximab 400mg/m² load followed by 250mg/m² weekly N = 115
- 6 cycles Cisplatin

- Cisplatin 75mg/m² D1 q 3 weeks N = 58

Maintenance Cetuximab

Median age: 52 years 1st line: 73%

Baselga J et al. JCO 2013;31:2586-2592
A

Progression-Free Survival (proportion)

No. of Events
Median PFS, mos
95% CI

Cetuximab + cisplatin
(n = 115)
3.7
2.8 to 4.3
Cisplatin alone
(n = 58)
1.5
1.4 to 2.8

HR (95% CI): 0.67 (0.47 to 0.97)
P = .032 (strat. log-rank)

B

Overall Survival (proportion)

No. of Events
Median OS, mos
95% CI

Cetuximab + cisplatin
(n = 115)
12.9
9.6 to 15.6
Cisplatin alone
(n = 58)
9.4
6.7 to 14.2

HR (95% CI): 0.82 (0.56 to 1.20)
P = .31 (strat. log-rank)

ORR: 20% vs 10%

Baselga J et al. JCO 2013;31:2586-2592
## Randomized Trials of Cetuximab in Triple Negative Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Treatment Arms</th>
<th>ORR</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carey et al TBCRC001</td>
<td>102</td>
<td>Cetuximab → Cet/carbo&lt;br&gt;Carboplatin + cetuximab</td>
<td>6% 17%</td>
<td>1.4 mo. 2.1 mo.</td>
</tr>
<tr>
<td>Baselga et al BALI-1</td>
<td>173</td>
<td>Cisplatin&lt;br&gt;Cisplatin + cetuximab</td>
<td>10% 20%</td>
<td>1.5 mo. 3.7 mo. (p=0.03)</td>
</tr>
<tr>
<td>O’Shaughnessy et al</td>
<td>154</td>
<td>Irinotecan + carbo → cetuximab&lt;br&gt;Irinotecan + carbo + cetuximab</td>
<td>28% 33%</td>
<td>4.5 mo. 4.7 mo.</td>
</tr>
</tbody>
</table>

Baselga J et al. JCO 2013;31:2586-2592  
O’Shaughnessy et al. Proc SABCS 2008; Abstract 308.
EGFR Inhibitors in TN

- Disappointing results with cetuximab
- ORR 5-10% as single agent in unselected TN patients
- Small molecule inhibitors (TKIs)
  - Single agent trials
  - Erlotinib RR 3%
  - Gefitinib RR 0%
Disappointing Results with EGFR inhibitors: Another Hypothesis

EGFR on Breast Cancer Cell Surface

Translocation to nucleus

MUC-1

EGFR interacts with DNA/promoters of cell cycling genes (Cyclin D1)

Cell Growth and Cancer Progression

Signaling through receptor

Nonessential pathway of cell growth?

Cetuximab
Erlotinib
Gefitinib

Refs: Schroeder, *MUC1 regulates nuclear localization and function of the epidermal growth factor receptor*, J Cell Sci., 2010
Schroeder, Cancer Res, 2007
- MB-MDA-468 (TN breast cancer cell line)
- EGFR = green staining
- Presence of EGF and MUC-1 $\rightarrow$ EGFR translocates to the nucleus
- In presence of EGF and siRNA to MUC-1 $\rightarrow$ no EGFR in the nucleus, but instead trapped at the nuclear membrane

Inhibition of cell growth
Targeting Angiogenesis

- TNBC have higher levels of VEGF compared to ER+ BC
- Mutated p53 associated with increased plasma and intratumoral levels of VEGF and BL subtypes
- Wildtype p53 increases levels of the natural inhibitor of angiogenesis, thrombospondin-1
Meta-analysis of First-line Bevacizumab Plus Chemotherapy Trials

- E2100, AVADO, RIBBON-1 trials
- \(N = 2447\)
- TN subgroup = 621 pts

<table>
<thead>
<tr>
<th></th>
<th>All Patients ((N = 2447))</th>
<th>Triple Negative Patients ((N = 621))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chemo</td>
<td>Chemo + Bev</td>
</tr>
<tr>
<td>ORR</td>
<td>32%</td>
<td>49%</td>
</tr>
<tr>
<td>PFS (mo)</td>
<td>6.7</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td>(0.57-0.71)</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>26.4</td>
<td>26.7</td>
</tr>
<tr>
<td>1 year survival</td>
<td>77%</td>
<td>82%</td>
</tr>
</tbody>
</table>

Miles D W et al. Ann Oncol 2013;1-8
Phase III RIBBON 2 Trial of Chemotherapy/Bevacizumab in Second-line HER2-Negative MBC

Inclusion criteria:
• 1 prior chemotherapy

Exclusion criteria:
• > 1 cytotoxic regimen for MBC
• HER2+
• Prior VEGF-targeted therapy

Primary endpoint: progression-free survival
Chemotherapy regimen is determined by investigator prior to randomization.

Cytotoxic regimens:
- Taxane* (docetaxel, paclitaxel, or albumin-bound paclitaxel)
- Gemcitabine
- Vinorelbine
- Capecitabine

Bevacizumab dosing:
- 10 mg/kg q 2 weeks
- 15 mg/kg q 3 weeks

Placebo q 2 weeks or q 3 weeks

RIBBON 2 allows docetaxel, paclitaxel, or albumin-bound paclitaxel.

* RIBBON 2 allows docetaxel, paclitaxel, or albumin-bound paclitaxel.

(n = 684)

Brufsky et al. JCO 2011;29:4286-93.
## RIBBON 2: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy/Placebo</th>
<th>Chemotherapy/Bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Response Rate</strong></td>
<td>29.6%</td>
<td>39.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$P = .0193$</td>
</tr>
<tr>
<td><strong>Median Progression-Free Survival</strong></td>
<td>(n = 225)</td>
<td>(n = 459)</td>
</tr>
<tr>
<td></td>
<td>5.1 months</td>
<td>7.2 months</td>
</tr>
<tr>
<td></td>
<td>HR 0.78 (95% CI, 0.64-0.93); $P = .0072$</td>
<td></td>
</tr>
<tr>
<td><strong>Median Overall Survival (Interim)</strong></td>
<td>16.4 months</td>
<td>18 months</td>
</tr>
<tr>
<td></td>
<td>HR 0.90 (95% CI, 0.71-1.14); $P = .3741$</td>
<td></td>
</tr>
</tbody>
</table>

Chemotherapy: taxanes (44%), gemcitabine (23%), capecitabine (21%), vinorelbine (11%)

Duration of response was similar with or without bevacizumab (7.3 months vs. 7.5 months).

Bruisky et al. SABCS 2009; abstract 42.
RIBBON-2 TN Subset

-N = 159 pts (23%)
-Majority received taxane chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Chemo+ Bev N = 112</th>
<th>Chemo alone N = 47</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS (months)</strong></td>
<td>6.0</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>HR (CI)</strong></td>
<td>0.494 (0.33 – 0.74)</td>
<td></td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>0.0006</td>
<td></td>
</tr>
<tr>
<td><strong>OS (months)</strong></td>
<td>17.9</td>
<td>12.6</td>
</tr>
<tr>
<td><strong>HR (CI)</strong></td>
<td>0.624 (0.39 – 1.007)</td>
<td></td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>0.0534</td>
<td></td>
</tr>
</tbody>
</table>

Brufsky et al. Breast Cancer Res Treat 2012; 133: 1067
AVADO Trial Biomarker Discovery

- Extensive Search for a predictive biomarker
- Plasma: VEGF-A_{121}, VEGFR-1, VEGFR-2, E-selectin, VCAM, ICAM-1
- Tumor: (IHC and qRT-PCR)
  - VEGF-A, VEGF-C, VEGF-D
  - VEGFR-2, VEGFR-3
  - Placental Growth Factor
  - Neuropilin-1
- Germline DNA for SNPs in VEGF pathway
- No formal P-value testing for multiple comparisons
AVADO Trial Biomarker Discovery
Plasma VEGF-A, VEGFR-2

Genentech developed ELISA that preferentially measure VEGF$_{121}$
Confirmatory Study Schema: MERiDiAN

MBC, HER2-Negative Chemo-naïve N=480

Stratification
- VEGF-A (low/high)
- Adjuvant therapy (yes/no)
- Hormonal status (ER +/-)

Randomized

Paclitaxel 90 mg/m2 weekly x 3 q4 weeks / Bevacizumab 10 mg/kg q2w

Paclitaxel 90mg/m2 weekly x 3 q4 weeks / Placebo 10 mg/kg q2w

Co-Primary Endpoints: PFS (All Patients), PFS (VEGF high subset)

Secondary Endpoints: OS; ORR; Symptoms/QoL; Safety
Anti-Androgen therapy in LAR Triple Negative Subtype

PFS on oral daily bicalutamide 150 mg

Clinical benefit rate of 19%

$N = 26$ (PFS events = 23)
Median PFS: 12 wks, 95% CI: (11–22)

All ER/PR Negative
-Majority HER2 neg
-12% TN had $\geq 10\%$ AR expression by IHC
-92% postmenopausal
-Median age 66 yrs
-Recur late ($>3$ years)
-Metastatic sites nodal, soft tissue, bone
-All responders had $\text{AR} > 20\%$ -90%

Antibody-Drug Conjugates

**Antibody:**
- Specificity for tumor
- Abundant expression of target on tumor cell surface
- Rapid internalization of Ab
- Target recognition unaltered compared with naked Ab

**Drug:**
- Highly potent antitumor agent (MMAE or Maytansine)
- Validated MOA (microtubule inhibitor or DNA damaging)

**Linker:**
- Stable in plasma
- Labile once internalized
CDX-011 (Glembatumumab) EMERGE Trial

• Fully human monoclonal antibody that targets GPNMB linked to MMAE (dolastatin-like tubulin inhibitor)
• GPNMB overexpressed in ~40-75% of breast cancer—expressed on both tumor cells and stromal cells
• Increased expression on TN associated with poor prognosis
EMERGE: Randomized Phase II Study

- Endpoints: overall response rate [primary], progression-free survival, duration of response, safety, PK/PD

**Planned sample size = 120**
- Locally advanced or metastatic, GPNMB+ breast cancer
- Refractory/resistant to approved therapies (taxane, anthracycline, capecitabine; and if HER2+, trastuzumab and lapatinib)
- 2-7 prior lines of cytotoxic chemotherapy for advanced disease
- Progression within 6 months of last regimen

**CDX-011 (1.88 mg/kg, 90 minute IV infusion, once every three weeks)**

Cross-over to CDX-011 permitted upon centrally confirmed PD and continued eligibility

“Investigator’s Choice” single-agent chemotherapy (IC)

Yardley et al. SABCS 2012
## Progression-Free Survival (PFS) and Overall Survival (OS)

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>TN</th>
<th>High GPNMB</th>
<th>TN and High GPNMB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CDX-011 IC</td>
<td>CDX-011 IC</td>
<td>CDX-011 IC</td>
<td>CDX-011 IC</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>2.1 (n=96) 2.0 (n=41)</td>
<td>2.3 (n=31) 1.6 (n=11)</td>
<td>2.7 (n=27) 1.5 (n=11)</td>
<td>3.0 (n=12) 1.5 (n=6)</td>
</tr>
<tr>
<td></td>
<td>P=0.38</td>
<td>P=0.43</td>
<td>P=0.14</td>
<td>P=0.008*</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>7.5 (n=81) 7.4 (n=41)</td>
<td>6.9 (n=28) 6.5 (n=11)</td>
<td>10.0 (n=22) 5.7 (n=11)</td>
<td>10.0 (n=10) 5.5 (n=6)</td>
</tr>
<tr>
<td></td>
<td>P=0.24</td>
<td>P=0.30</td>
<td>P=0.18</td>
<td>P=0.003*</td>
</tr>
</tbody>
</table>

High GPNMB \( \geq 25\% \) tumor cell expression
Diagnosing the Molecular Subtype Does Not Direct Therapy

Understand the patient’s disease course

• Determine type and number of prior therapies
  – Is the cancer *hormone-resistant*?
    • After 3-4 endocrine agents – unlikely to gain further benefit
    • Hormone receptor positive disease recurrence within a short DFI

• Know the disease-free interval
  – Hormone receptor positive < 2 years = short DFI
  – Was the adjuvant chemotherapy < 1 year or > 2 years prior to metastasis?
    • Recurrence > 2 years – cancer may be responsive to same drugs
    • Recurrence < 1 year – resistant to adjuvant therapy treatment

• Patient’s PFS and co-morbidities
Predicting Resistance to Hormone Therapies: Oncotype RS in *de novo* Metastatic Disease

128 patients with *de novo* MBC or MBC within 3 months of surgery → Treatment as per Physician → Follow For PFS and OS

Objective: To determine whether the 21-gene RS provides clinically meaningful information in pts with *de novo* stage IV breast cancer enrolled in TBCRC 013.

King et al. ASCO 2013
### Time to First Progression by Risk Group

![Graph showing time to first progression by Recurrence Score result](image)

<table>
<thead>
<tr>
<th></th>
<th>Recurrence Score(^\circ) &lt;18</th>
<th>Recurrence Score result 18-30</th>
<th>Recurrence Score result ≥31</th>
<th>Log rank, p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts (n=102)</td>
<td>32 (16-NR)</td>
<td>20 (15-NR)</td>
<td>15 (9-21)</td>
<td>0.046</td>
</tr>
<tr>
<td>ER+ (n=86)</td>
<td>32 (16-NR)</td>
<td>20 (15-NR)</td>
<td>15 (9-25)</td>
<td>0.034</td>
</tr>
<tr>
<td>ER+HER2- (n=70)</td>
<td>32 (16-NR)</td>
<td>20 (15-NR)</td>
<td>15 (9-26)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

King et al. ASCO 2013.
Two Year Overall Survival by Risk Group

Two Year Overall Survival, %

<table>
<thead>
<tr>
<th></th>
<th>Recurrence Score*</th>
<th>Recurrence Score result 18-30</th>
<th>Recurrence Score result ≥31</th>
<th>Log rank, p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts (n=102)</td>
<td>100 (78-100)</td>
<td>100 (78-100)</td>
<td>80 (69-93)</td>
<td>0.049</td>
</tr>
<tr>
<td>ER+ (n=86)</td>
<td>100 (78-100)</td>
<td>100 (78-100)</td>
<td>77 (64-94)</td>
<td>0.016</td>
</tr>
<tr>
<td>ER+HER2- (n=70)</td>
<td>100 (78-100)</td>
<td>100 (75-100)</td>
<td>69 (51-93)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

King et al. ASCO 2013.
21-gene Recurrence Score®

- Independently prognostic for both time to progression and 2 yr OS in ER+ HER2- *de novo* stage IV breast cancer
- High RS (≥31) may be a surrogate for relative endocrine resistance in metastatic disease
- **Hypothesis**: RS ≥31 can be used to select patients with ER+ HER2- *de novo* stage IV breast cancer who may benefit from first line chemotherapy

*A randomized trial to address this hypothesis is warranted.*
Single Agent vs Combination Chemotherapy
Is More Really Better?

• Combinations regimens:
  – Typically have higher response rates, time to progression, and progression free survival
  – Toxicity is usually higher
  – Cost higher
  – Overall survival benefit not often achieved, due to crossover to other treatment arm

• True synergistic interaction that may have the potential to increase survival
Doxorubicin vs Paclitaxel vs Doxorubicin/Paclitaxel in Metastatic Breast Cancer E1193 trial

- 739 patients, first-line therapy for metastatic breast cancer
- Randomization to 3 arms:
  1) Doxorubicin 60mg/m$^2$, q3 weeks
  2) Paclitaxel 175mg/m$^2$ over 24 hours, q3 weeks
  3) Doxorubicin 50mg/m$^2$, Paclitaxel 150mg/m$^2$ over 24 hours, q3 weeks plus G-CSF

E1193 Trial

• Large published randomized trial comparing single agent to combination therapy in 1st line MBC patients
  – Used Modern age therapies
  – Cross-over mandated at time of progression
  – Phase III, cooperative setting

## Results E1193

<table>
<thead>
<tr>
<th></th>
<th>Response (CR + PR)</th>
<th>Median TTF (Months)</th>
<th>Median Survival (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOX</td>
<td>36</td>
<td>6</td>
<td>18.9</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>34</td>
<td>6</td>
<td>22.2</td>
</tr>
<tr>
<td>Dox/Pac</td>
<td>47</td>
<td>8</td>
<td>22</td>
</tr>
</tbody>
</table>

# Pivotal RCT Used for Approval of Agents 2000 to 2011

<table>
<thead>
<tr>
<th>Study Design</th>
<th>PFS HR</th>
<th>∆ mos</th>
<th>OS HR</th>
<th>∆ mos</th>
<th>Ratio ∆ PFS/∆ OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine/Paclitaxel vs Pac</td>
<td>0.70</td>
<td>6.1/4.0 2.1</td>
<td>0.78</td>
<td>18.6/15.8 2.8</td>
<td>1.33</td>
</tr>
<tr>
<td>Ixabepilone/Cape vs Capecitabine</td>
<td>0.79</td>
<td>6.2/4.2 2.0</td>
<td>0.9</td>
<td>16.4/15.6 0.9</td>
<td>0.40</td>
</tr>
<tr>
<td>Cape/Docetaxel vs Docetaxel</td>
<td>0.65</td>
<td>6.1/4.2 1.9</td>
<td>0.77</td>
<td>14.5/11.5 3.0</td>
<td>1.58</td>
</tr>
<tr>
<td>Nab-paclitaxel vs paclitaxel</td>
<td>0.73</td>
<td>5.8/4.2 1.6</td>
<td>0.75</td>
<td>16.3/13.9 2.4</td>
<td>1.50</td>
</tr>
</tbody>
</table>

Ref: Ocana et al. CCR 2013:19:4931-4940
## Capecitabine +/- Ixabepilone

<table>
<thead>
<tr>
<th></th>
<th>048 (N=1221)</th>
<th>046 (N=752)</th>
<th>Dose-reduced</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I+C=609</td>
<td>C=612</td>
<td>I+C=375</td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>OS</td>
<td>PFS</td>
<td></td>
</tr>
<tr>
<td>ORR (%)</td>
<td>43</td>
<td>29</td>
<td>42</td>
</tr>
<tr>
<td>PFS mo</td>
<td>6.2</td>
<td>4.4</td>
<td>5.3</td>
</tr>
<tr>
<td>HR</td>
<td>0.79</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>P value (CI)</td>
<td>0.0005</td>
<td>0.001</td>
<td>0.98</td>
</tr>
<tr>
<td>OS mo</td>
<td>16.4</td>
<td>15.6</td>
<td>12.9</td>
</tr>
<tr>
<td>HR</td>
<td>0.90</td>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td>P value</td>
<td>0.1162</td>
<td></td>
<td>0.1936</td>
</tr>
<tr>
<td>HR (adj)</td>
<td>0.85*</td>
<td></td>
<td>0.87</td>
</tr>
<tr>
<td>P value</td>
<td>0.0231</td>
<td></td>
<td>0.0803</td>
</tr>
</tbody>
</table>

Sparano JCO; 2010;28.3256
Thomas. JCO 2007;26:5210;
Valero Clin Br Ca 2012;12:240
## Combination taxane chemotherapy options

<table>
<thead>
<tr>
<th></th>
<th>Line of Rx</th>
<th>ORR (%)</th>
<th>TTP (mo)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>X vs. XD (511)</strong></td>
<td>1\textsuperscript{st} – 3\textsuperscript{rd}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capecitabine (X)</td>
<td></td>
<td>30%</td>
<td>4.2</td>
<td>11.5</td>
</tr>
<tr>
<td>Cape/docetaxel (XD)</td>
<td></td>
<td>42%*</td>
<td>6.1*</td>
<td>14.5*</td>
</tr>
<tr>
<td><strong>T vs. GT (529)</strong></td>
<td>1\textsuperscript{st}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel (T)</td>
<td></td>
<td>26.9%</td>
<td>4.0</td>
<td>15.8</td>
</tr>
<tr>
<td>Gemcitabine/Paclitaxel (GT)</td>
<td></td>
<td>43.1%*</td>
<td>6.1*</td>
<td>18.6*</td>
</tr>
</tbody>
</table>

O’Shaughnessy J JCO 2002;20:2812  
Albain K JCO 2008;26:3950
Cochrane Analysis: Single Agent vs Combination Chemotherapy for MBC

- Metastatic breast cancer has inherent drug resistance
  - Combination chemotherapy should reduce the different sensitive subpopulations of cancer cells leading to an improved disease response

- Cochrane analysis (2009)
  - 43 randomized trials of single agent vs. combination chemotherapy (9742 pts)
    - Combination therapy improved OS: HR=0.88, p<.00001
    - Combination therapy improved OS with taxanes (HR = 0.83) but not with anthracyclines (HR = 0.94)
    - Cross-over design was absent in the majority of studies

- Conclusion – insufficient data to state the “net clinical benefit” of combination therapy c/w sequential therapy

April 15, 2009
Choosing Wisely - An ABIM Initiative

ASCO Top 10 List (released October 2013)

- Number 7:
- Don’t use combination chemotherapy (multiple drugs) instead of chemotherapy with one drug when treating an individual for metastatic breast cancer unless the patient needs a rapid response to relieve tumor-related symptoms.
Schedule is as Important as Dose

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>TTP (mo)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CALGB 9840</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wkly paclitaxel</td>
<td>42%</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>Q3w paclitaxel</td>
<td>29%</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td><strong>Nab-paclitaxel</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3w 300mg/m2</td>
<td>46%</td>
<td>11</td>
<td>27.7</td>
</tr>
<tr>
<td>Wkly 100mg/m2</td>
<td>63%</td>
<td>12.8</td>
<td>22.2</td>
</tr>
<tr>
<td>Wkly 150mg/m2</td>
<td>74%</td>
<td>12.9</td>
<td>33.8</td>
</tr>
<tr>
<td><strong>Docetaxel</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wkly docetaxel</td>
<td>20.3%</td>
<td>5.5</td>
<td>18.6</td>
</tr>
<tr>
<td>Q3w docetaxel</td>
<td>35.6%</td>
<td>5.7</td>
<td>18.3</td>
</tr>
</tbody>
</table>

Siedman JCO 2008;26:1642; Rivera E Cancer 112:1455, 2008; Gradishar WJ JCO 2009;27:3611
Meta-Analysis

• Weekly Paclitaxel comparable to docetaxel-based regimens for MBC in terms of OS (HR 0.87), PFS (HR 0.76), TTP (HR 1.13), ORR (1.01)

• Paclitaxel has fewer grade 3 or 4 adverse events including anemia (RR 0.64), thrombocytopenia (RR 0.62), mucositis (RR 0.08), diarrhea (RR 0.19), and fatigue (RR 0.43)

CALGB 40502/NCCTG N063H

Randomized Phase III Trial of Weekly Paclitaxel compared to Weekly Nanoparticle Albumin Bound Nab-Paclitaxel or Ixabepilone +/- Bevacizumab as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer

Rugo H et al, ASCO 2012
**Triple Negative Disease**

- **40502 overall findings:**
  - Weekly paclitaxel > ixabepilone
  - Weekly paclitaxel less toxic than either (in general)

- **TNBC Subset:**
  - No real difference from parent trial
  - 98% received bevacizumab

<table>
<thead>
<tr>
<th></th>
<th>Paclitaxel</th>
<th>Nab-paclitaxel (P=.12)</th>
<th>Ixabepilone (P=.001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (mo)</td>
<td>10.6</td>
<td>9.2</td>
<td>7.6</td>
</tr>
<tr>
<td>TTF (mo)</td>
<td>7.1</td>
<td>5.4 (P=.0005)</td>
<td>5.1 (P=.0014)</td>
</tr>
<tr>
<td>OS (mo)</td>
<td>26</td>
<td>27 (P=.92)</td>
<td>21 (P=.10)</td>
</tr>
</tbody>
</table>
Phase III EMBRACE Trial of Eribulin Versus Treatment of Physician’s Choice for Heavily Pretreated MBC

Eligibility criteria:
- Locally recurrent or metastatic breast cancer
- 2-5 prior chemotherapies:
  - ≥ 2 for advanced disease
  - Prior anthracycline and taxane
- Progression ≤ 6 months since last chemotherapy
- Neuropathy grade ≤ 2

Primary endpoint: OS
Secondary endpoints: PFS, ORR, safety

Eribulin mesylate 1.4 mg/m², days 1, 8 q 3 weeks

Treatment of Physician’s Choice (TPC)
Any monotherapy approved for treatment of cancer or supportive care only

Phase III EMBRACE Trial: Overall Survival

OS: 13.1 vs 10.7 mos
PFS: 3.7 vs 2.2 mos
### Phase III EMBRACE Trial: Grade 3/4 Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Eribulin (n = 503)</th>
<th>TPC (n = 247)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>45%</td>
<td>21%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>14%</td>
<td>6%</td>
</tr>
<tr>
<td>Anemia</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Asthenia/Fatigue</td>
<td>9%</td>
<td>10%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>8%</td>
<td>2%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nausea</td>
<td>1%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3%</td>
</tr>
<tr>
<td>Hand-Foot Syndrome</td>
<td>&lt; 1%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Grade 3 only

The incidence of fatal adverse events related to treatment was ≤ 1% in both arms.

Chemotherapy for TNBC

A Phase III, Randomized Trial Comparing Eribulin to Capecitabine In Patients With Metastatic Breast Cancer Previously Treated With Anthracyclines And Taxanes

**Patients (N=1102)**

Locally advanced or MBC
- ≤3 prior chemotherapy regimens (≤2 for advanced disease)
- Prior anthracycline and taxane in (neo)adjuvant setting or for locally advanced or MBC

**Randomization 1:1**

**Eribulin mesylate**
1.4 mg/m²² 2- to 5-min IV
Day 1 & 8 q21 days

**Capecitabine**
1250 mg/m² BID orally
Days 1-14, q21 days

**Co-primary endpoint**
- OS and PFS

**Secondary endpoints**
- Quality of life
- ORR
- Duration of response
- 1-, 2- and 3-year survival
- Tumor-related symptom assessments
- Safety parameters
- Population PK (eribulin arm only)

*Kaufmann P et al, SABCS 2012*
Progression-Free Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eribulin (n=554)</td>
<td>4.1</td>
</tr>
<tr>
<td>Capecitabine (n=548)</td>
<td>4.2</td>
</tr>
</tbody>
</table>

HR$^\dagger$ 1.079 (95% CI 0.932, 1.250)

p value$^\dagger$=0.305
Overall Survival By Receptor Status

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>Eribulin Median (months)</th>
<th>Capecitabine Median (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.879 (0.770, 1.003)</td>
<td>15.9</td>
<td>14.5</td>
</tr>
<tr>
<td>HER2 status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0.965 (0.688, 1.355)</td>
<td>14.3</td>
<td>17.1</td>
</tr>
<tr>
<td>Negative</td>
<td>0.838 (0.715, 0.983)</td>
<td>15.9</td>
<td>13.5</td>
</tr>
<tr>
<td>n=755</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ER status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0.897 (0.737, 1.093)</td>
<td>18.2</td>
<td>16.8</td>
</tr>
<tr>
<td>Negative</td>
<td>0.779 (0.635, 0.955)</td>
<td>14.4</td>
<td>10.5</td>
</tr>
<tr>
<td>n=449</td>
<td></td>
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<tr>
<td>Triple negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.702 (0.545, 0.906)</td>
<td>14.4</td>
<td>9.4</td>
</tr>
<tr>
<td>n=284</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.927 (0.795, 1.081)</td>
<td>17.5</td>
<td>16.6</td>
</tr>
</tbody>
</table>

ITT population: Favors eribulin ← favorer 1.0 → favors capecitabine
Conclusions

• Eribulin equivalent to capecitabine after anthracycline/taxane therapy
• Eribulin appears superior for TN disease
• Different toxicity profiles
  - Eribulin (IV): neutropenia, alopecia, neuropathy
  - Capecitabine (Oral): HFS, diarrhea
Optimal Duration of First Line Chemotherapy for MBC

Progression Free Survival

<table>
<thead>
<tr>
<th>Study</th>
<th>HR ± 95% CI</th>
<th>% Weight</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coates 1987</td>
<td></td>
<td>13</td>
<td>0.56</td>
<td>0.44 to 0.71</td>
</tr>
<tr>
<td>Harris 1990</td>
<td></td>
<td>2</td>
<td>1.18</td>
<td>0.65 to 2.15</td>
</tr>
<tr>
<td>Muss 1991</td>
<td></td>
<td>3</td>
<td>0.26</td>
<td>0.16 to 0.43</td>
</tr>
<tr>
<td>Ejlertsen 1993</td>
<td></td>
<td>28</td>
<td>0.71</td>
<td>0.61 to 0.83</td>
</tr>
<tr>
<td>Gregory 1997</td>
<td></td>
<td>10</td>
<td>0.70</td>
<td>0.53 to 0.92</td>
</tr>
<tr>
<td>Falkson 1998</td>
<td></td>
<td>5</td>
<td>0.46</td>
<td>0.31 to 0.68</td>
</tr>
<tr>
<td>Bastit 2000</td>
<td></td>
<td>11</td>
<td>0.65</td>
<td>0.50 to 0.84</td>
</tr>
<tr>
<td>Nooij 2003</td>
<td></td>
<td>8</td>
<td>0.67</td>
<td>0.50 to 0.90</td>
</tr>
<tr>
<td>Gennari 2006</td>
<td></td>
<td>6</td>
<td>1.01</td>
<td>0.71 to 1.43</td>
</tr>
<tr>
<td>Majordomo 2009</td>
<td></td>
<td>8</td>
<td>0.77</td>
<td>0.57 to 1.05</td>
</tr>
<tr>
<td>Alba 2010</td>
<td></td>
<td>6</td>
<td>0.53</td>
<td>0.37 to 0.76</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td><strong>100</strong></td>
<td>0.64</td>
<td><strong>0.55 to 0.76</strong></td>
</tr>
</tbody>
</table>

11 trials
2,269 pts

Test for heterogeneity, \( P = .01 \)
Test for treatment effect, \( P < .001 \)

36%
Overall Survival (1st Line Chemo)

11 trials
2,269 pts

Test for heterogeneity, $P = .69$
Test for treatment effect, $P = .046$

Gennari A et al. JCO 2011;29:2144-2149
- Used modern day taxane regimen that is well-tolerated and shown to have increased PFS and OS as first line therapy without clinically meaningful increase in toxicity
- Hormonal therapy was not allowed in either group (~75% of pts ER+)
- Median age 47.5 years
- Primary endpoint: PFS in patients with disease control after 6 cycles
- Mean of 6 additional cycles in maintenance group (range: 3 – 20 cycles)
- 28% of patients assigned to maintenance did not receive chemo
- 3.7 mos improvement in PFS associated with 8.8 mos improvement in OS
- PFS in TN patients HR 0.52 (CI 0.30 – 0.90)
- Benefit driven by impact in younger, premenopausal, ER negative women with extensive, yet responsive disease

Park et al. JCO 2013;31: 1732
Future Therapies

- Clinical trials.gov: 400 studies currently recruiting and open for MBC
  - TN specifically: 41 studies
  - Many targeting specific pathways related to molecular profiling

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Study</th>
<th>Pathway</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARP inhibitors</td>
<td></td>
<td>GPNMB (CDX-011)</td>
<td></td>
</tr>
<tr>
<td>HSP 90</td>
<td></td>
<td>Angiogenesis</td>
<td></td>
</tr>
<tr>
<td>MET</td>
<td></td>
<td>FGFR</td>
<td></td>
</tr>
<tr>
<td>ADC (folate)</td>
<td></td>
<td>EGFR</td>
<td></td>
</tr>
<tr>
<td>γ-Secretase</td>
<td></td>
<td>estradiol</td>
<td></td>
</tr>
<tr>
<td>LIV-1</td>
<td></td>
<td>AKT</td>
<td></td>
</tr>
<tr>
<td>PIK3CA</td>
<td></td>
<td>Aurora Kinase</td>
<td></td>
</tr>
<tr>
<td>mTOR</td>
<td></td>
<td>HER3</td>
<td></td>
</tr>
<tr>
<td>JAK2</td>
<td></td>
<td>Src</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

• Optimal therapy for MBC: Combine Clinical Picture, Patient Preferences, and Molecular Subtyping to formulate the best treatment plan

• Molecular Profiling is evolving, but not yet validated for clinical decisions

• Sequential therapies are less toxic and likely as good as combination therapy for the majority of patients

• New therapies are on the horizon, but will require tissue biopsies, target validation, and screening many for the accrual of one
<table>
<thead>
<tr>
<th>Year</th>
<th>Leading Causes of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1900</td>
<td>1. Pneumonia</td>
</tr>
<tr>
<td></td>
<td>2. Tuberculosis</td>
</tr>
<tr>
<td></td>
<td>8. Cancer</td>
</tr>
<tr>
<td>2000</td>
<td>1. Heart disease</td>
</tr>
<tr>
<td></td>
<td>2. Cancer</td>
</tr>
<tr>
<td></td>
<td>7. Influenza/pneumonia</td>
</tr>
</tbody>
</table>
Learning from the Past

Pneumonia
- Antibiotics
- Vaccination
- Improved sanitation and refrigeration

Breast Cancer
- Targeted Therapies
- Immune modulation
- Prevention and Early Diagnosis
Thank you for your attention
First, isolated, ipsilateral, resectable recurrence
  – IBTR or CW recurrence
  – Axillary or IM LN
• Fully excised

CALOR Trial

Strata
• Prior Chemo-Tx
• ER+ and/or PR+
• Location ILRR

Randomize

Chemotherapy
> 1 drug, 3-6 cycles

No chemotherapy

+ Endocrine therapy for ER+ and/or PR+
+ HER2-directed therapy (optional)
CALOR: Disease-Free Survival

N=162

5-yr DFS

Chemotherapy (CT) 69%
No Chemotherapy (no CT) 57%

<table>
<thead>
<tr>
<th></th>
<th>Pts</th>
<th>Events</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>85</td>
<td>24</td>
<td>0.59</td>
<td>0.35-0.99</td>
<td>0.0455</td>
</tr>
<tr>
<td>No CT</td>
<td>77</td>
<td>34</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ER + subset

5-yr DFS

Chemotherapy (CT) 70%
No Chemotherapy (no CT) 69%

<table>
<thead>
<tr>
<th>Pts</th>
<th>Events</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>56</td>
<td>16</td>
<td>0.94</td>
<td>0.47-1.89</td>
</tr>
<tr>
<td>No CT</td>
<td>48</td>
<td>16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ER neg subset

5-yr DFS

Chemotherapy (CT) 67%
No Chemotherapy (no CT) 35%

<table>
<thead>
<tr>
<th>Pts</th>
<th>Events</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>29</td>
<td>8</td>
<td>0.32</td>
<td>0.14-0.73</td>
</tr>
<tr>
<td>No CT</td>
<td>29</td>
<td>18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5-yr OS 88% vs 76%, HR 0.41, P=.02

Aebi S et al, SABCS 2012