Breast Cancer: from the past to the future

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ESMO President
I. FOCUS ON "EARLY" BREAST CANCER
BREAST CANCER

Localize disease Curable

Metastatic disease Very difficult to cure

"Benefit" established through periodic meta-analyses

• Risk of overtreatment
• Risk of undertreatment
• Risk of choosing the wrong treatment

« Adjuvant » medical therapies

... BUT
Adjuvant systemic therapy for early BC in 2010: “personalized”?

Post-menopausal woman
Invasive Ductal Cancer
2 cm
HER\(_2^+\)
ER\(_+\) PgR\(_-\)

« *On average*, chemotherapy, trastuzumab (the anti-HER\(_2\) monoclonal antibody) and an aromatase inhibitor (an endocrine therapy) are good for you »
Treatment selection relies on a few prognostic / predictive biomarkers, evaluated by the pathologist...
“There is no way to identify patients who will or will not benefit from a specific chemotherapy regimen after 15y of clinical research!”

“Our traditional biomarkers allow for “stratified” medicine (not “personalized” medicine)... and we prescribe our anticancer drugs mostly in the dark”
Empirical oncology  
Tailored oncology

Only if a cultural revolution in clinical & translational research takes place
Today:
45 research groups in 38 countries

Over 75,000 pts in >30 studies
Headquarters: Brussels, Belgium
The contribution of BIG (Breast International Group) to this cultural revolution

1. Fighting the fragmentation in adjuvant clinical trials
2. Working together at reducing overtreatment
MICROARRAYS (RNA): THE FIRST STEP FORWARD IN BIOMARKER RESEARCH

Courtesy of Cordon-Cardo C, ECCO 13
Gene prognostic signatures:

- Genomic Grade

- Mammaprint
  - Ma et al. Cancer Cell. 2004
  - Paik et al. NEJM, 2004

- H/I + MGI

- Oncotype DX
  - Proliferation
    - Ki67
    - STK15
    - Survivin
    - CCNB2 (cyclin B1)
    - MT1E/L2
    - HER2
    - GNRH
    - ER
  - Inhibition
    - GSTM1
    - CD68
    - BAG1
  - Reference
    - ACTB (β-actin)
    - GAPDH
    - RPLPO
    - GLIS
    - TFRC

Add **additional information** to current clinico-pathological parameters for treatment decision making and are able to identify relatively very low proliferative tumors with an excellent prognosis (if the tumor burden is low)
<table>
<thead>
<tr>
<th>Amsterdam gene-expression prognostic signature N=78</th>
<th>Independent validation study on archive material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 5 and 4</td>
<td>• Other populations</td>
</tr>
<tr>
<td></td>
<td>• Internal + external quality assurance</td>
</tr>
<tr>
<td></td>
<td>Level 3</td>
</tr>
<tr>
<td>High powered clinical trial specifically addressing the gene signature’s utility: MINDACT</td>
<td>Level 1</td>
</tr>
</tbody>
</table>

Levels of evidence for biomarkers studies

E.U. GRANT, 6th Framework Programme
TAILORx (n=11,000 women) and MINDACT (n=6,600 women)

Bringing molecular prognostic signatures to daily clinical practice

Node-negative B.C. population

- High risk 21-gene R.S.
- High risk 70-gene signature
- High risk adjuvant on line

- Medium risk 21-gene R.S.
- Discordant risk group
  (mostly low risk 70-gene signature but high risk adjuvant on line)

- Low risk 21-gene R.S.
- Low risk 70-gene signature
- Low risk adjuvant on line

CHEMOTHERAPY

- RANDOMIZE
  CHEMO YES or NO (TailorX)

ENDOCRINE THERAPY

- RANDOMIZE FOR the decision-making tool (Mindact)
MINDACT TODAY

6600 PATIENTS ENROLLED!

6600 full genome expression arrays
6600 blood samples for DNA analysis

First results expected in 2015

Hope: decrease by 10% adjuvant chemotherapy prescription
## Treatment decision outcome

<table>
<thead>
<tr>
<th></th>
<th>C-HIGH / G-HIGH</th>
<th>C-HIGH / G-LOW</th>
<th>C-LOW / G-HIGH</th>
<th>C-LOW / G-LOW</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CT N (%)</strong></td>
<td>1827 (63.3)</td>
<td>718 (24.9)</td>
<td>340 (11.8)</td>
<td>0 (0.0)</td>
<td>2885 (100)</td>
</tr>
<tr>
<td><strong>No CT N (%)</strong></td>
<td>0 (0.0)</td>
<td>718 (19.7)</td>
<td>338 (9.3)</td>
<td>2586 (71)</td>
<td>3642 (100)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1827</td>
<td>1436</td>
<td>678</td>
<td>2586</td>
<td>6527</td>
</tr>
</tbody>
</table>

The core group! No CT and Clinical High Risk

*NB: Compliance with assigned treatment ranging from 85 to 98%*
The contribution of BIG (Breast International Group) to this cultural revolution

1. Fighting the fragmentation in adjuvant clinical trials
2. Working together at reducing overtreatment
3. Moving away from the “one strategy fits all” approach
Clinical trials: OUR SUCCESSES

- **Rapid recruitment with large participation from BIG groups**
- **“Academic” arms with surprising results**
  
  Letrozole x 2y → Tam x 3y ≈ Letrozole x 5y
- **Partnership between academia and pharma reinforced while keeping faith with trial volunteers**

**BIG 1-98**

(N=8010)

- Optional adjuvant CT
  - TAMOXIFEN
  - LETROZOLE
  - TAM
  - LETROZOLE TAM

**BIG 1-00 (Hera)**

(N=5100)

- “Standard” adjuvant CT
  - Observation
  - TRAST x 1y
  - TRAST x 2y
  - (endocrine therapy)

**BIG 2-06/N063D (ALTTO)**

(N=8000)

- Adjuvant CT before or together with anti-HER2 drug(s)
  - TRASTUZUMAB
  - LAPATINIB
  - TRAST LAPATINIB
  - TRAST + LAPATINIB
  - (endocrine therapy)
“We are constructing an ever increasing and costly polypharmacy with the addition of new targeted drugs to existing best practice...”

D. Dodwell & al, the Lancet, August 2009
Anti HER2 therapies

a. Inhibition through direct antibody binding
   - Dimerization domain
   - Trastuzumab

b. Inhibition through dimerization inhibition
   - Pertuzumab
   - Dimerization domain

C. Inhibition of tyrosine kinase activity
   - Lapatinib
   - Small-molecule tyrosine kinase inhibitor

J Baselga, S Swain, Nature Reviews Cancer, 2009
THE CHALLENGE OF PERSONALIZED THERAPY

THE ADD-ON APPROACH

- New targeted agent
- Superiority trial
  - Absolute gain in DFS of $\geq 3\%$
  - $80\%$ power, 2-sided sign. level of $5\%$
  - $5.250$ patients

$$ + $$ = $$$$

Existing best practice

$$ + $$ = $$$$$$

Non-inferiority trial

- Acceptable level of equivalence margin $\leq 2\%$
- $80\%$ power, 2-sided $p 5\%$
- $13.590$ patients

THE FINE-TUNING APPROACH

- New targeted agent
- Simplified therapy $$

$ + $$ = $$$$

An ever-increasing and unaffordable polypharmacy
ADJUVANT TRASTUZUMAB

DIFFERENT DURATIONS OF ADJUVANT TRASTUZUMAB
N ≈ 14,000

FinHER
N = 231

SOLD
N = 3000

Short-HER
N = 1250

≤3 months

BCIRG 006

N ≈ 12000

PHARE
N = 3380

PERSEPHONE
N = 4000

HELLENIC
N = 478

6 months

HERA (arm 3)
N = 1701

2 years

HERA (arm 2)

NCCTG N9831

NSABP-B31
PHARE trial - design

Study design

- Trastuzumab up to 12 months
- Trastuzumab 6 months
- Stop trastuzumab

Stratification:
1. ER pos / neg
2. Chemo: concom/ seq

Clinical exam:
- LVEF
  - 0, 3, 6, 9, 12, 15, 18, 21, 24, 30 mos

Mammography:
- Up to 60 mos.

R: Randomization after informed consent

Pivot et al, ESMO & SABCS, 2012
PHARE TRIAL RESULTS COMPARING 6 TO 12 MONTHS OF TRASTUZUMAB IN ADJUVANT EARLY BREAST CANCER

Disease free survival

PHARE failed to show that 6 months of trastuzumab is non-inferior to 12 months

Pivot, X et al. Presented at SABCS 2012. Abstract number S5-3
## Pending results

<table>
<thead>
<tr>
<th>Studies</th>
<th>Estimated enrollment</th>
<th>Current accrual</th>
<th>Expected results (Yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOLD (9 ws vs. 12 mos)</td>
<td>3000</td>
<td>1700</td>
<td>2016</td>
</tr>
<tr>
<td>Short-HER (3 vs. 12 mos)</td>
<td>1250</td>
<td>1130</td>
<td>2014</td>
</tr>
<tr>
<td>Persephone (6 vs. 12 mos)</td>
<td>4000</td>
<td>2450</td>
<td>2016</td>
</tr>
<tr>
<td>Hellenic Group (6 vs. 12 mos)</td>
<td>?</td>
<td>478</td>
<td>?</td>
</tr>
</tbody>
</table>

*Courtesy information from Trial groups (also from ClinicalTrials.gov)*
CHALLENGE N°1

TREATMENT DE-ESCALATION

IS AN IMPOSSIBLE TASK NOWADAYS!

...
THE NEW PIVOTAL BIG TRIAL FOR HER2+ BREAST CANCER: APHINITY

No room for one arm exploring a shorter treatment duration or intermittent anti HER2 therapy!
TDM1 registration strategy in early HER2 positive BC

1. Post neoadjuvant setting

Residual disease after anthracyclines, taxanes and trastuzumab

2. Adjuvant setting

Standard chemo regimen

± T-DM1
Time for academia to wake up…

!!

Can we move away from the expensive « add on » approach and exploit the full potential of targeted therapies ?
Results obtained with dual HER2 blockade alone or with chemotherapy in Hormone Receptor Negative Disease

Based on the neoadjuvant trials NeoSphere, NeoAltto, Tryphaena
Metabolic Responder...

... and metabolic non-responder

NeoALTTO PET imaging substudy

HER2 blockade (w/o CTX) produces complete metabolic responses on PET!
The "CRs" on PET are far more frequent in HRneg disease... and seem to correlate with pCR.
The dream of de-escalating chemotherapy in HER2+ B.C. 

Close to 1/3 of HER2+ HR- pts achieve pCR with dual HER2 blockade and no chemo (Neosphere) 

Early PET imaging identifies complete metabolic responders to HER2 blockade (mostly among HR- pts) (NeoALTTO) 

In HER2+ HR- disease pCR is strongly correlated to excellent EFS 

These complete metabolic responders predict for pCR when taxol alone is added (NeoALTTO)
I-DREAM Study Design

**DIAGNOSIS**

- TD M1 + P

**EARLY ASSESSMENT**

- FDG-PET/CT (blinded to Oncologist)

**RESPONSE**

- TD M1 + P

**CLINICAL ASSESSMENT**

- TD M1 + P

**CLINICAL ASSESSMENT**

- TD M1 + P

**Surgery**

- TD M1 + P

- TD M1 + P

- TD M1 + P

**US**

- BX

- BX

**FDG-PET/CT**

- FDG-PET/CT

- P.D.: off study

- pCR

- Salvage therapy

- Continue same treatment (x 1y)

P = pertuzumab
**Hypothesis:** 30% of pts show mCR on early PET and 80% of those will have a pCR. A total of 126 such pts are required for a 95% C.I. width of 14% around the estimated pCR. Therefore, 420 patients need to be recruited (460 for security margin).

**Dream:** TDM1 + P could become the future «standard of care» for these pts.
CHALLENGE N°2

VERY SLOW PROGRESS

IN BIOMARKER DISCOVERY

AND VALIDATION
No single biomarker validated in the clinic!

1707 publications on preclinical resistance to anti-HER2 therapy 1999-2009
The contribution of BIG (Breast International Group) to this cultural revolution

1. Fighting the fragmentation in adjuvant clinical trials
2. Working together at reducing overtreatment
3. Moving away from the « one strategy fits all » approach
4. Incorporating modern translational science into clinical trials
II. FOCUS ON METASTATIC BREAST CANCER
Decoding the genome of the tumor

From 3 billion $ in several months

To 2000$ in 2 weeks

... in just a decade...!
CHAPTER I

Advancements in therapeutic drug development have resulted in a wealth of targeted agents in clinical trials. Unfortunately, 20 years on from trastuzumab, few new targets in breast cancer (BC) have passed the difficult and costly phases of traditional drug development to reach regulatory approval. A new approach to drug development is required due to the substantial investments for drug maturity resulting in escalating costs simultaneously with a fall in new therapies approved by the Federal Drug Administration.

Advancements in therapeutic drug development have resulted in a wealth of targeted agents in clinical trials. NAD trials offer great potential for translational research, particularly if the results of this research are shared early on, while valuable knowledge can be gained, several qualifying factors need to be considered when interpreting data from these trials or using a NAD study design including appropriate validation of the surrogate endpoints used and validation of the findings in larger prospective clinical trials. As we move towards the era of personalized therapy, it is important that regulatory and government bodies recognize the supplementary worth neoadjuvant trials offer and encourage approving new therapies.

Identifying predictors of response or resistance to therapies has been a great obstacle in moving towards personalized medicine. Biomarkers development and predictors of response are thought to be facilitated by NAD studies; however, the experience so far shows that the road to “success” might be longer than originally foreseen.
A revolution in medicine is at the door step

THE
PAST

DRUG X

No Benefit

Benefit

Benefit > no benefit
=> drug X = standard of care

Drug X or Drug Y or Drug Z

THE
FUTURE

Aberration X
Aberration Y
Aberration Z

Extensive molecular characterization of disease

« Personalized Therapy »
Cancer: rapidly evolving technologies to dissect its genome aberrations

<table>
<thead>
<tr>
<th>Method</th>
<th>Percentage of Genome Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single gene sequencing</td>
<td>0.000075%</td>
</tr>
<tr>
<td>Targeted seq. of 20-40 genes</td>
<td>0.005%</td>
</tr>
<tr>
<td>Targeted seq. of 200-400 genes</td>
<td>0.03%</td>
</tr>
<tr>
<td>Whole exome seq. (&gt; 22,000 genes) EXONS</td>
<td>1%</td>
</tr>
<tr>
<td>Whole genome seq. (&gt; 22,000 genes) EXONS + INTRONS</td>
<td>100%</td>
</tr>
</tbody>
</table>

- **Impact on new drug development**
- **Impact on access to targeted drugs**
- **Huge potential for improved understanding of the disease and identification of new targets**
First / second line MBC: n = 1000 pts with biopsy accessible metastatic lesions + archived primary tumor + whole blood

PRISM Academic Research Program

« Real-time » targeted gene sequencing (TS) of metastatic lesion (n≈400 genes) and « differed » targeted gene sequencing of primary tumor

Technical failure rate (≈10%)

« Actionable » mutations (n≈300)

New targeted drugs in downstream BIG trials in collaboration with Pharma

Separate consent

« Non actionable » mutations (n≈600)

Standard therapies

Endocrine therapies

Chemotherapy

Chemotherapy + anti HER2 therapies

Q3 months clinical follow-up program with in depth characterization of response outliers = Exceptional responders (R*) or rapid progressors (P*)

30 R*

10 R*

10 P*

10 R*

10 P*

10 R*

10 P*

Whole exome (genome?) sequencing + RNA sequencing (primary + met lesions)
Goals of PRISM

- Improve our understanding of B.C. genetic heterogeneity and « clonal evolution » over time.

- Try to determine which clones are most biologically relevant (those that confer risk of progression or drug resistance) and to which pathways they correspond, with the hope to identify new therapeutic targets.

- To map clonal genotypes with extreme responses to current therapies (exceptional responders or rapid progressors).

- To facilitate access of MBC patients to trials of new promising targeted drugs (FGFR inhibitor, pi3Kα selective inhibitor, AKT inhibitor, MEK inhibitor…).
PRISM-BC: SISTER PROJECTS

Sister project 1
Study of the microenvironment (immune system)

Sister project 2
Monitoring of plasma tumor DNA

Sister project 3
Unveiling drug resistance mechanisms

PRISM ACADEMIC Research “core” project
n = 900

- Central pathology (all)
- GEP (all)
- Target gene seq (all)
- Whole exome seq / RNA seq (n=90)
The BIG Molecular Screening Feasibility Study (BIG MS Pilot) (April-September 2013)

Metastatic biopsies n= 30 pts

- Cellularity
  - ER/ HER2
  - Ki67
  - PiK3CA mut
  - PTEN loss

- « Real time » sequencing of 400 genes (IPG – Ion Proton Technology)

- « Delayed » sequencing of 400 genes (Sanger) (Illumina MiSeq)

- aCGH + GEP

- Frozen

- FFPE
The BIG MS pilot (MSPP= MS prototype platform)
N=30 (MBC)
Empirical oncology

Tailored oncology

Only if a cultural revolution in clinical & translational research takes place
By believing in our dreams, we turn them into reality...