Personalized adjuvant therapy based on clinical trials in breast cancer: dream or reality?

Martine J. Piccart-Gebhart, MD, PhD
Institut Jules Bordet, Brussels, Belgium
Université Libre de Bruxelles
Breast International Group (BIG aisbl), Chair
BREAST CANCER TODAY
5 year survival rates (SEER)

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Female Breast Cancer

- Localized (61%)
  - Confined to Primary Site
- Regional (31%)
  - Spread to Regional Lymph Nodes
- Distant (6%)
  - Cancer Has Metastasized
- Unknown (2%)
  - Unstaged

5-Year Relative Survival:
- Localized: 98.8%
- Regional: 85.2%
- Distant: 26.3%
- Unstaged: 52.5%

SEER 9 Incidence & U.S. Mortality 1975-2013, All Races, Females. Rates are Age-Adjusted.
The Age of Escalation

Targeted therapy

Targeted therapy

SX | Chemo | RT

Cure a substantial proportion of women

Endocrine therapy

Treatment duration: anywhere from 1 day to 15 years!
More Patients Treated

Longer Drug Exposure

More Drugs

Therapeutic Escalation
The cost threatens to blow up our health care systems – the ones that actually pay for treatments!

Many women live longer but bear the consequences of our aggressive treatments – and we can never ignore this!
TREATMENT ESCALATION
The “HERA Paradox”

3 Types of patients:
1. Patients who needed more to be cured
2. Patients who had just enough
3. Patients who did not need trastuzumab to be cured

HERA Trial 11 Year Update

Cameron D, Lancet Oncol 2017
DE - ESCALATION
Surgeons can be proud!

Radical mastectomy

Modified radical mastectomy

Breast conservation

Veronesi

B. Fisher
Axillary dissection for all

Axillary dissection only if SN+

Sentinel node only if up to 2+ nodes

No more axillary surgery?

T1 or T2, No, Mo

Veronesi, U. et al.
N Engl J Med 2003

Gentilini O et al
The Breast 2012

T1, No, Mo

Giuliano A, Morrow M.
Annals of Surgery 2016

T1 or T2, No, Mo

The SOUND trial
De-Escalation in Radiotherapy
Selective towards Better Resource Management

Duration in Days

AWBI – Accelerated Whole Breast Irradiation, APBI – Accelerated Partial Breast Irradiation, IORT – Intraoperative Radiotherapy
DE-ESCLATION IN LOCOREGIONAL TREATMENT

What are the Keys to this Success?

- Breast cancer as a systemic disease - therefore there is a limit to how much local therapy can achieve

- Focus on sequelae and functional outcomes – living after cancer is already hard enough

- Patient-centered approach – “more is not better for everyone”! 
Tailoring of adjuvant systemic therapy for early breast cancer:

A critical look at the past and the future
TAILORING OF ADJUVANT SYSTEMIC THERAPY

What have we tried?

- De-escalation attempts
- «Selective» escalation attempts
What have we tried?

<table>
<thead>
<tr>
<th>DE-ESCALATION attempts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multigene expression signatures to forego chemotherapy</td>
</tr>
<tr>
<td>Shorter treatment duration</td>
</tr>
<tr>
<td>« Walling-off » populations with good prognosis</td>
</tr>
</tbody>
</table>
ADJUVANT SYSTEMIC THERAPY
De-escalation attempts

Multigene expression signatures to forego chemotherapy: 15 years of research efforts!
EORTC-BIG MINDACT Trial Design
6.694 node negative & 1-3 node positive women

70-gene signature (Mammaprint®) risk AND Clinical-Pathological risk

- Both low risk
- Both high risk
- Discordant cases

No chemotherapy
Randomization
Chemotherapy

Supported by the EU 6th framework grant (7 million euros)
Total cost of trial ≈ 45 million euros!
The MINDACT Study: Patient Demographics

N = 6693

Median age = 55y
Node - 79%
Node + 21%
T1 tumours 72%
Grade 2 49%
HR positive 88%
HER2+ 10%

Discordant

N = 2745
clinical Low/ genomic Low

N = 592
clinical Low/ genomic High

N = 1550
clinical High/ genomic Low

N = 1806
clinical High/ genomic High

Clinical « low risk » (50%)

Clinical « high risk » (50%)
The MINDACT study at a median follow-up of 5 years

N = 6693 women

N = 672 relapses

N = 362 distant relapses

208 deaths
Clinical outcome of the MINDACT population at 5y median follow-up.

DMFS IN ALL 4 RISK GROUPS

The « key » population of MINDACT!
Clinical outcome of the MINDACT population at 5y median follow-up.

**DISCORDANT RISK GROUPS: PRIMARY TEST**

The primary statistical test (DMFS at 5Y in those randomized NOT to receive chemo) (N = 644 eval.)

**Clinical High/Genomic Low Risk group (N = 1550)**

- T2 54%
- N+ 48%
- Grade 3 29%

Null Hypothesis: set at 92%

Observed 5Y DMFS = 94.7%

95% CI ≈ 92.5 – 96.2% excludes 92% !!!
MINDACT not powered to rule out a chemotherapy (CTX) benefit in the clinical high – genomic low risk group

HR 0.78 (95% CI: 0.50 – 1.21)

A small CTX benefit (≤ 2%) is possible and must be discussed with patients

A **prognostic** signature does not imply that giving the treatment will be successful.
## SYSTEMIC THERAPY FOR EARLY BC

### Gene Signatures assisting with decision making

<table>
<thead>
<tr>
<th>Provider</th>
<th>MammaPrint</th>
<th>Oncotype DX</th>
<th>Breast Cancer Index</th>
<th>OnCoGGl</th>
<th>PAM 50 ROR</th>
<th>EndoPredict</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agenda</td>
<td>Genomic Health</td>
<td>Biotheranostics</td>
<td>oncoDNA</td>
<td>NanoString</td>
<td>Sivodon/Myriad</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of Assay</th>
<th>70-gene assay</th>
<th>21-gene recurrence score</th>
<th>2-gene ratio (H/I) and molecular grade index</th>
<th>Genomic grade</th>
<th>50-gene assay</th>
<th>12-gene assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Sample</td>
<td>Fresh or frozen or FFPE</td>
<td>FFPE</td>
<td>FFPE</td>
<td>Fresh or frozen or FFPE</td>
<td>FFPE</td>
<td>FFPE</td>
</tr>
<tr>
<td>Technique</td>
<td>DNA microarray or qRT-PCR</td>
<td>qRT-PCR</td>
<td>qRT-PCR</td>
<td>DNA microarray or qRT-PCR</td>
<td>qRT-PCR</td>
<td>qRT-PCR</td>
</tr>
<tr>
<td>Clinical Application</td>
<td>Prognosis of N0, &lt; 5 cm, stage I/II, age &lt; 61</td>
<td>Prediction of recurrence risk in ER+ and N0 treated with TAM</td>
<td>Prognostic in ER+, prediction of response to TAM</td>
<td>Molecular grading for ER+, histologic grade II disease</td>
<td>Originally for intrinsic subtyping, recurrence prediction</td>
<td>Recurrence prediction for ER+ HER2–</td>
</tr>
<tr>
<td>Results Presentation</td>
<td>Dichotomous, good or poor prognosis</td>
<td>Continuous variable</td>
<td>Continuous variable</td>
<td>Dichotomous, GGI I or GGI III</td>
<td>Continuous variable</td>
<td>Dichotomous, low or high risk</td>
</tr>
</tbody>
</table>

**Most useful in Node negative disease**

*Ribinikar D - ASCO Educational Book 2016*
SYSTEMIC THERAPY FOR EARLY BC
De-escalation attempts

Shorter treatment duration
SYSTEMIC THERAPY FOR EARLY BC
Treatment Duration - FinHER

9 weeks of trastuzumab is effective!

Joensuu H, JCO 2009
# Trials Exploring Shorter Durations of Adjuvant Trastuzumab

<table>
<thead>
<tr>
<th>Trial</th>
<th>N° of pts</th>
<th>Time needed</th>
<th>Pt charact</th>
<th>CTX/Trast</th>
<th>Non inf margins</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6 months vs 12 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHARE</td>
<td>3380</td>
<td>4(+2)Y</td>
<td>N- 55%</td>
<td>A/T with trast concom or seq</td>
<td>1.15</td>
<td>HR 1.28 (1.05-1.56) (mostly driven by ER-sequential CTX group)</td>
</tr>
<tr>
<td>HELLENIC</td>
<td>481</td>
<td>8 Y (!)</td>
<td>N- 17%</td>
<td>A/T with trast concomitant</td>
<td>1.53</td>
<td>DFS events : 13% vs 10.4% HR 1.58 (0.86-2.10)</td>
</tr>
<tr>
<td>PERSEPHONE</td>
<td>4089</td>
<td>8 Y (!)</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td><strong>3 months vs 12 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHORT-HER</td>
<td>1250</td>
<td>≈ 5 Y</td>
<td>N- 51%</td>
<td>Conv A-&gt;T+H for 12m TH-&gt;A for 3m arm</td>
<td>1.29</td>
<td>?</td>
</tr>
<tr>
<td>SOLD</td>
<td>2176</td>
<td>≈ 6 Y</td>
<td>?</td>
<td>TH-&gt;A-&gt;Tx9m(12m) TH-&gt;A (3m)</td>
<td>Superior OS by 4%</td>
<td>?</td>
</tr>
</tbody>
</table>
SYSTEMIC THERAPY FOR EARLY BC
Treatment Duration – Where Have We Failed?

- Essentially the same non-inferiority study being run by different countries in an independent manner...

- Ex post facto determination of treatment length is hard to achieve – the registration trial is THE moment to explore treatment duration - and this is when governments should intervene and provide support, in a “risk-sharing” model with Pharmaceutical Industry...
SYSTEMIC THERAPY FOR EARLY BC
De-escalation attempts

« Walling-off » populations with good prognosis
HER2+ mostly ER+ (67%)
Node Negative mostly T1 tumors (91%)

Planned N=400

Enroll

- PACLITAXEL 80 mg/m² + TRASTUZUMAB 2 mg/kg x 12

- FOLLOWED BY 13 EVERY 3 WEEK DOSES OF TRASTUZUMAB (6 mg/kg)*

* Dosing could alternatively be 2 mg/kg IV weekly for 40 weeks
** Radiation and hormonal therapy was initiated after completion of paclitaxel

Tolaney, NEJM 2015
SYSTEMIC THERAPY FOR EARLY BC "Walling Off" Populations – APT Trial Results

Tolaney, NEJM 2015

Update in 2017!
## TAILORING OF ADJUVANT SYSTEMIC THERAPY: What have we tried?

<table>
<thead>
<tr>
<th>DE-ESCALATION attempts</th>
<th>SELECTIVE ESCALATION attempts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multigene expression signatures to forego chemotherapy</td>
<td>• The post-neoadjuvant model</td>
</tr>
<tr>
<td>Shorter treatment duration</td>
<td>• The neoadjuvant model with intensive biomarker (BM) research</td>
</tr>
<tr>
<td>«Walling-off» populations with good progression</td>
<td>• The adjuvant model with intensive BM research</td>
</tr>
</tbody>
</table>
SYSTEMIC THERAPY FOR EARLY BC
Selective Escalation

The post-neoadjuvant model
« Low-Tech Selective Escalation »
AILORING OF SYSTEMIC THERAPY FOR EARLY BREAST CANCER

Selective Escalation

The post-neoadjuvant model: 2 examples

**CREATE X (HER2-) [Japan]**

- Neoadj CTX
- ↓ SURGERY
- ↓ Non pCR
  - Standard therapy
  - Capecitabine + standard therapy

**PENELOPE (luminal B)**

- Neoadj CTX
- ↓ SURGERY
- ↓ Non pCR
  - Standard endocrine therapy
  - Palbociclib + standard endocrine therapy

and CPS-EG score of 3-6 (or 2 if ypN+)
SYSTEMIC THERAPY
Post-Neoadjuvant Design – CREATE-X

DFS

OS

Adapted from Lee SJ - SABCS 2015
Given the plasticity of the cancer cell isn’t it « too late » to escalate therapy after a few months?

Can we find static biomarkers at baseline or dynamic biomarkers after a short drug exposure linked to excellent or poor outcome and use them to improve adjuvant treatment tailoring?
The neoadjuvant/adjuvant model « High-Tech Selective Escalation » through extensive biomarker research.

- « Day 0 » Approach
  - "Static biomarkers"
- The « ADAPT » Design
  - "Dynamic biomarkers"
The conventional way of running adjuvant systemic trials in early BC

Selected patient population

R

Standard adjuvant systemic therapy

New adjuvant systemic therapy

Retrospective exploration of static biomarkers on “Day 0”
Translational Research efforts in HER2+ BC: Day 0 approach

- HER2 itself
- Other membrane receptors & their ligands
- Downstream signaling pathways
- Microenvironment
- Tumor heterogeneity

SABCS 2015
We have been unable to go beyond HER2 for improved treatment tailoring!
Candidate biomarkers for treatment (de)-escalation: TILs in NEOALTTO correlate with EFS.

TiLs and Event-Free Survival:

Could patients with high TILs be treated with less aggressive chemotherapy?
TAILORING OF SYSTEMIC THERAPY FOR EARLY PROSTATE CANCER

The neoadjuvant/adjuvant model
» High-Tech Selective Escalation »
through extensive biomarker research

« Day 0 » Approach

“Static biomarkers”

The « ADAPT » Design

“Dynamic biomarkers”
REOPERATIVE SYSTEMIC THERAPY AND DYNAMIC BIOMARKERS

The path to improved systemic treatment tailoring?

 Ideal « pCR » patients should not get further therapy!

This model incorporates a key variable for treatment tailoring: «what the host does to the drug»

Poor responders: explore drug escalation in a randomized fashion

Standard therapy
- 3 wk exposure
- BX

New therapy
- 3 wk exposure
- BX

Good responders continue standard therapy (off study)

Ideally « pCR » patients should not get further therapy!
Do we know that drastic molecular changes occur very early in tumors upon drug exposure and are linked to « response » ?

! YES !

Luminal BC/endocrine therapy : Ki67
HER2 positive BC/antiHER2 therapy : PAM50
IMPACT Trial: Tam vs Anastrozole vs Tam + Ana

Ki67 d0

Ki67 d14

3 months

Relapse-Free Survival

Highly Correlated

Dowsett, JNCI 2007
NEOADJUVANT SYSTEMIC THERAPY
De-escalation – PAMELA (N = 144 pts)

N=150

HER2+
Breast
Cancer
stage I-IIIA

Trastuzumab 6 mg/kg every 3 weeks
Lapatinib 1000 mg/day
+ Letrozole or Tamoxifen if HR+

Baseline
PAM50

Week 2
PAM50

40% for baseline HER2 – e
49% for switch to normal-like

No Relev correlation
EFS possible

Adjuvant systemic treatment was at the discretion of the treating physician

A. Llombart-Cussac et al., Lancet Oncology, 2017
POETIC I (N ~ 4500)  
(Results expected in 2017)

Building on POETIC I: escalation based on patient's specific patterns of drug resistance.

POETIC II  
(The next research model?)

- Good responders continue AI (off study)
- Poor responders: drug escalation (CDK4-6 inh 
  ....)

Patient-specific mechanisms of resistance be identified within a 2 wk window of drug exposure?
CONCLUDING REMARKS

- The current paradigm for drug development in early BC has permitted significant advances.
- However, the weaknesses of this framework become ever clearer.

We need to move away from the conservative clinical trial designs of the 20th century!
The path to “tailored” adjuvant therapy

- Multidimensional, preferably « dynamic » TR models
- Results from one trial to be validated in another trial

Only possible through

Academia & Pharma
strong partnerships

Requirement for Pharma to download TR data on an accessible platform (after primary endpoint reached)

If your collaborative research group has not yet joined BIG... please consider doing so!
Back-ups
Translational Research Efforts in Early HER2+ BC

Neoadjuvant setting

High HER2 protein = \(\uparrow\) pCR
- NeoALTTO (1)

High HER2 mRNA = \(\uparrow\) pCR
- TRYPHAENA (2)
- GeparQuattro (3)

HER2 enriched (PAM50) = \(\uparrow\) pCR
- NOAH (4)
- CALGB 40601 (5)
- Pamela (6)

Adjuvant setting

HER2 staining \(\leftrightarrow\) no impact
- HERA (7)

HER2 amplif/FISH ratio/polysomy NOT linked to outcome
- HERA (8)/N9831 (9)/NSABP-B31 (10)

HER2 enriched (PAM50): no impact
- NSABP-B31 (11)

Worriesome lack of correlation between biomarkers predicting pCR and those predicting DFS/OS!