Neoadjuvant Therapy for Breast Cancer

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Washington Hospital Center
Professor of Medicine
Georgetown University
Washington DC
Drug development has occurred at a snail’s pace

- Large trials are cumbersome, slow, use high amount of resources both human and financial
- Even if active takes years to get to a patient
- Loses lives
Innovative Ideas for Breast Cancer Drug Approval

The Neoadjuvant Model
Inflammatory Breast Cancer
Standard Treatment

Primary Chemotherapy*

\[ \downarrow \]

Surgery

\[ \downarrow \]

RT

\[ \downarrow \]

Hormonal Therapy

*Trastuzumab for HER2 positive tumors
IBC Survival: NCI MB 198

Non-Inflammatory (42%)

Inflammatory (20%)

Years from On-Study Date

Breast Cancer Intrinsic Subtypes

- Luminal A
- Luminal B
- Claudin Low
- Basal-like
- HER2

- HER2
- Basal
- Luminal
- Proliferation
- Claudin 3
- Claudin 4
- Claudin 7
- E-Cadherin

Perou CM The Oncologist 2010;15:39-48
Breast Cancer Subtypes and Outcomes

All molecular subtypes are present in IBC

IBC (298 probe sets)  Non-IBC (251 probe sets)

Subtypes of TNBC and targeted therapy selection

- Basal1
- Basal2
- Immune Module
- Mesenchymal
- Mesenchymal – Stem Cell
- Luminal
- Luminal – Androgen Receptor


Cell cycle, DNA damage
GFR, glycolysis, p63
B/TCR, cytokines, JAK/STAT
ECM receptors
TGF-β
Rho
Wnt/β-Cat
EMT
Stem cell markers
Luminal CK’s
AR
FOXA1
XBP1

No TNBC subtyping approach is yet of clinical utility
Correlation of Breast Cancer Axillary Metastases with Stem Cell Mutations

N=30

- 9/10 Tumors with BCSC Mutations
- 4/20 Tumors without BCSC Mutations

Donovan, et al JAMA Surg  epub July 2013
Personalizing Breast Cancer Treatment: Current State of Affairs

- Despite acceptance of expression-based subtyping, receptor status remains cornerstone of personalizing treatment in clinic.

Molecular Profiling Assays

Developed to identify patients for treatment

Need treatment

Will benefit from a specific treatment

Will not benefit from treatment
Large Randomized Neoadjuvant Trials in Breast Cancer
NSABP B-18: Preop vs. Postop AC: Overall Survival Update

NSABP B-27 Schema

Operable Breast Cancer (2411 pts)

Randomization

AC x 4 Tam X 5 Yrs

Surgery

AC x 4 Tam X 5 Yrs

Docetaxel x 4

Surgery

AC x 4 Tam X 5 Yrs

Surgery

Docetaxel x 4
NSABP B-27: Pathologic Response in Breast and Axillary Nodes

pCR in Breast

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No Tumor</th>
<th>Non-Invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC (1,492 pts)</td>
<td>9.8%</td>
<td>25.6%</td>
</tr>
<tr>
<td>AC→Docetaxel (718 pts)</td>
<td>18.7%</td>
<td>6.9%</td>
</tr>
</tbody>
</table>

Positive Nodes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>P &lt; 0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>49</td>
</tr>
<tr>
<td>AC Docetaxel</td>
<td>41</td>
</tr>
</tbody>
</table>

NSABP B-27:
Disease-Free Survival

Bear H et al: SABCS 2004
NSABP B-27
pCR as a Surrogate for Clinical Endpoints

Hypothesis: Mixed with good prognosis patients who did not benefit from chemotherapy?
(or who benefited but did not achieve a pCR)?
NSABP B-27
Gene Expression and Survival Outcome

Low-risk (n=163)
High-risk (n=163)

Paik S: Unpublished data
Low-Risk Patients Have Good Outcome Regardless of pCR

Paik S: Unpublished data
Combination of Prognostic Genes and pCR Defines Residual Risk after Chemotherapy

Candidates for post-neoadjuvant chemotherapies for targeted therapy

Paik S: Unpublished data
In Vivo Chemosensitivity-Adapted Neoadjuvant Chemotherapy: the GEPPAR-TRIO Trial

N=2072

Core biopsy: uni/bilateral
cT2-4a-d
cN0-3
size ≥ 2 cm*

Sonography

NC

R

CR/PR

Response-guided arms

Conventional arms

TACx6

TACx6

TACx8

*low risk patients were excluded (T2 + ER/PR pos. + cNO + G1/2 + > 35 yrs)

Von Minckwitz G et al J Clin Oncol 2013:31;3623-3631
Short Term Efficacy
(pCR = ypT0 ypN0)

Responders
N=1344

Non-Responders
N=604

TACx6
21.0
P=0.27

TACx8
23.5

TACx6
5.3

TAC-NX
6.0
P=0.73

Von Minckwitz G et al J Clin Oncol 2013:31;3623-3631
pCR Rates by Subtype

Von Minckwitz G et al, SABCS 2011
DFS in Luminal A Tumors

by pCR

by Treatment

Von Minckwitz G et al, SABCS 2011
DFS in Triple Negative Tumors

by pCR

by Treatment

Von Minckwitz G et al, SABCS 2011

Hazard ratio, 6.67 (95% CI, 3.61 to 11.9)
P<0.001 log rank test

Hazard ratio, 0.87 (95% CI, 0.61 to 1.27)
P=0.464 log rank test
Subtype Specific Targeted Therapy

N=595
centrally confirmed
TNBC
or
Her2-positive
breast cancer

PM
PMCb

Surgery

Paclitaxel 80 mg/m² q1w
Non-pegylated liposomal
doxorubicin 20 mg/m² q1w
Carboplatin AUC 1.5* q1w

Her2-pos:
Trastuzumab 6(8) mg/kg q3w (for 1 year)
+ Lapatinib 750 mg/d 18 wks

TNBC:
Bevacizumab 15 mg/kg q3w

*reduced from AUC 2 at amendment 1 after enrolment of 330 patients

Presented at the 2013 ASCO Annual Meeting. Presented data is the property of GBG and AGO-B.
Primary Endpoint: pCR

ypT0 ypN0

PM
N=293

PMCb
N=295

P<0.2*

37.2% 46.7%

* Level for significance \( \alpha = 0.2 \)

Presented at the 2013 ASCO Annual Meeting. Presented data is the property of GBG and AGO-B.
pCR Rates by Subtype

ypT0 ypN0

TNBC

HER2-positive

<table>
<thead>
<tr>
<th></th>
<th>PM</th>
<th>PMCb</th>
<th></th>
<th>PM</th>
<th>PMCb</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=157</td>
<td>N=158</td>
<td>N=136</td>
<td>n=137</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P<0.05

n.s.

37.9% 58.7%

36.3% 33.1%
Neoadjuvant Studies Summary

• No improvement in survival overall with nonspecific treatment
  – Pts with pCR have improved survival
• Triple negative disease has highest pCR with chemotherapy
  – Carboplatin increases pCR
• Luminal A disease outcome not related to pCR
FDA Public Breast Cancer Workshop
Innovations in Breast Cancer Drug Development
NEOADJUVANT BREAST CANCER WORKSHOP

March 22, 2013
8:00 a.m. to 5:00 p.m.
Federal Research Center

CO-SPONSORED BY THE:
U.S. Food & Drug Administration (FDA) &
American Society of Clinical Oncology (ASCO)
with support from the American Association for Cancer Research (AACR)

CO-CHAIRS: DR. SANDRA SWAIN AND DR. PATRICIA CORTAZAR
CTNeoBC Selected Trials

- 12 neoadjuvant randomized controlled trials
- pCR clearly defined with all necessary data collected
- Long-term follow-up EFS and OS data collected

<table>
<thead>
<tr>
<th>TRIALS</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBG/AGO: 7</td>
<td>6377</td>
</tr>
<tr>
<td>NSABP: 2</td>
<td>3171</td>
</tr>
<tr>
<td>EORTC/BIG: 1</td>
<td>1856</td>
</tr>
<tr>
<td>ITA: 2</td>
<td>1589</td>
</tr>
<tr>
<td>Total # patients</td>
<td>12993</td>
</tr>
</tbody>
</table>
pCR Rates by Tumor Subtypes

- **HR+**
  - Grade 1-2: 7
  - Grade 3: 16

- **HER2+ HR+**
  - No Tras: 18
  - Yes Tras: 30

- **HER2+ HR-**
  - No Tras: 31
  - Yes Tras: 50

- **TRIPLE NEG**
  - 34
EFS Definition

- **SURGERY**
- **ADJUVANT SYSTEMIC THERAPY**
- **DFS ***
- **NEOADJUVANT SYSTEMIC THERAPY**
- **SURGERY**
- **EFS ***

*loco-regional or distant recurrence or deaths from any cause
Association of pCR on EFS and OS

Individual patients who attain a pCR have a more favorable long-term outcome

Event-free Survival

Overall Survival

HR=0.48, \( P^* < 0.001 \)

HR=0.36, \( P^* < 0.001 \)
Association of pCR with EFS in HR+ HER2-Subtype

- HR=0.49, $P^* < 0.001$
  - pCR (n=270)
  - no pCR (n=2491)

- HR=0.63, $P^* = 0.07$
  - pCR (n=148)
  - no pCR (n=1838)

- HR=0.27, $P^* < 0.001$
  - pCR (n=102)
  - no pCR (n=528)

pCR=ypT0/is ypN0

* Nominal p-value
Association of pCR with EFS in Her2+ Subtype

pCR=ypT0/is ypN0

* Nominal p-value
Association of pCR with EFS in Triple Negative Subtype

**pCR=ypT0/is ypN0**

HR=0.24, P* < 0.001

* Nominal p-value
A perfect scenario example (simulated-data)

\[ R^2 \sim 1 \]
The magnitude of improvement in pCR rate did not predict EFS and OS effect.
A Hypothetical Example Limitations of Responder Analysis

Although patients with pCR have better EFS irrespective of treatment. There is no difference on EFS between the two randomized treatment arms.
Summary

1. pCR association with long term outcomes (EFS and OS):
   - Individual patients who attain a pCR have a more favorable long-term outcome.

2. Association of pCR with EFS by breast cancer subtype:
   - Larger Association in patients with aggressive breast cancer tumor subtypes
   - Smaller Association in patients with less aggressive tumors
Innovative approaches to Drug Development

• Use of pCR as surrogate endpoint in breast cancer
• Smaller trials use less resources and are quicker
• Saves lives
• Molecular era discovers better targets
• Transformative
Draft Guidance for Industry: Pathological Complete Response in Neoadjuvant Treatment of Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval

- High risk early breast cancer
- RCT powered for EFS and OS
- Superiority design
- Add-on design to Standard tx
- Pathologists blinded to therapy
- Standard operating procedures for collection, handling and interpretation of pathology specimens
- Standard postop therapy should be the same in both arms
HER 2:  
A model target
Milestones of HER2/anti-HER2 therapies in BC

- **1978**
  - EGFR discovery
  - Cohen

- **1982**
  - neu oncogene discovery
  - Weinberg

- **1983**
  - Her2 cloned
  - Ullrich and Coussens

- **1984**
  - EGFR MoAb
  - inhibited growth
  - Mendelsohn

- **1985**
  - Her2 amplification in breast cancer
  - Aaronson

- **1987**
  - Amplification of Her2/neu correlates with shorter survival
  - Slamon

- **1998**
  - FDA approves single agent trastuzumab for 2nd line
  - and in combination with paclitaxel for 1st line MBC

- **2006**
  - FDA approves lapatinib + capecitabine for MBC

- **2007**
  - FDA approves pertuzumab + trastuzumab + docetaxel for MBC

- **2012**
  - FDA approves TDM1 for MBC

- **2013**
  - FDA approves Pertuzumab + Trastuzumab neoadjuvant

**Abbreviations:**
- MBC: metastatic breast cancer
- MoAb: monoclonal antibody
- MBC: metastatic breast cancer
- TDM1: Tucatinib dihydrochloride monohydrate (adjuvant)

**Timeline:**
- 1978
- 1982
- 1983
- 1984
- 1985
- 1987
- 1998
- 2006
- 2007
- 2012
- 2013

**SM SWAIN**
Oncology Drugs Advisory Committee Meeting

September 12, 2013
sBLA submission for Pertuzumab

• “PERJETA is a HER2/neu receptor antagonist indicated for: Neoadjuvant treatment of breast cancer, in combination with trastuzumab and docetaxel for patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (>2 cm in diameter) as part of a complete early breast cancer regimen containing either fluorouracil, epirubicin and cyclophosphamide (FEC) or carboplatin
HER2-positive Population Has a High Risk

NOAH Trial: 5 yr EFS/OS

Event Free Survival Probability

<table>
<thead>
<tr>
<th>Months</th>
<th>With H</th>
<th>Without H</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>12</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>24</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>36</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>48</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>60</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.64 (0.44 - 0.93), p-value = 0.016

Overall Survival Probability

<table>
<thead>
<tr>
<th>Months</th>
<th>With H</th>
<th>Without H</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<td>0.1</td>
</tr>
<tr>
<td>60</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.66 (0.43 - 1.01), p-value = 0.055
NeoSphere: Study design and objectives

- Phase II design
- Primary endpoint: Comparison of pCR rates
  - TH vs THP
  - TH vs HP
  - THP vs TP
- Secondary endpoints:
  - Clinical response
  - DFS
  - Breast conservation rate
  - Biomarker evaluation

Patients with operable or locally advanced/inflammatory* HER2-positive BC
Chemo-naïve & primary tumors >2cm (N=417)

**TH (n=107)**
docetaxel (75→100 mg/m²)
trastuzumab (8→6 mg/kg)

**THP (n=107)**
docetaxel (75→100 mg/m²)
trastuzumab (8→6 mg/kg)
pertuzumab (840→420 mg)

**HP (n=107)**
trastuzumab (8→6 mg/kg)
pertuzumab (840→420 mg)

**TP (n=96)**
docetaxel (75→100 mg/m²)
pertuzumab (840→420 mg)

Study dosing: q3w x 4
NeoSphere: Primary endpoint – pathologic complete response (breast only) (ITT population)

p values from Cochran-Mantel-Haenszel test and adjusted for multiplicity


H, trastuzumab; P, pertuzumab; T, docetaxel

pCR, % ± 95% CI

TH: 29.0
THP: 45.8
HP: 16.8
TP: 24.0
NeoSphere

*Higher pCR rates with P+H+T*

<table>
<thead>
<tr>
<th>Arm</th>
<th>Breast pCR</th>
<th>Total pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: H + T</td>
<td>21.5</td>
<td>21.5</td>
</tr>
<tr>
<td>B: P + H + T</td>
<td>39.3</td>
<td>39.3</td>
</tr>
<tr>
<td>C: P + H</td>
<td>11.2</td>
<td>11.2</td>
</tr>
<tr>
<td>D: P + T</td>
<td>17.7</td>
<td>17.7</td>
</tr>
</tbody>
</table>

Δ pCR %

Arm A vs B

- Breast pCR: 16.8
- Total pCR: 17.8
NEOSPHERE

Hormone receptor status – tpCR rates higher with $P+H+T$

Pathologic complete response (%)

<table>
<thead>
<tr>
<th>Arm:</th>
<th>H + T</th>
<th>P + H + T</th>
<th>P + H</th>
<th>P + T</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>29.8</td>
<td>54.4</td>
<td>22.0</td>
<td>26.0</td>
</tr>
<tr>
<td>B</td>
<td>12.0</td>
<td>20.0</td>
<td>2.0</td>
<td>8.7</td>
</tr>
</tbody>
</table>

Δ tpCR %
Arm A vs B

| Hormone receptor neg | 24.6 |
| Hormone receptor pos | 10.0 |
TRYPHAENA: Study Design

Locally advanced, inflammatory, or operable HER2+ EBC, & primary tumors >2cm (N=225)

Randomized

Primary endpoint: cardiac safety
Key secondary endpoint: breast pCR

A
(n=73)

Pertuzumab(P) + Trastuzumab(H) x6

FEC x3
docetaxel x3

B
(n=75)

P + H x3

FEC x3
docetaxel x3

C
(n=77)

P + H x6
docetaxel x6
carboplatin x6

Surgery

Trastuzumab to complete 1 year

Trastuzumab to complete 1 year
TRYPHAENA:

Total pCR rates by hormone receptor status

Pathologic complete response (%)

hormone receptor negative

hormone receptor positive

Arm: A  B  C

P+H+FEC→P+H+T (n = 73)  73.5

FEC→P+H+T (n = 75)  62.5  45.7

TCH+P x6 (n = 77)  81.1  47.5
<table>
<thead>
<tr>
<th></th>
<th>ARM A</th>
<th>ARM B</th>
<th>ARM C</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF Decline</td>
<td>6.9</td>
<td>16</td>
<td>10.5</td>
</tr>
<tr>
<td>LVSD Grade ≥ 3</td>
<td>0</td>
<td>2.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Ongoing LVEF &lt; 50%</td>
<td>0</td>
<td>1.3</td>
<td>0</td>
</tr>
</tbody>
</table>

LVEF decline ≥ 10% and < 50%
CLEOPATRA
confirmatory overall survival analysis

HR=0.66
95% CI 0.52–0.84
p=0.0008

Stopping boundary for concluding statistical significance at this second interim analysis was p≤0.0138

D, docetaxel; Pla, placebo; Ptz, pertuzumab; T, trastuzumab

Swain SM et al. Lancet Oncology 2013
APHINITY: Study Schema

N=3,806

Central confirmation of HER2 status

Randomisation

Chemotherapy plus trastuzumab and pertuzumab

Chemotherapy plus trastuzumab and placebo

Follow up 10 years

Accrual: 11/11 – 8/13
HR: .75

Anti HER2 therapy for a total of 1 year (52 weeks)

Radiotherapy and/or endocrine therapy may be started at the end of adjuvant chemotherapy
Locally advanced, inflammatory, or operable HER2+ EBC, and primary tumors >2cm (N~240). Parallel cohorts.

**Neoadjuvant Anthracycline Study Design**

**BERENICE**

- **AC, dose dense**
- Paclitaxel, weekly
- **P + H**

- **FEC**
- Docetaxel
- **P + H**

Primary endpoint: cardiac safety
Key secondary endpoint: total pCR

AC = doxorubicin + cyclophosphamide.
P+H = Perjeta + Herceptin.
Will pCR Improvement With AntiHer2 Therapies Be Associated With Improved Long-term Outcome?

<table>
<thead>
<tr>
<th>NEOADJUVANT</th>
<th>ADJUVANT</th>
<th>METASTATIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRIALS</td>
<td>TRIALS</td>
<td>DFS HR</td>
</tr>
<tr>
<td>Trastuzumab NOAH Trial</td>
<td>19%*</td>
<td>4 Trials **</td>
</tr>
<tr>
<td>Pertuzumab NEOSPHERE Trial</td>
<td>18%</td>
<td>APHINITY</td>
</tr>
</tbody>
</table>

* EFS HR: 0.59 p= 0.031 Gianni: Lancet 2010
** NSABP B-31/ NCCTG 9831, BCIRG 006, HERA
NR= not reached
“Has Perjeta® demonstrated a favorable benefit to risk evaluation for the neoadjuvant treatment of early breast cancer?”

– Vote: 13 yes, 1 abstention

– Reasons for yes
  • Totality of evidence
  • CLEOPATRA survival benefit
  • APHINITY already accrued
  • Robust clinical development by company: N of 1
  • Safety reasonable
Pertuzumab accelerated approval
September 27, 2013

• Neoadjuvant indication for Perjeta® is for use prior to surgery in combination with Herceptin® and docetaxel chemotherapy in people with HER2-positive, locally advanced, inflammatory, or early stage (tumor is greater than two centimeters in diameter or node positive) breast cancer. Perjeta should be used as part of a complete treatment regimen for early stage breast cancer.
Molecular Profiling Assays

Developed to identify patients for treatment

Need treatment

Will benefit from a specific treatment

Will not benefit from treatment
I-SPY 2 TRIAL Schema

* HER2 positive participants will also receive Trastuzumab. An investigational agent may be used instead of Trastuzumab.
Frequency and Combination of Mutated Cancer Genes

40 Mutated Cancer Genes → 100 Breast Cancers

- 7 mutated in >10% of cases
- 58% of driving genetic events

- 33 mutated in <10% of cases
- 42% of driving genetic events

→ 73 different combinations of mutated cancer genes:
  - most tumors differed from all others
  - Substantial variation in numbers and types of mutations between tumors (base substitutions, indels)

Lessons Learned

• Breast cancer complex and diverse
• Multiple distinct mutational processes
• Driver mutations operative in many genes
• Many infrequent mutations collectively contribute to driving events

Gene and Transcript Analysis Reveals 10 Breast Cancer Subgroups

• Analysis of copy number and gene expression in 997 primary breast tumors revealed 10 integrative clusters, validated in 995 tumors

• Integrative clusters split intrinsic subtypes

10 Integrative Clusters

PAM50 Intrinsic Subtype

10 Clusters Associated With Distinct Clinical Outcomes

Cluster 3 associated with a lower risk of death

- Future studies may identify patients in this cluster who can forgo chemotherapy

Multidisciplinary Tumor Boards Required to Implement Cancer Genomics

http://www.huck.psu.edu/center/medical-genomics
Incorporating Genomic Information Into Clinical Decision Making

1. Consent and screening
2. Blood sample
3. DNA extracted
4. Somatic mutation genotyping
5. Targeted exome sequencing
6. Mutations identified
7. Sanger sequencing
8. Validated mutations
9. Expert panel
10. Molecular profile report generated
11. Clinician
12. Treatment decisions
13. Follow-up
14. Recording of efficacy and toxicity of matched treatments
15. Patient
16. Recording of impact of molecular profile on treatment
17. Follow-up
US Food and Drug Administration Approvals in Metastatic Breast Cancer

Adapted from Cortazar, et al. J Clin Oncol 2012: 30; 1705-1711
MAHALO!