Is the neoadjuvant model an accelerated path towards BC treatment tailoring? Experience of the NeoALTTO trial

Martine J. Piccart-Gebhart, MD, PhD

Jules Bordet Institute, Brussels, Belgium
Université Libre de Bruxelles
Breast International Group (BIG aisbl), Chair
ESMO President
THE PIPELINE PROBLEM

Likelihood of success (%)

- Arthritis: 5%
- Cardiovascular: 15%
- CNS: 5%
- Infectious diseases: 11%
- Oncology: 11%
- Metabolic disease: 5%
- Ophthalmology: 11%
- Urology: 5%
- Women's health: 11%
- All: 11%

Cost of bringing a new cancer drug to clinical practice is $1.8 Billion!
SPECIAL ISSUES IN NEW DRUG DEVELOPMENT FOR BC

• The likelihood of success is low

• The cost is huge

• The understanding of who benefits is poor, even in the era of « personalized oncology »
POTENTIAL WAYS OF ACCELERATING DRUG DEVELOPMENT AND REDUCING THE RISK OF "FAILURE"

- Presence of a reliable surrogate endpoint (pCR), at least for triple negative/HER2+ BC
- Significantly faster, smaller
- Would avoid waiting 10 years for a negative adjuvant trial
- Easy integration of biomarker research
NSABP-B18: A LANDMARK TRIAL
NEOADJUVANT VS ADJUVANT "AC"

Neo-adjuvant = Adjuvant

pCR is a good surrogate marker for long-term outcome

Fisher et al JNCI 2001
Identifying clinically useful biomarkers of response

Predicting the success of new agents or fine-tuning their schedule of administration

NeoAdjuvant Trials

Identifying clinically useful biomarkers of response

?
1. CYTOTOXIC AND ENDOCRINE AGENTS
Predicting the success of new agents for the «average» patient...

or fine-tuning their schedule of administration
### Key findings

<table>
<thead>
<tr>
<th>Location</th>
<th>Details</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aberdeen</td>
<td>Docetaxel in sequence with anthracycline better than anthracycline alone (pCR)</td>
<td>Many adjuvant trials N ~ 44,000</td>
</tr>
<tr>
<td>MD Anderson</td>
<td>Paclitaxel q3wks better than weekly (pCR)</td>
<td>ECOG 1199 trial N = 5,000</td>
</tr>
<tr>
<td>M. Ellis / M. Dowsett</td>
<td>Aromatase inhibitor better than tamoxifen (clinical response)</td>
<td>Many adjuvant trials N &gt; 40,000</td>
</tr>
</tbody>
</table>
LESSONS LEARNED FROM NEOADJUVANT TRIALS IN THE PRE-GENOMIC ERA

Identifying clinically useful biomarkers of response...
**PREOPERATIVE ENDOCRINE THERAPY**

**DOUBLE BLIND STUDIES**

Letrozole (L) vs Tamoxifen (T)

M. ELLIS (N=324)

- Higher response rate with L
- Higher rate of breast conservation with L

Anastrozole (A) vs Tamoxifen (T)

M. DOWSETT (N=330)

- Similar response rate
- Trend for higher rate of breast conservation with A

- Benefit of L confined to tumors with HER-1/HER-2 receptors
- Trend for greater A benefit in HER2 +++ tumors
- Significantly greater Ki67 drop at 2 wks with A

**NOT confirmed in the large AI trials!**
IMPACT Trial:
Tam vs Anastrozole vs Tam + Ana

Ki67 d0
Ki67 d14
3 months
Relapse-Free Survival

Highly Correlated

Dowsett, JNCI 2007
2. TARGETED DRUGS
Lessons learned from neoadjuvant trials in the post-genomic era: predicting the success of new targeted agents

a) Bevacizumab

b) Dual HER2 targeting
Lessons learned from neoadjuvant trials in the post-genomic era

Predicting the success of new targeted agents…

and the subpopulation where the benefit will be substantial…
GEPARQUINTO trial in HER2 negative BC

- **N** = 1948
- Median age: 48
- Median T: 4 cm
- Clinic N⁺: 58%
- Triple -: 35%

**R**

**EVALUATE**

- no clinical response
  - BEV
  - BEV

**SURGERY**

Trial powered for ↑ in PCR by 1.43
Early signal in TNBC

- **EC-D+ Bevacizumab**
- **EC-D**

<table>
<thead>
<tr>
<th>All BC subtypes</th>
<th>TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.3</td>
<td>18.5</td>
</tr>
<tr>
<td>39.4</td>
<td>32.3</td>
</tr>
</tbody>
</table>

*pCR* = breast + LN

Not significant

P = 0.013

Von Minckwitz, G, Eidtmann H, Rezai M et al, SABC, 2010; Abstract no: S4-6
NSABP-B40

Neoadjuvant Bevacizumab in HER2-BC
Phase III

Patients with operable HER2-BC
Chemo-naïve & primary tumors ≥2cm

Randomize
N = 1206

End points: pCR rate

Study dosing: q3w (4 cycles Docetaxel + 4 cycles AC)

- Bevacizumab Docetaxel → AC
- Docetaxel → AC
- Bevacizumab Xeloda + Docetaxel → AC
- Xeloda + Docetaxel → AC
- Bevacizumab Gemcitabine + Docetaxel → AC
- Gemcitabine + Docetaxel → AC

Surgery

Bevacizumab q3 wk x 10

Adjuvant treatment

AC, Adriamycin and cyclophosphamide

**EARLY SIGNAL IN HR+**

- **Bevacizumab regimens**
  - All BC Subtypes: N=1180
  - pCR* %: 34.5
    - p = 0.027
  - ER+: pCR* %: 23.3
    - p = 0.008
  - ER-: pCR* %: 51.3
    - P = 0.44

- **Docetaxel-AC**
  - All BC Subtypes: N=1180
  - pCR* %: 28.4
  - ER+: pCR* %: 15.2

*pCR = breast + LN*
Neoadjuvant results with bevacizumab... very confusing...and probably not helpful
Lessons learned from neoadjuvant trials investigating dual HER2 blockade

- **NEO ALTTO**
  - N = 450
  - Trastuzumab
  - Lapatinib
  - Paclitaxel
  - PCR 51%

- **NEOSPHERE**
  - N = 417
  - Trastuzumab
  - Pertuzumab
  - Paclitaxel
  - PCR 51%

- **NSABP-B41**
  - N = 529
  - Trastuzumab
  - Lapatinib
  - Docetaxel
  - PCR 62%

**DUAL HER2 BLOCKADE WORKS BETTER THAN SINGLE HER2 BLOCKADE!**

- **NEO ALTTO**
  - Trastuzumab
  - Lapatinib
  - Paclitaxel
  - PCR 51%

- **NEOSPHERE**
  - Trastuzumab
  - Pertuzumab
  - Paclitaxel
  - PCR 51%

- **NSABP-B41**
  - Trastuzumab
  - Lapatinib
  - Docetaxel
  - PCR 53%

(All trials preceded by ACx4)
Lessons learned from neoadjuvant trials investigating dual HER2 blockade

**TRYPHAENA**

$N = 225$

- Trastuzumab
- Pertuzumab
- Docetaxel
- Carboplatin

**Sequential**

- FEC
- Docetaxel

PCR $66\%$

**Concomitant**

- Trastuzumab
- Pertuzumab
- FEC → Docetaxel
  - a. sequential
  - b. concomitant

PCR $57\%/62\%$
Results obtained with dual HER2 blockade alone or with chemotherapy in Hormone Receptor Negative Disease

Based on NeoSphere, NeoAltto, NSABP-B41, Tryphaena
HER2 positive B.C.

Neoadjuvant results with dual HER2 targeting:

- Suggest that a subgroup of HER2 positive tumors, primarily HR negative, are exquisitely sensitive to dual HER2 blockade and may not need aggressive chemotherapy.

- Are in line with results obtained in advanced BC.

- Should predict the success of the strategy in the adjuvant setting...!
EGF104900: significant OS benefit with Herceptin + lapatinib following disease progression

**Median OS (months)**
- Herceptin + lapatinib: 9.5* (n=146)
- Lapatinib: 14.0* (n=145)

**Probability of survival (%)**
- 0 to 100%

**Hazard ratio**: 0.74, p=0.026

* Median OS (months)

Not within EMEA-approved indication for Herceptin

Blackwell et al 2010
Cleopatra trial in advanced HER2+ BC: pertuzumab plus trastuzumab superior to trastuzumab

Primary endpoint: Independently assessed PFS
n = 433 PFS events

HR = 0.62
95% CI 0.51–0.75
p<0.0001

Δ = 6.1 months

D, docetaxel; PFS, progression-free survival; Pla, placebo; P, pertuzumab; T, trastuzumab

8000 women with HER2 positive breast cancer

Design 1 = sequential administration

Design 2 = concomitant administration

Trastuzumab x 1y

Lapatinib x 1y

Trastuzumab ↓ then lapatinib

Trastuzumab combined with lapatinib
THE NEW PIVOTAL BIG TRIAL FOR HER2+ BREAST CANCER: APHINITY

Chemotherapy

N = 3,800

Placebo
Trastuzumab
Trastuzumab
Pertuzumab
Lessons learned from neoadjuvant trials in the post-genomic era

Identifying clinically useful biomarkers of response...
NeoSPHERE study : N = 417 women

BC, breast cancer; FEC, 5-fluorouracil, epirubicin and cyclophosphamide

*Locally advanced=T2–3, N2–3, M0 or T4a–c, any N, M0; operable=T2–3, N0–1, M0; inflammatory = T4d, any N, M0
H, trastuzumab; P, pertuzumab; T, docetaxel

Study dosing: q3w x 4

TH (n=107)
docetaxel + trastuzumab

THP (n=107)
docetaxel + trastuzumab + pertuzumab

HP (n=107)
trastuzumab + pertuzumab

TP (n=96)
docetaxel + pertuzumab

PCR 29%

PCR 46%

PCR 17%

PCR 24%

L. Gianni, SABCS 2010
None of these markers found to be clinically useful!!!

<table>
<thead>
<tr>
<th>Assay method</th>
<th>Biomarker</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC</td>
<td>HER2 mem H-score</td>
<td>339</td>
</tr>
<tr>
<td></td>
<td>HER3 mem H-score</td>
<td>377</td>
</tr>
<tr>
<td></td>
<td>IGF1R mem H-score</td>
<td>339</td>
</tr>
<tr>
<td></td>
<td>PTEN cyt H-score</td>
<td>373</td>
</tr>
<tr>
<td></td>
<td>PTEN nuc H-score</td>
<td>373</td>
</tr>
<tr>
<td></td>
<td>pAKT cyt H-score</td>
<td>299</td>
</tr>
<tr>
<td></td>
<td>pAKT nuc H-score</td>
<td>299</td>
</tr>
<tr>
<td>qRT-PCR</td>
<td>HER2/HER3 - CR</td>
<td>384</td>
</tr>
<tr>
<td></td>
<td>HER3 - CR</td>
<td>384</td>
</tr>
<tr>
<td></td>
<td>HER2 - CR</td>
<td>387</td>
</tr>
<tr>
<td></td>
<td>EGFR - CR</td>
<td>377</td>
</tr>
<tr>
<td>ELISA</td>
<td>c-myc</td>
<td>275</td>
</tr>
<tr>
<td>ELISA</td>
<td>sHER2 (ng/mL)</td>
<td>381</td>
</tr>
<tr>
<td></td>
<td>Amphiregulin (pg/mL)</td>
<td>384</td>
</tr>
<tr>
<td></td>
<td>TGF-alpha (pg/mL)</td>
<td>384</td>
</tr>
<tr>
<td></td>
<td>EGF (pg/mL)</td>
<td>384</td>
</tr>
<tr>
<td>Mutational analyses</td>
<td>PIK3CA mutation</td>
<td>273</td>
</tr>
</tbody>
</table>

Courtesy L. Gianni, SABCS 2011
Neo-ALTTO Study
N = 455 patients in 23 countries

PET Substudy
N = 86 patients in 14 countries

N = 9 patients excluded

N = 77 evaluable
Metabolic Responder…

... and metabolic non-responder
Complete Metabolic Response at week 6

NeoALTTO subpopulation evaluable at week 6
N=65

Apparent higher rate of complete metabolic responses – linked to higher pCR probability – in ER negative HER2+ patients
Lessons learned from neoadjuvant trials

Conclusions

1. In general, neoadjuvant trials are a very efficient tool to screen for new active drugs…

2. Biomarker research remains highly challenging, poorly efficient and needs new models of collaboration

3. Neoadjuvant trials contribute to an improved understanding of the disease…
   …but do not tell the whole story!
The Breast International Group
Board Members
THANK YOU!
BACK-UP
CHALLENGES

Long, complex and resource intensive → $400-900 million → >10 years

High attrition rate in the later phases → 5% to marketing

Drug Development Process
Many Bottlenecks

For Patients: Delayed access and more expensive therapies
PATHOLOGICALLY COMPLETE RESPONSE TO CHEMOTHERAPY IS RELATED TO HORMONE RECEPTOR STATUS: THE MD ANDERSON EXPERIENCE

N=1,018 women receiving 6 preoperative CT regimens (Anthracycline ± Taxane-based)

ER -

pCR = 20%

ER +

pCR = 5%

$p < 0.001$

Buzdar, San Antonio, 2003
Caution: is pCR a good « surrogate marker » of survival in ER positive B.C. ?
Anthracycline-based regimen vs. No chemotherapy

**BREAST CANCER MORTALITY**

**ER-poor**

- **Control**: 42.1%
- **Anthr.**: 35.0%
- **10-y gain**: 7.1% (SE 2.4)
- **Logrank 2p = 0.003**

**ER+**

- **Control**: 31.9%
- **Anthr.**: 26.0%
- **10-y gain**: 5.9% (SE 1.5)
- **Logrank 2p = 0.00004**

Death rates (%/year; total rate – rate in women without recurrence) & logrank analyses

<table>
<thead>
<tr>
<th>Allocation</th>
<th>Years 0–4</th>
<th>Years 5–9</th>
<th>Year 10+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anth.</td>
<td>5.01 SE 0.33</td>
<td>3.46 SE 0.33</td>
<td>2.67 SE 0.36</td>
</tr>
<tr>
<td>Control</td>
<td>6.85 SE 0.42</td>
<td>4.56 SE 0.43</td>
<td>2.96 SE 0.41</td>
</tr>
<tr>
<td>Rate ratio, from (O–E)/V</td>
<td>0.77 SE 0.06</td>
<td>0.79 SE 0.13</td>
<td>0.86 SE 0.20</td>
</tr>
<tr>
<td></td>
<td>-28.3 / 107.3</td>
<td>-11.2 / 48.6</td>
<td>-0.8 / 24.1</td>
</tr>
</tbody>
</table>

EBCTCG September 2010
ABERDEEN NEOADJUVANT STUDY (I)

First Phase

- All patients
  - N = 162
  - 4 cycles of CVAP
    - T₂ (>3cm)
    - T₃ T₄ Tx N₂

Second Phase

- No response
- 4 cycles of Docetaxel
  - N=47
    - 2% pCR
- Response
  - 4 cycles of CVAP
    - N=50
      - 31% pCR
      - 15% pCR

Hutcheon AW, San Antonio 2003
PREOPERATIVE ENDOCRINE THERAPY
DOUBLE BLIND STUDIES

Letrozole (L) vs Tamoxifen (T)
M. ELLIS (N=324)
- Higher response rate with L
- Higher rate of breast conservation with L

Anastrozole (A) vs Tamoxifen (T)
M. DOWSETT (N=330)
- Similar response rate
- Trend for higher rate of breast conservation with A

Did predict for the results of BIG 01-98
Did predict for the results of ATAC
## Pathologic Complete Response

<table>
<thead>
<tr>
<th></th>
<th>Node positive</th>
<th>Node Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weekly (n=50)</td>
<td>Weekly (n=68)</td>
</tr>
<tr>
<td>PCR</td>
<td>28.0%</td>
<td>29.4%</td>
</tr>
<tr>
<td></td>
<td>Q3 weeks (n=51)</td>
<td>Q3 weeks (n=67)</td>
</tr>
<tr>
<td>PCR</td>
<td>13.7%</td>
<td>13.4%</td>
</tr>
</tbody>
</table>

* P < 0.01*

* Weekly versus q3 weeks/clinical nodal status

Green MC, ASCO 2002
SECOND GENERATION OF RANDOMIZED CLINICAL TRIALS
DOCETAXEL (D) VERSUS PACLITAXEL (P)
3-WEEKLY versus WEEKLY ADMINISTRATION

American Intergroup (ECOG 1199)

Node positive
High-risk Node negative

N = 5000

**The « winning arms » !**
A Note of CAUTION

Which is correct?

GeparQuinto
Bevacizumab
achieves higher
pCR rates in
TNBC

NSABP-40
Bevacizumab
achieves higher
pCR rates in
ER+
Early signal & guide to adjuvant therapies

HER2+ EBC

The APHINITY Study: Adjuvant Pertuzumab and Herceptin in Initial Therapy

BIG 4-11 / BO25126 / TOC4939g

**Approach 1**
- Central Confirmation Of HER2 status

**Randomization**
- Arm 1: Anthracycline based chemotherapy
  - Trastuzumab IV 3-weekly
  - Pertuzumab IV 3-weekly
- Arm 2: Placebo IV 3-weekly

**Follow Up**
- 10 years

**Approach 2**
- Central Confirmation Of HER2 status

**Randomization**
- Arm 1: Non-A anthracycline based chemotherapy
  - Trastuzumab IV 3-weekly
  - Pertuzumab IV 3-weekly
- Arm 2: Placebo IV 3-weekly

**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

Total N=3806

www.clinicaltrials.gov, NCT01358877
Pooled analysis of gene expression studies to predict neoadjuvant (taxanes and/or anthracyclines) chemotherapy response

Several molecular processes (including immune signatures) and molecular pathways

? Response to chemotherapy
Mainly seen in HER2+ and ER-/HER2- BC

**HER2+**
(N=118 pts; pCR=42)

**ER-/HER2-**
(N=394 pts; pCR=120)

M Ignatiadis
Lessons learned from neoadjuvant trials in the post-genomic era

2. Identifying clinically useful biomarkers of response...

→ to chemotherapy

→ to targeted drugs
pCR by Metabolic Response in Primary Tumor

**WEEK 2**

- **PET NON-RESPONDER (n =19)**: 21%
- **PET RESPONDER (n =48)**: 42%

**WEEK 6**

- **PET NON-RESPONDER (n =26)**: 19%
- **PET RESPONDER (n =39)**: 44%
Absolute value of day 14 Ki67 is prognostic

Relapse Free Survival

Day 14 Ki67

- <2.7%
- 2-7-7.3%
- >7.3%

Dowsett et al. JNCI 2007
OS analysis by pCR

No pCR

Virtually no relapses in pts reaching pCR with a trastuzumab-containing regimen!
Lessons learned from neoadjuvant trials in the post-genomic era
The neoadjuvant letrozole ± Everolimus study

Randomized 1:1, 2-Arm, Open-Label, Multicenter Trial

Primary Efficacy Endpoint:
Clinical response by palpation

Everolimus daily

Letrozole daily

Biopsy 2 Weeks

N=270

mTOR inhibitor + Letrozole versus Letrozole

- **Clinical response by palpation**
  - Everolimus + Letrozole: 68.1%
  - Letrozole: 59.1%
  - P = 0.0616

- **Response by Ultrasound**
  - Everolimus + Letrozole: 58.0%
  - Letrozole: 47.0%
  - P = 0.0352

- **Ki67 antiproliferative response on d15**
  - Everolimus + Letrozole: 57.0%
  - Letrozole: 30.0%
  - P < 0.01

- **pCR**
  - Everolimus + Letrozole: 1.0%
  - Letrozole: 0.8%

(significance threshold P ≤ 0.10)
BOLERO-2 Primary Endpoint: PFS
Local Assessment

HR = 0.43 (95% CI: 0.35–0.54)
Log rank $P$ value = $1.4 \times 10^{-15}$
EVE + EXE: 6.9 months
PBO + EXE: 2.8 months

Presented by J. Baselga at the 2011 European Multidisciplinary Cancer Congress (ECCO/ESMO), September 26, 2011. Abstract: 9LBA.
Neoadjuvant results with Everolimus:

- Are in line with results obtained in advanced BC particularly the Ki67 proliferative response

- Should predict the success of mtor inhibitors in combination with endocrine therapy in the adjuvant setting
Results obtained with dual HER2 blockade alone or with chemotherapy

Based on NeoSphere, NeoAltto, NSABP-B41, Tryphaena

- Dual HER2 blockade alone: 17%
- Dual HER2 blockade + taxane: 50%
- Dual HER2 blockade + Taxane + other agent (anthrac., carbo): 62-66%

pcR rates