ADJUVANT THERAPY IN BREAST CANCER

Quo vadis?

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Breast International Group (BIG asbl), Chair
DISCLOSURES

- **Board member**: PharmaMar

- **Consultant (honoraria)**: Amgen, Astellas, AstraZeneca, Bayer, Invivis, Lilly, MSD, Novartis, Pfizer, Roche-Genentech, Sanofi-Aventis, Symphogen, Synthon, Verastem

- **Research grants to Jules Bordet Institute**: most companies

- **Speakers bureau/stock ownership**: none
Plan of the talk

• Rapid overview of current adjuvant treatment practice

• Lessons and questions in:
  1. Luminal BC
  2. Triple Negative BC
  3. HER2 positive BC
Changes in clinical practice for early Breast Cancer

1900
1980
2000
2005
2015

Halsted Mastectomy

Breast conserving surgery and RT

Adjuvant Hormonal therapy

Adjuvant Chemotherapy

Sentinel node

PBI

Anti HER2 treatment
ADJUVANT HORMONAL THERAPY (Tamoxifen) IMPROVES SURVIVAL

Recurrence

Breast cancer mortality

EBCTCG, Lancet 2005
BIG 1-98: CUMULATIVE INCIDENCE OF BREAST CANCER EVENTS - ABSOLUTE BENEFIT

Years from randomization

Proportion failure (%)

5-y difference

LET – TAM = –3.4%

P<0.001

Letrozole

Tamoxifen

6.2% Letrozole

10.2%

13.6%

3.4%
ATAC: TIME TO RECURRENCE HR+ PATIENTS CARRY OVER EFFECT

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2618</td>
<td>2598</td>
<td>2541</td>
<td>2516</td>
<td>2453</td>
<td>2400</td>
<td>2361</td>
</tr>
<tr>
<td></td>
<td>2306</td>
<td>2196</td>
<td>2075</td>
<td>1896</td>
<td>1711</td>
<td>1396</td>
<td>547</td>
</tr>
</tbody>
</table>

Follow-up time (years)

- **HR+**
  - HR: 0.76
  - 95% CI: (0.67, 0.87)
  - p-value: 0.0001

**At risk:**
- **A**
  - 2618
  - 2541
  - 2453
  - 2361
  - 2278
  - 2159
  - 1995
  - 1801
  - 1492
  - 608
- **T**
  - 2598
  - 2516
  - 2400
  - 2306
  - 2196
  - 2075
  - 1896
  - 1711
  - 1396
  - 547

**Follow-up time (years):**
- 5 years: 12.5%
- 9 years: 21.8%

**Absolute difference Tamoxifen (T) vs Anastrozole (A):**
- 4.8%
ADJUVANT CHEMOTHERAPY IMPROVES SURVIVAL

Breast cancer mortality

Age: < 50

- Control 42.4%
- Polychemotherapy 32.4%

15-year gain 10.0% (SE 1.6)
Logrank 2p < 0.00001

Age: 50-69

- Control 50.4%
- Polychemotherapy 47.4%

15-year gain 3.0% (SE 1.3)
Logrank 2p < 0.00001

EBCTCG, Lancet 2005
Taxanes + Anthracyclines > CMF > none
ADJUVANT TRASTUZUMAB IMPROVES SURVIVAL

B-31 and NCCTG N9831
10-year disease free survival

HERA 8-year disease free survival

HERA 8-year overall survival

ADJUVANT TRASTUZUMAB IMPROVES SURVIVAL
Patients in control arms of recent adjuvant BC trials do very well!

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mostly Luminal</th>
<th>TNBC</th>
<th>HER2 positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>E5103 48m</td>
<td>26%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BEATRICE 3y</td>
<td>63%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BETH 3y</td>
<td>48%</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>ALTTO 4.5y</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Control arms (DFS%)

- Chemo±HT
- Chemotherapy
- Chemotherapy+Trastuzumab±HT

Node negative%
- 26%
PROGRESS IN BREAST CANCER TREATMENT

Empirical oncology  2007-2014  Molecular oncology

- Breast cancer = 2 diseases (HR+ or -)
- Rough estimation of relapse risk
- « One size fits all » treatment strategy
- Breast cancer = 4 diseases (luminal A/B, HER2+, triple negative)
- Improved estimation of relapse risk
- Improved tailoring of adjuvant treatment
CLASSIFICATION Surrogates

Simple tools

Complex tools

Figure 3. Molecular Classification, Gene-Expression Signatures, and Clinical Outcome.
Genes that are associated with tumor differentiation and cell cycle drive the prognostic power of the intrinsic molecular classification and several gene-expression signatures.
**Systemic treatment recommendations for early breast cancer subtypes**

**ESMO Guidelines 2013**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Recommended therapy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A-like</td>
<td>ET alone in the majority of cases.</td>
<td>Consider CT if</td>
</tr>
<tr>
<td>Luminal B-like (HER2-negative)</td>
<td>ET + CI for the majority of cases</td>
<td>(i) high tumour burden (four or more positive LN, T3 or higher)</td>
</tr>
<tr>
<td>Luminal B-like (HER2-positive)</td>
<td>ET + CI for the majority of cases</td>
<td>(ii) grade 3</td>
</tr>
<tr>
<td>HER2-positive (non-luminal)</td>
<td>CI + anti-HER2</td>
<td>If contraindications for the use of CT, one may consider ET + anti-HER2 therapy, although no randomised data exist.</td>
</tr>
<tr>
<td>Triple-negative (ductal)</td>
<td>CT</td>
<td></td>
</tr>
</tbody>
</table>
Focus on Luminal B.C.

• What did we learn?

• Which questions do we still have to answer?
Adjuvant therapy for Luminal Breast Cancers

What did we learn?

- Some patients do not need chemotherapy
- Consideration for the incorporation of an “AI” in the treatment scheme should be given (in post menopausal women)
- Some patients benefit from extended (10y) hormonal treatment
- Exemestane+OFS is an emerging option for premenopausal women
- Bisphosphonates (mostly zoledronic acid) are to be considered for some women
- There is no role for adjuvant Bevacizumab
- BC mortality is increased in high BMI premenopausal women
# Multigene “Prognostic” Signatures

- More than a decade of translational research...
- Rapid uptake of ONCOTYPE DX in the USA (<18 = no chemotherapy)
- Slower uptake of any of the signatures by European oncologists

<table>
<thead>
<tr>
<th>Name</th>
<th>Oncotype DX™</th>
<th>MammaPrint™</th>
<th>GGI</th>
<th>PAM50</th>
<th>Breast Cancer Index</th>
<th>EndoPredict</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Provider</strong></td>
<td>Genomic health</td>
<td>Agendia</td>
<td>Ipsogen</td>
<td>nanoString</td>
<td>Biotheranostics</td>
<td>Savidon Diagnostics</td>
</tr>
<tr>
<td><strong>Type of Assay</strong></td>
<td>21 gene recurrence score</td>
<td>70 Gene Assay</td>
<td>97 Gene Assay</td>
<td>50 Gene Assay</td>
<td>2 gene ratio HOXB13 to IL17R and molecular grade index</td>
<td>combines RNA score with nodal status and tumor size</td>
</tr>
<tr>
<td><strong>Tissue samples</strong></td>
<td>FFPE</td>
<td>From fresh moving to FFPE</td>
<td>From fresh moving to FFPE</td>
<td>FFPE</td>
<td>FFPE</td>
<td>FFPE</td>
</tr>
<tr>
<td><strong>Technique</strong></td>
<td>qRT-PCR</td>
<td>Microarray</td>
<td>From Microarray moving to qRT-PCR</td>
<td>qRT-PCR</td>
<td>qRT-PCR</td>
<td>qRT-PCR</td>
</tr>
</tbody>
</table>
Very good RFS in patients with “low-risk” genomic signatures

OncotypeDx (JCO 2006)

mammaPrint (NEJM 2002)

ENDOPREDICT (Annals of Oncology 2013)
Impact of adjuvant endocrine treatment strategies on breast cancer mortality

- TAMOXIFEN x 5y: HR 0.53 vs no TAM
  - EBCTG 2011
- A.I. x 5y: HR 0.82 vs TAM x5y
  - BIG 1-98
- TAM and A.I.: no significant differences
  - aTTOM/ATLAS vs TAM x5y
  - MA17-NCIC vs TAM x5y

Impact of adjuvant endocrine treatment strategies on breast cancer mortality

Years:
- 0
- 5
- 10
## 10 vs 5-yr BREAST CANCER MORTALITY IN ER+ rate ratio* by period in aTTom and ATLAS

<table>
<thead>
<tr>
<th></th>
<th>10 yrs tam. vs 5: aTTom trial (n=6934 ER+/UK)</th>
<th>10 yrs tam. vs 5: ATLAS trial* (n=10,543 ER+/UK)</th>
<th>10 yrs tam. vs 5: aTTom &amp; ATLAS combined (n=17,477 ER+/UK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>years 5-9</td>
<td>1.08 (0.85-1.38)</td>
<td>0.92 (0.77-1.09)</td>
<td>0.97 (0.84-1.15)</td>
</tr>
<tr>
<td>years 10+</td>
<td>0.75† (0.63-0.90)</td>
<td>0.75§ (0.63-0.90)</td>
<td>0.75† (0.65-0.86)</td>
</tr>
<tr>
<td>All years</td>
<td>0.88‡ (0.74-1.03)</td>
<td>0.83‡ (0.73-0.94)</td>
<td>0.85‡ (0.77-0.94)</td>
</tr>
</tbody>
</table>

†p=0.007  
‡p=0.1  
§p=0.002  
‡p=0.004  
†p=0.00004  
‡p=0.001

*Inverse−variance−weighted estimate of the effect in ER+.(ATLAS, Lancet 2013)

Courtesy of R. Gray
Assessing benefits and risks of prolonged tamoxifen

**Benefits** will depend on

- Tumor burden
- Tumor biology
- Comorbidity & age

**Risks** include

- « SAE ’s »
  - ↑ end.cancer from 1.6% to 3.1%
  - ↑ pulm embolism
    (but ↓ ischemic heart disease)
- Quality of life alteration
  - Vasomotor symptoms
  - Mood alterations
  - Sexual dysfunctions
Exemestane+OFS is an emerging option for premenopausal women

TEXT and SOFT trials

---

**TEXT and EXEMESTANE TRIAL**

- Enrolled: Nov 2003 - Apr 2011
- Randomize:
  - Premenopausal
  - ≤12 wks after surgery
  - Planned OFS
  - No planned chemo OR planned chemo
  
- Joint Analysis (N=2672)
  - Tamoxifen+OFS x 5y
  - Exemestane+OFS x 5y

**SOFT TRIAL**

- Enrolled: Nov 2003 - Apr 2011
- Randomize:
  - Premenopausal
  - ≤12 wks after surgery
  - No chemo
  - OR
  
- Suppressing OVARIAN FUNCTION (N=3066)
  - Tamoxifen x 5y
  - Exemestane+OFS x 5y

---

**Joint Analysis**

- Median follow-up 5.7 years
- OFS=ovarian function suppression

Olivia Pagani, NEJM 6/2014
OFS + E

<table>
<thead>
<tr>
<th></th>
<th>H.R.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>0.72</td>
</tr>
<tr>
<td>BCFI</td>
<td>0.66</td>
</tr>
<tr>
<td>DDFI</td>
<td>0.78</td>
</tr>
<tr>
<td>OS</td>
<td>1.14</td>
</tr>
</tbody>
</table>

All significant

Not yet significant

... but

Long accrual: 2003-2011
Heterogenous populations
Revised analysis plan needed
Results different from ABCSG12

Goserelin + A vs Goserelin + T (3y)
(± zoledronic acid)
DFS H.R. 1.08 (0.81 - 1.44)
OS H.R. 1.75 (1.08 - 2.83)
First results of TEXT/SOFT combined

Absolute gain in 5y DFS of 3.8% to be balanced against grade 3 or 4 side effects

<table>
<thead>
<tr>
<th></th>
<th>E &gt; T</th>
<th>T &gt; E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculo-skeletal</td>
<td>11% &gt; 5%</td>
<td>1.9% &gt; 0.8%</td>
</tr>
<tr>
<td>Fractures</td>
<td>1.3% &gt; 0.8%</td>
<td></td>
</tr>
<tr>
<td>Cardiac ischemia</td>
<td>0.3% &gt; 0.1%</td>
<td></td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>2.3% &gt; 1.4%</td>
<td></td>
</tr>
<tr>
<td>Discontinuation of therapy</td>
<td>16% &gt; 11%</td>
<td></td>
</tr>
</tbody>
</table>

Thromboembolic events
Effects of bisphosphonate treatment on recurrence in women with early breast cancer: a meta-analysis

- 41 randomised trials, 17,751 women
- There were no improvements in recurrence for premenopausal women
- In Post menopausal: 3.1% decrease in breast cancer mortality

<table>
<thead>
<tr>
<th>Event Type</th>
<th>No. events</th>
<th>HR (SE)</th>
<th>10 year gain</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer mortality</td>
<td>1,107</td>
<td>0.83 (0.06)</td>
<td>3.1%</td>
<td>0.004</td>
</tr>
<tr>
<td>Breast cancer recurrence</td>
<td>1,809</td>
<td>0.86 (0.05)</td>
<td>3.0%</td>
<td>0.002</td>
</tr>
<tr>
<td>Distant recurrence</td>
<td>1,503</td>
<td>0.83 (0.05)</td>
<td>3.3%</td>
<td>0.0007</td>
</tr>
<tr>
<td>Bone recurrence</td>
<td>445</td>
<td>0.65 (0.08)</td>
<td>2.9%</td>
<td>0.00001</td>
</tr>
<tr>
<td>Other distant recurrence</td>
<td>1,058</td>
<td>0.93 (0.06)</td>
<td>0.7%</td>
<td>0.26</td>
</tr>
</tbody>
</table>

R Coleman, SABCS 2014, abstract S4-07
E5103 Adjuvant Bevacizumab (64% ER+)

A large, well powered adjuvant trial – E5103 – fails to show any benefit from the incorporation of bevacizumab into adjuvant chemotherapy regimens!

K. Miller, SABCS 2013
The negative impact of obesity in early BC

EBCTCG: 80,000 women in 70 trials

ER negative disease (N = 20,000)
- No impact of obesity on BC mortality

ER positive disease (N = 60,000)
- Premenopausal women (N = 20,000)
  - Increased BC mortality with ↑BMI
    - RR 1.34 (1.22-1.47)
- Postmenopausal women (N = 20,000)
  - No increased BC mortality
    - RR 1.06 (0.99-1.14)

• CTX dose reductions or biology?
• No information on subsequent weight gain

H. Pau, abst 503
Adjuvant therapy for Luminal Breast Cancers

Interesting questions for the future

✓ Can patients with intermediate genomic risk or discordant risk (low genomic risk/high clinical risk) be treated safely with endocrine therapy only?

✓ Will manipulation of endocrine resistance further improve outcome? (CDK4-6 inhibitors/Everolimus)
Should patients with intermediate risk or Discordant risk be treated with chemotherapy
Ongoing trials TAILORX AND MINDACT

<table>
<thead>
<tr>
<th></th>
<th>TAILORx</th>
<th>MINDACT</th>
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</thead>
<tbody>
<tr>
<td>Groups</td>
<td>TBCI</td>
<td>BIG/EORTC</td>
</tr>
<tr>
<td>Population</td>
<td>Node-neg, ER+</td>
<td>N0-N1 ER+/-</td>
</tr>
<tr>
<td>Assay</td>
<td>21 gene ODX™</td>
<td>Mammaprint®</td>
</tr>
<tr>
<td>Utility Scale &amp; Level of Evidence</td>
<td>+ or ++ II</td>
<td></td>
</tr>
<tr>
<td>Tissue</td>
<td>FPET</td>
<td>Fresh Frozen</td>
</tr>
<tr>
<td>No.</td>
<td></td>
<td>6,700</td>
</tr>
<tr>
<td>No. randomized</td>
<td></td>
<td>2,142</td>
</tr>
<tr>
<td>Randomized group</td>
<td>RS 11-25 (40%)</td>
<td>Discordant risk (32%)</td>
</tr>
<tr>
<td>Randomization</td>
<td>Treat with hormones +/- chemotherapy</td>
<td>Treat by clinical vs genomic risk</td>
</tr>
<tr>
<td>Non-randomized groups</td>
<td>RS&lt;11: Hormones</td>
<td>Both low risk (41%): Hormones</td>
</tr>
<tr>
<td></td>
<td>RS&gt; 25: Chemo+ hormones</td>
<td>Both high risk (27%): Chemo +/- hormones</td>
</tr>
</tbody>
</table>
Circumventing endocrine resistance
Blocking CDK’s

↑ cyclin D1/CDK4-6 « traps » p27 away from cyclin E/CDK2 which will then also phosphorylate Rb

Many mitogenic signals converge at Cyclin D1!

Phosphorylated Rb = positive regulator of G1/s transition

Fernández V et al. JCO 2005; 23:6364-6369
CDK4-6 inhibitors in clinical trials for advanced BC

- **LEE011**
  - Started Phase 3
  - Mild GI toxicity
  - Reversible Neutropenia ± thrombocytopenia

- Abemaciclib
- Palbociclib
## Ongoing Phase 3 Studies assessing CDK4/6 inhibition

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>PALOMA-2</td>
<td>Palbociclib + Letrozole vs. Letrozole For 1st Line Treatment Of Postmenopausal Women (NCT01740427)</td>
<td></td>
</tr>
<tr>
<td>PALOMA-3</td>
<td>Palbociclib + Fulvestrant vs. Fulvestrant + Placebo After Endocrine Failure (NCT01942135)</td>
<td></td>
</tr>
<tr>
<td>PEARL</td>
<td>Palbociclib + Exemestane vs. Capecitabine in Resistance to NSAI (NCT02028507)</td>
<td></td>
</tr>
<tr>
<td>MONARCH2</td>
<td>Fulvestrant With or Without Abemaciclib (LY2835219) (NCT02107703)</td>
<td></td>
</tr>
<tr>
<td>MONALEESA2</td>
<td>LEE011 in Combination With Letrozole (NCT01958021)</td>
<td></td>
</tr>
</tbody>
</table>
The Alliance – ABCSG – BIG

“Pallas” adjuvant trial

« High risk » luminal BC

Standard adjuvant therapy

+ palbociclib

or placebo

... under construction!
Fueling endocrine resistance
Circumventing endocrine resistance

PI3K/Akt/mTOR

- PI3K Inhibitor
- mTOR Inhibitor
- PI3K/mTOR Inhibitor
- Akt Inhibitor

Endocrine resistance
BOLERO-2 Study in advanced luminal BC with secondary resistance to non-steroidal AI

**PFS Central Assessment**

- Hazard ratio, 0.36 (95% CI, 0.27–0.47)
- P<0.001 by log-rank test

- Everolimus plus exemestane (median PFS, 10.6 mo)

- Placebo plus exemestane (median PFS, 4.1 mo)

**OS**

- Kaplan-Meier medians
  - EVE+EXE: 30.88 months
  - PBO+EXE: 26.55 months

PFS benefit but no OS benefit


*Piccart M.J. et al., Annals of Oncology, in press.*
S1207/SWOG and UNIRAD studies:
Adjuvant endocrine therapy +/- Everolimus

Phase III randomized double-blind trial adding everolimus to adjuvant endocrine therapy who are disease-free following 3y of adjuvant ET for a total adjuvant therapy duration of 5y

**Population:**
- >18y
- Non metastatic
- ER+/Her2-
- PN+
- Disease free 3y HT

**End points:**
- **Primary:** DFS
- **Secondary:** OS, DMFS

**UNIRAD**
- Planned Number = 1984

**SWOG-S1207**
- Planned Number = 3,500 an effective hazard ratio of 0.75 for everolimus versus placebo corresponding to a gain in DFS of approximately 4.3% at 5 years

**Phase III randomized, placebo-controlled trial adding 1 year of everolimus to adjuvant endocrine therapy for patients with high-risk, HR+, HER2- breast cancer.**

**Everolimus**
- + ongoing ET to 5y

**Placebo**
- End points:
  - Recurrence Score evaluation by OncotypeDX
  - Node-negative tumor ≥ 2 cm: ≥ 4 positive nodes
  - Node-negative tumor < 2 cm: 1-3 positive nodes:
  - Node-negative tumor < 2 cm: ≥ 4 positive nodes:

**Safety**
- Planned Number = 1984
- Effective hazard ratio of 0.75 for everolimus versus placebo corresponding to a gain in DFS of approximately 4.3% at 5 years

**Randomization**
- Stratification factors:
  - Node negative
  - 1 - 3 positive nodes
  - ≥ 4 positive nodes Adjuvant
  - ≥ 4 positive nodes Neoadjuvant
Focus on Triple negative B.C.

• What did we learn?

• Which questions do we still have to answer?
Adjuvant Therapy for triple negative BC

What did we learn?

✓ TNBC is a heterogeneous disease

✓ There is a potential role for chemotherapy dose intensity

✓ There is no role for adjuvant bevacizumab

✓ There is a potential role for Platinum based therapy (confined to BRCA mutations carriers ?)
Subtyping of TNBC reveals marked heterogeneity in probabilities of pCR to neoadjuvant CT (anthracycline + docetaxel)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal-like 1</td>
<td>++</td>
</tr>
<tr>
<td>Basal-like 2</td>
<td>-</td>
</tr>
<tr>
<td>Immunomodulatory</td>
<td>+(+)</td>
</tr>
<tr>
<td>Mesenchymal-like</td>
<td>+(+)</td>
</tr>
<tr>
<td>Mesenchymal stem-like</td>
<td>±</td>
</tr>
<tr>
<td>Luminal androgen-receptor</td>
<td>±</td>
</tr>
<tr>
<td>Unclassified</td>
<td>+(+)</td>
</tr>
</tbody>
</table>

B. D. Lehmann, J Clin Invest 2011

H. Masuda ASCO 2013
DOSE-DENSE (DD) CHEMOTHERAPY IS AN OPTION FOR TNBC – CALGB 6y update

- Number: 2,005
- Population: LN +
- Dose dense > conventional
  - DFS [RR: 0.80; p=0.018]
  - OS [RR: 0.85; p=0.07]
- ER- DFS [RR: 0.75; p=0.03]

Citron M et al; JCO 2003, Hudis SABCC 2005
Adjuvant CTX for TNBC

2009 - 2014

Renewed interest in Platinum compounds
# PLATINUM SALTS & TNBC

**Data from neo-adjuvant studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Regimen</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gronwald et al</td>
<td>2009</td>
<td>25</td>
<td>Cisplatin x 4 (Q3w)</td>
<td>pCR: 72%</td>
</tr>
<tr>
<td>Garber et al</td>
<td>2006</td>
<td>28</td>
<td>Cisplatin x 4 (Q3w)</td>
<td>pCR: 22%</td>
</tr>
<tr>
<td>Torrisi et al</td>
<td>2008</td>
<td>30</td>
<td>Cisplatin + Epi +5Fu – Pac x 3</td>
<td>ORR: 86% pCR: 40%</td>
</tr>
</tbody>
</table>
| Frasci et al  | 2009 | 74 | Cisplatin + Epi + Pac x 8 (Q1w) + GCSF | pCR: 62% 5y DFS  
• 90% (pCR)  
• 56% (no pCR) |
Randomized neoadjuvant trials in TNBC suggest a benefit from the addition of carboplatin to chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Sikov et al.</th>
<th>Von Minckwitz et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt population</td>
<td>N = 443 ♀ with TNBC</td>
<td>N = 595 ♀ with HER2+ and TNBC</td>
</tr>
<tr>
<td>Chemo backbone</td>
<td>Weekly paclitaxel (80mg/sqm)</td>
<td>Weekly paclitaxel (80mg/sqm) + Weekly pegylated doxo (20mg/sqm)</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC 6 q3wks</td>
<td>AUC 1.5 weekly</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>By randomization (2x2)</td>
<td>Added automatically for TNBC (15mg/kg q3wks)</td>
</tr>
<tr>
<td>Incremental pCR gain</td>
<td>41% → 54% (13%)</td>
<td>38% → 58% (20%)</td>
</tr>
<tr>
<td>Who benefits?</td>
<td>Ongoing analyses may lead to the identification of clinically relevant subsets</td>
<td>BRCA+ or strong familial Hx or TILs +++</td>
</tr>
</tbody>
</table>
Optimal adjuvant chemotherapy for TNBC

No consensus – as of today – on the role of Platinum compounds!

(will the incremental 20% gain in pCR translate into improved DFS, OS?)
Adjuvant Therapy for triple negative BC

Interesting questions for the future

✓ The role of PARP inhibitors in BRCA mutation carriers

✓ The role of metronomic chemotheraphy
Exploiting DNA Damage Repair Deficits to Kill Cancer Cells

PARP plays a pivotal role in repairing single strand DNA breaks (SSBs). PARPi traps PARP on SSBs.

Normal cell: Repair by Homologous Recombination → Survival

Cancer cell with BRCA mutation: continuous PARP inhibition leads to CUMULATIVE DNA DAMAGE, GENOMIC INSTABILITY AND CELL DEATH → Death
Flow Chart- Olympia study design (a collaboration between BIG and NSABP)

BRCA mutation carriers with « high risk » TNBC

If residual tumor after neoadj CTX

Following adjuvant chemotherapy for node+ disease or T ≥ 2cm if node−

Randomization

Olaparib (300mg daily) X 1 year

Placebo X 1 year
Metronomic Chemotherapy
International Breast Cancer Study Group
(IBCSCG Trial 22–00)

ER/PgR-Negative Breast Cancer following breast cancer surgery and standard induction chemotherapy

Randomization
12 months of CM
Maintenance chemotherapy (CMM)

CMM - Cyclophosphamide 50/mg/day orally continuously;
Methotrexate 2.5 mg/twice a day orally days 1 and 2 of every week for 1 year

Trial completed many years ago. Results in San Antonio 2014!
Efficacy of Capecitabine Metronomic Chemotherapy in Triple-negative Breast Cancer (SYSUCC-001)

TNBC, « node positive or ≥ 0.5cm »

Randomization

standard chemotherapy
To all

1 year of metronomic Capecitabine (650mg/m2, twice every day)

No metronomic Treatment

This study is currently recruiting participants
Focus on HER2+ B.C.

• What did we learn?

• Which questions do we still have to answer?
Adjuvant Therapy for HER2+ BC

What did we learn?

✓ HER2+ BC is an heterogeneous disease
✓ There is no role for dual adjuvant blockade using T+L in the presence of aggressive chemotherapy
✓ There is still benefit from delayed adjuvant antiHER2 therapy
✓ For T₁N₀ tumors, the Dana Farber regimen offers a very favourable Benefit/Harm ratio
✓ TILs are now accepted as important stratification and prognostic factor in clinical trials for HER2+ BC
✓ There is no role for adjuvant bevacizumab
HER2 positive breast cancer

* Enrichment for proteins encoded by genes in the HER2 amplicon (EGFR, FGFR, CDK4, Cyclin D1...)

Gene-expression (PAM$_{50}$) analysis

« HER2 – enriched »
Subtype*
~ 50%

« Luminal subtype »
~ 50%

HER2+ BC by IHC /FISH
AVAILABLE RESULTS OF DUAL HER2 BLOCKADE PRIOR TO ASCO 2014

**Advanced Disease**

↑ PFS and OS (2 trials)

- EGF104900 (N= 296)
- NeoALTTO (N= 455)
- Cherlob (N= 121)
- LPT 109096 (N= 78)
- NeoSPHERE (N= 417)
- NeoALTTO (N= 8,381)
- ALTTTO (N= 8,381)

**Neoadjuvant setting**

Significant ↑ ↑ pCR (4 trials)

- ALTTO (N= 8,381)
- NeoALTTO (N= 455)
- Cherlob (N= 121)
- LPT 109096 (N= 78)
- NeoSPHERE (N= 417)
- NSABP B-41 (N= 529)
- CALGB 40601 (N= 305)

**Non significant ↑ pCR** (2 trials)

- Cleopatra (N= 808)
- ALTTTO (N= 8,381)

**Adjuvant setting**

- APHINITY (N= 4,805)
ALTTO STUDY DESIGN

Anti-HER2 therapy: 4 groups assigned by randomization

3 modalities of adjuvant CT administration per physician’s choice

**Design 1**
- **Chemotherapy**
  - 12 to 18 weeks

- **Anti-HER2 therapy**
  - 52 weeks

**Design 2a**
- **Anthracycline**
  - 9 to 12 weeks

- **Taxane**
  - 12 weeks

- **Anti-HER2 therapy**
  - 52 weeks

**Design 2b**
- **Docetaxel + Carboplatin**
  - 18 weeks

- **Anti-HER2 therapy**
  - 52 weeks

* R: refers to the timing of randomization

- **Trastuzumab** (T) x 52 weeks
- **Lapatinib** (L) x 52 weeks
- **T x 12 wks** L x 34 weeks
- **Trastuzumab** and **Lapatinib** x 52 weeks

* R: refers to the timing of randomization
## ASCO 2014

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Assumptions</th>
<th>Result (HR, 97.5% CI, P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>L + T vs. T</strong></td>
<td>Test superiority in intention-to-treat (ITT) population at alpha = 0.025</td>
<td>0.84 (0.70, 1.02), p = <strong>0.048</strong></td>
</tr>
<tr>
<td><strong>T → L vs. T</strong></td>
<td>Test non-inferiority in per protocol population (PPP) at alpha = 0.025</td>
<td>0.93 (0.76, 1.13), p = <strong>0.044</strong></td>
</tr>
</tbody>
</table>
CONCLUSIONS

• The ALTTO trial did not meet its endpoints (DFS): Neither the L + T vs. T comparison nor the T → L vs. T comparison.

• The doubling in pCR observed with L + T in NeoALTTO did not translate into improved survival outcomes in ALTTO
LESSONS LEARNED from the ALTTO TRIAL RESULTS

✓ A substantial proportion of women with HER2+ BC are cured by today’s adjuvant chemotherapy and trastuzumab

✓ Moving a new drug (eg: lapatinib) too quickly to the adjuvant setting carries significant risks

✓ For the neoadjuvant model to have a chance to predict outcome in the adjuvant setting, most « key players » must be given prior to surgery (in NeoALTTO, anthracyclines were given postoperatively)

✓ The best use of dual HER2 blockade might be in the context of adjuvant chemotherapy de-escalation
Does Lapatinib have some activity in the adjuvant setting?

A press release in the US has announced positive results of the Neratinib adjuvant trial!

Paul E Goss Lancet Oncology 2013
Small HER2+ BC: the Dana Farber prospective phase II study

Can aggressive chemotherapy be avoided?

N=406 pts

Median age 55

T1 (a) 20% T1 (b) 35%
T1 (c) 42% T2 9%

HR positive 67%

(1316 pts years)

P weekly x12

Trastuzumab weekly x52

3y DFS = 98,7%* (95% CI: 97,6-99,8%)

*10 « events », only 2 distant metastases

Tolaney SM et al., abst S1-04, SABCS 2013
LYMPHOCYTIC INFILTRATION PREDICTS FOR TRASTUZUMAB RESPONSE IN THE FINHER TRIAL

<table>
<thead>
<tr>
<th>TILs (10% increments)</th>
<th>HR</th>
<th>95% CI</th>
<th>DDFS interaction P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Tras</td>
<td>1.22</td>
<td>1.0 to 1.47</td>
<td>2.5e-02</td>
</tr>
<tr>
<td>With Tras</td>
<td>0.82</td>
<td>0.58 to 1.16</td>
<td></td>
</tr>
</tbody>
</table>

**Hazard Ratio**

**LPBC phenotype**

Denkert et al, JCO 2010; Loi et al, JCO 2013
Loi et al, ASCO 2012

**Non-LPBC phenotype**

Lymphocyte Predominant Phenotype LPBC >50% infiltration

Sherene LOI Annals of Oncology 2014
The negative results of the BETH trial (BCRIG + NSABP + independent centers) at a median followup of 38 months

N = 3509 women* with centrally confirmed HER2+ BC

- relatively « low risk »: T1 (50%), N- (48%), HR+ (60%)
- Few women aged ≥ 65y: 9%

**Chemo + trastuzumab**
N=1757

<table>
<thead>
<tr>
<th>TCHX6</th>
<th>THX3 → FECX3</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1617</td>
<td>N=140</td>
</tr>
</tbody>
</table>

**Chemo + trastuzumab + bevacizumab**
N=1752

<table>
<thead>
<tr>
<th>TCHX6</th>
<th>THX3 → FECX3</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1614</td>
<td>N=138</td>
</tr>
</tbody>
</table>

**I.D.F.S.**
H.R.=1.00
(0.79-1.26) (p0.97)

**D.F.S.**
H.R.=1.00
(0.80-1.25) (p0.99)

* Study with 86% power to detect HR0.70 in IDFS

D. Slamon, abst 51-03, SABCS 2013
Adjuvant Therapy for HER2+ BC

Interesting questions for the future

✓ Who is cured by current practice?

✓ Who can be cured with less aggressive chemotherapy?
  TDM1 neoadjuvant trial in preparation!

✓ Will there be a role for Pik3 CA inhibitors?
  Or for anti PD1 / PDL1 drugs?
Possible reasons for failure in incorporating new drugs in the adjuvant treatment scheme

- Stage shifting- Improved radiological examination (PET-CT)
- Improved local treatments.
- Benefit in the metastatic or neoadjuvant settings not large enough (bevacizumab) or not optimally demonstrated (lapatinib)
- Lack of imagination or “courage” to move to innovative clinical trial designs
ADJUVANT THERAPY IN BREAST CANCER

Quo vadis?

General conclusions
The present...

- Avoiding chemotherapy in case of a genomically-defined low risk luminal cancer

The future?

- Improving the selection of cytotoxic drugs (+ PARP inh) in the case of TNBC
- De-escalating chemotherapy in case of exquisit sensitivity to targeted drugs (in the case of HER2+ BC)
The future of management of early BC could change dramatically!

- **Tumor specific mutations** identified with targeted Next Generation Sequencing

- **More Treatments?**
  - **Personalized plasma tumor DNA follow-up**

*N. Turner, ASCO 2014*
THANK YOU!
Back-up
TAXANES IN TNBC

Triple–ve tumors seem to derive higher benefit when taxanes are added to anthracyclines.
Exemestane+OFS Improved DFS

![Graph showing the percent alive and disease-free with Exemestane+OFS (N=2346) and Tamoxifen+OFS (N=2344).]

**Difference 3.8% at 5 years**

5-yr DFS
- Exemestane+OFS: 91.1%
- Tamoxifen+OFS: 87.3%

**5.7 years median follow-up**

### Percent Alive and Disease-Free

<table>
<thead>
<tr>
<th>Year</th>
<th>Exemestane+OFS (N=2346)</th>
<th>Tamoxifen+OFS (N=2344)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>92.9</td>
<td>90.8</td>
</tr>
<tr>
<td>2</td>
<td>86.6</td>
<td>84.3</td>
</tr>
<tr>
<td>3</td>
<td>81.5</td>
<td>78.6</td>
</tr>
<tr>
<td>4</td>
<td>77.3</td>
<td>74.8</td>
</tr>
<tr>
<td>5</td>
<td>73.3</td>
<td>70.6</td>
</tr>
<tr>
<td>6</td>
<td>69.4</td>
<td>66.3</td>
</tr>
</tbody>
</table>

### Median Follow-up

- Exemestane+OFS: 91.1%
- Tamoxifen+OFS: 87.3%

### Table: Endocrine Therapy Comparison

<table>
<thead>
<tr>
<th></th>
<th>No. Patients</th>
<th>HR (95% CI)</th>
<th>5-yr DFS %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E+OFS</td>
<td>2346</td>
<td></td>
<td>91.1</td>
</tr>
<tr>
<td>T+OFS</td>
<td>2344</td>
<td></td>
<td>87.3</td>
</tr>
<tr>
<td><strong>Cohort</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No chemotherapy, TEXT</td>
<td>526</td>
<td>96.1</td>
<td>93.0</td>
</tr>
<tr>
<td>No chemotherapy, SOFT</td>
<td>470</td>
<td>95.8</td>
<td>93.1</td>
</tr>
<tr>
<td>Chemotherapy, TEXT</td>
<td>806</td>
<td>89.8</td>
<td>84.6</td>
</tr>
<tr>
<td>Prior chemotherapy, SOFT</td>
<td>544</td>
<td>84.3</td>
<td>80.6</td>
</tr>
<tr>
<td><strong>Lymph Node Status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1362</td>
<td>95.1</td>
<td>91.6</td>
</tr>
<tr>
<td>Positive</td>
<td>984</td>
<td>85.6</td>
<td>81.4</td>
</tr>
</tbody>
</table>

Olivia Pagani, NEJM 6/2014
Exemestane+OFS Reduced Recurrence

• 4% absolute improvement in 5-yr freedom from breast cancer for exemestane+OFS

No Survival effect

Olivia Pagani, NEJM 6/2014
Luminal ER+ Cancers

Genomic Grade

Recurrence Score

Rotterdam

Other Prognostic Signatures ...
Ki67%

High Proliferation

Relative Endocrine « Resistance »

Relative Chemotherapy « Sensitivity »
Luminal ER+ Cancers
What did we learned

✓ Increased BC mortality in high BMI premenopausal woman
✓ Extending tamoxifen to 10y is preferred over 5y – after risk assessment
✓ Exemestane+OFS is an emerging option for premenopausal woman
✓ Paclitaxel alone not proven equivalent to AC
✓ Low proliferating tumours probably can be spared from taxanes
✓ No role for adjuvant Bevacizumab
**Adjuvant Chemotherapy trials**

**5 year follow-up**

**NSABP-B38 (N+)**

- TACx6
- ddACx4
- dd paclitaxel x4
- dd ACx4
- dd paclitaxel + gemcitabine x4

*N=4894*

80% ER+

**Geicam 2003-02 (N- high risk)**

- FAC x6
- ddACx4
- dd paclitaxel x4

*N=1920*

73% ER+

- FAC x4
- P wkly

(100/sqm)x8

All arms equal as far as DFS/OS

(a): no difference

(b): no difference

**Sequential arms**: more neuropathy and anemia

**Combination arm**: more neutropenia, diarrhea

**Sequential arm better**

- H.R. DFS = 0.73 (p0.04) (90%→93%)
- H.R. OS = 0.76 (p0.26)

**Sequential arm**: more short term toxicity (fatigue + neurotoxicity)

**Combination arm**: 5 late cardiac deaths!
META-ANALYSIS OF 4 TRIALS
BCIRG 001, CALGB 9344, GEICAM & TACT

Can Taxanes be omitted in some ER+ tumors?

ER +ve HER2 +ve
ER -ve HER2 +ve
ER +ve HER2 -ve
ER -ve HER2 -ve

Heterogeneity p=0.056

Can Taxanes be omitted in some ER+ tumors?
TAXANES IN ADDITION TO ANTHRACYCLINES ARE NOT OF UNIVERSAL BENEFIT

EVIDENCE SUGGESTS LITTLE BENEFIT IN ER+ HER-ve TUMOURS WHICH ALSO HAVE KI67 OR ARE LUMINAL A
Clinical Advances in Adjuvant Triple negative BC

Take home messages

- TNBC is a heterogeneous group
- There is potential role for dose intensity.
- There is no role for adjuvant bevacizumab
- Potential fertility preservation using LHRH agonist Goserelin during adjuvant treatment
- BRCA germline testing should be encouraged in TNBC especially in Pt<60.
- Potential role for Platinume
  - Potential enrolment to the Olympia trial (PARP inhibitor)
Predictive tools in TNBC

Neoadjuvant setting

- Anthracycline benefit
  - Multidimensional gene signature incorporating topo2/apoptosis and immune genes: AUC = 0.71
    - (N = 147 TNBC receiving A but no T; 28 with pCR)

Neoadjuvant setting

- Platinum benefit in GeparSixto
  - TILs, better than immune mRNAs predict for ↑pCR and carboplatin benefit
    - (N = 481/595 pts pCR overall 53% vs 37; pCR if TILs 74% vs 43)

Metastatic setting

- Platinum benefit (single agent)
  - BRCA status and family Hx predict carbo effect with 25% absolute ↑pCR
    - (N = 315/41 BRCA)

- Only Homologous Recombination Deficiency assays predictive!
  - (N = 86 pts incl. BRCA mut carriers)

_abst 1025 (Di Leo), 510 (Denkert), 1005 (Von Minckwitz) and 1020 (Boston)_
Early disease: fertility preservation

The « POEM » trial for < 50y women with ER-/PgR- tumors*

Standard adjuvant CTX (with cyclophosphamide)

Goserelin started ≥ 1wk prior to CTX (q4wk administration)
Standard adjuvant CTX (with cyclophosphamide)

Primary goal: detect an absolute ↓ by 15% in « ov failure » at 2y (80% power)
Secondary: pregnancy outcomes
Exploratory: EFS, OS

N = 416 women needed

* Cutoff: <10% ± cells
Early disease: fertility preservation

The « POEM » trial

N = 218 analyzable women among 257 randomized

Ovarian failure

Pregnancies attempted/achieved

DFS HR: 0.47 (0.24 – 0.95)
OS HR: 0.45 (0.19 – 1.04)
Clinical Advances in Adjuvant HER2+ BC

Take home messages

✓ S.C. trastuzumab is likely to « take over » the role of I.V. trastuzumab

✓ For T₁N₀ tumors, the Dana Farber regimen offers a very favourable Benefit/Harm ratio but the f-up is only 3 years

✓ Older women (≥ 65y) should not be denied adjuvant CT + trastuzumab in view of a favorable benefit/harm ratio

✓ There is no role for adjuvant bevacizumab

✓ There is no role for dual adjuvant blockade using T+L

✓ TILs are accepted as important stratification and prognostic factor in clinical trials for HER2+ BC and standardization efforts among pathologists are ongoing
TARGETING HER2 IN BREAST CANCER: EVOLVING CONCEPTS

Trastuzumab + Lapatinib: synergistic in the lab and, potentially, in the clinic

Single HER2 blockade with trastuzumab ↑↑ DFS (B-31, N9831, HERA)

ALTTO Recruitment

Trastuzumab (T): immune mechanism of action poorly appreciated

Lapatinib: more potent signalling network inhibitor with additional attractive features (oral drug, low cardiotoxicity, some activity against brain mets, encouraging single agent activity in pts, no cross resistance with T)

Will dual HER2 blockade further ↑ DFS? (ALTTO)

Further clinical evidence supporting dual HER2 blockade in the clinic
MAIN DIFFERENCES IN AEs BY TREATMENT ARM

% of AEs by treatment arm

Diarrhoea | Hepatobiliary | Rash or Erythema

<table>
<thead>
<tr>
<th>AEs</th>
<th>L + T</th>
<th>T → L</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs ≥G3</td>
<td>(15)</td>
<td>(3)</td>
<td>(5)</td>
</tr>
<tr>
<td></td>
<td>(5)</td>
<td>(3)</td>
<td>(4)</td>
</tr>
<tr>
<td></td>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
</tr>
</tbody>
</table>

p < 0.001 for incidence for all arms when compared to T
Adjuvant trastuzumab (T) benefits/risks in Older women

• The prevalence of abnormal baseline LVEF (<50%) in 702 women considered for anthracycline or trastuzumab is low: 2% and unrelated to age, BMI, preexisting cardiac risk factors

• A large observational study of adjuvant T use in Germany shows similar 5y recurrence free survival in 2927 women aged < 65y and 1013 women aged ≥ 65y, with only a slight increase in grade 3-4 cardiac function toxicity in the latter (1.6% vs 0.9 %)

SABCC 2013
(1) Abst P6-06-09
(2) Abst P2-15-02
Subcutaneous trastuzumab preferred to i.v. trastuzumab

Results from Cohort 2 of the PrefHER trial (handheld syringe) are consistent with those of cohort 1 (single use injection device) and indicate a clear preference of patients (and health care professionals) for the sc delivery method!
Kaplan–Meier plot of distant metastasis-free survival (MFS) by (A) German S3, (B) National Comprehensive Cancer Center Network (NCCN), (C) St Gallen guidelines and (D) EPclin risk groups. 95% confidence intervals (CI) of hazard ratios (HR) are indicated.

C9741: DFS by ER Status & Dose Density

Disease-free survival

Year

ER+ DD

ER+

ER- DD

ER-

p =0.014

p =NS

DOSE DENSE TAXANES MAY BE AN OPTION FOR TNBC

<table>
<thead>
<tr>
<th></th>
<th>Disease Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q 2 wk</td>
<td>Q 3 Wk</td>
</tr>
<tr>
<td></td>
<td>Pts (n)</td>
<td>Failures</td>
</tr>
<tr>
<td>ER-</td>
<td>335</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+</td>
<td>636</td>
<td>113</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>988</td>
<td>215</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER-</td>
<td>335</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+</td>
<td>636</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>988</td>
<td>159</td>
</tr>
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</tr>
</tbody>
</table>

Randomized Phase II Trial of Everolimus in Combination With Tamoxifen in Patients With ER=/HER2-, Metastatic Breast Cancer With Prior Exposure to Aromatase Inhibitors

Overall survival benefit in the intention-to-treat population

Thomas Bachelot JCO 2012
Phase 3 Trials in breast cancer inhibiting CKDs

### PALOMA1-3

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Type of Inhibitor</th>
<th>Disease Type</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>palbociclib (PD-0332991)</td>
<td>CDK 4,6 Kinase Inhibitor</td>
<td>1st Line Advanced Breast Cancer, *Cancer</td>
<td>Phase 3</td>
</tr>
<tr>
<td>palbociclib (PD-0332991)</td>
<td>CDK 4,6 Kinase Inhibitor</td>
<td>High Risk Early Breast Cancer</td>
<td>Phase 3</td>
</tr>
<tr>
<td>palbociclib (PD-0332991)</td>
<td>CDK 4,6 Kinase Inhibitor</td>
<td>Recurrent Advanced Breast Cancer</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>

**MONARCH 2:**
A Study of Abemaciclib (CDK 4/6 Dual Inhibitor) Combined With Fulvestrant in Women With Hormone Receptor Positive HER2 Negative Breast Cancer
# Phase 3 Trials in breast cancer inhibiting CKDs

<table>
<thead>
<tr>
<th>Compound</th>
<th>Trial name</th>
<th>Company</th>
<th>Design</th>
<th>NCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEE011</td>
<td>MONALEESA-2</td>
<td>Novartis</td>
<td>A Randomized Double-blind, Placebo-controlled Study of LEE011 in Combination With Letrozole for the Treatment of Postmenopausal Women With Hormone Receptor Positive, HER2 Negative, Advanced Breast Cancer Who Received no Prior Therapy for Advanced Disease</td>
<td>NCT01958021</td>
</tr>
<tr>
<td>Abemaciclib</td>
<td>MONARCH 2</td>
<td>Lilly</td>
<td>Combined With Fulvestrant in Women With Hormone Receptor Positive HER2 Negative Breast Cancer</td>
<td>NCT02107703</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>PENELOPE-B</td>
<td>Pfizer</td>
<td>A Study of Palbociclib in Addition to Standard Endocrine Treatment in Hormone Receptor Positive Her2 Normal Patients With Residual Disease After Neoadjuvant Chemotherapy and Surgery</td>
<td>NCT01864746</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>PEARL</td>
<td>Pfizer</td>
<td>Phase III Study of Palbociclib in Combination With Exemestane Versus Chemotherapy (Capecitabine) in Hormonal Receptor (HR) Positive/HER2 Negative Metastatic Breast Cancer (MBC) Patients With Resistance to Non-steroidal Aromatase Inhibitors</td>
<td>NCT02028507</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>PALOMA-2</td>
<td>Pfizer</td>
<td>A Study of Palbociclib (PD-0332991) + Letrozole vs. Letrozole For 1st Line Treatment Of Postmenopausal Women With ER+/HER2- Advanced Breast Cancer</td>
<td>NCT01740427</td>
</tr>
</tbody>
</table>
PiK3CA pathway inhibitors

- Dual Pi3K-mTor inhibitors
  - BEZ 235
  - BGT 226
  - SF1126
  - GSK 1059615
  - GDC-0980
  - XL765
  - PF-4691502

- Pi3K
  - Pi3K inhibitors
    - BKM120
    - GDC-0941
    - XL147
    - PKI-587

- mTORC2

- mTORC1

- AKT
  - AKT inhibitors
    - GSK 690693
    - MK 2206

- mTOR CATALYTIC SITE inhibitors
  - AZD 8055
  - OSI 027
  - INK 128

- mTORC1 inhibitors
  - Everolimus
  - Ridaforolimus

- RTK

- PAN-Pi3K inhib.
  - Isoform specific Pi3K inhib.
Subcutaneous trastuzumab preferred to i.v. trastuzumab
Results Cohort 2 – Handheld syringe

- In total, 199 (86.1%) of 231 patients preferred SC trastuzumab.
- Overall preference for subcutaneous trastuzumab was “very strong” in 62.3% of patients, “fairly strong” in 15.6%, and “not very strong” in 8.2%.

Pivot et al. SABCS 2013.
Beth trial: more toxicity in bev. arm

Chemo + trastuz. + bevac.

<table>
<thead>
<tr>
<th>Event</th>
<th>Chemo + trastuz.</th>
<th>Chemo + trastuz. + bevac.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab completion</td>
<td>92%</td>
<td>←</td>
</tr>
<tr>
<td>Bevacizumab completion</td>
<td>NA</td>
<td>←</td>
</tr>
<tr>
<td>Grade 3-4 A.E.</td>
<td>5%</td>
<td>←</td>
</tr>
<tr>
<td>Grade 5 A.E.</td>
<td>n=0</td>
<td>←</td>
</tr>
<tr>
<td>L.V. systolic dysfunction</td>
<td>7%</td>
<td>←</td>
</tr>
<tr>
<td>CHF</td>
<td>&lt; 1%</td>
<td>←</td>
</tr>
<tr>
<td>Cardiac Ischemia</td>
<td>n=3</td>
<td>←</td>
</tr>
</tbody>
</table>

n=3 (2 cardiac)

D. Slamon, abst S1-03, SABCS 2013
PFS by BRCAm status

- 82% reduction in risk of disease progression or death with olaparib

Most compelling evidence in BRCAg

**BRCAm (n=136)**

<table>
<thead>
<tr>
<th>Events: total pts (%)</th>
<th>Olaparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>26:74 (35.1)</td>
<td>11.2</td>
<td>4.3</td>
</tr>
</tbody>
</table>

**BRCAwt (n=118)**

<table>
<thead>
<tr>
<th>Events: total pts (%)</th>
<th>Olaparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>32:57 (56.1)</td>
<td>5.6</td>
<td>5.5</td>
</tr>
</tbody>
</table>

**Median PFS, months**

<table>
<thead>
<tr>
<th>BRCAm (n=136)</th>
<th>Olaparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11.2</td>
<td>4.3</td>
</tr>
</tbody>
</table>

**HR=0.18**

95% CI (0.11, 0.31); 

*P* <0.00001

**HR=0.53**

95% CI (0.33, 0.84); 

*P*=0.007

---

**Number at risk**

<table>
<thead>
<tr>
<th>BRCAm</th>
<th>Olaparib</th>
<th>Placebo</th>
<th>BRCAwt</th>
<th>Olaparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>74</td>
<td>59</td>
<td>33</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Placebo</td>
<td>62</td>
<td>35</td>
<td>13</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Olaparib</td>
<td>57</td>
<td>44</td>
<td>17</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Placebo</td>
<td>61</td>
<td>35</td>
<td>10</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

---

**BRCAwt**, wild type (includes patients with no known BRCAm or a mutation of unknown significance)

**Ledermann JA et al. J Clin Oncol 2013;31(15 suppl):abst 5505**
Can we identify sub-groups that will benefit from dual blockade?

Immune signatures?

TILs?
P-STAT3?

Immune tolerance: less benefit from Trastuzumab and maybe more benefit from Lapatinib?

TIL- Tumor infiltrating lymphocytes
Rational P-STAT3: Potential role in Anti-Immunity

Preliminary data evidence for immune inhibition in p-STAT3+ tumors

Can P-STAT3 be inhibited by Lapatinib?

Molecular Cancer Therapeutics
Combined lapatinib and ontakabib enhance cytotoxicity against gefitinib-resistant lung cancer cells
# Examples and suggestions

<table>
<thead>
<tr>
<th>Problems</th>
<th>Suggestion</th>
<th>Good examples</th>
<th>Wrong example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterogeneity</td>
<td>Predefine the sub-set of population most likely to benefit from the drug</td>
<td>HER2 -trastuzumab&lt;br&gt;BRCA carriers- PARP inhibitors?</td>
<td>ER and TNBC in the same trial&lt;br&gt;HER2/ER+ and HER2/ER- in the same trial?</td>
</tr>
<tr>
<td>Stage shifting (PET-CT) Improved local and systemic management.</td>
<td>Take action in advance to overcome stage shifting and improved local and systemic treatments</td>
<td>Statistical power considerations based on present practice</td>
<td>Statistical power considerations based on previous studies</td>
</tr>
<tr>
<td>Launching adjuvant trials without clear evidence of benefit in the metastatic or neoadjuvant setting</td>
<td>Have clear evidence of benefit in the metastatic a/o neoadjuvant setting</td>
<td>Tamoxifen, Aromatase inhibitors, taxanes, trastuzumab</td>
<td>Controversies about the efficacy of the drug in the metastatic or neoadjuvant setting</td>
</tr>
</tbody>
</table>
ADJUVANT TRASTUZUMAB IMPROVES SURVIVAL

Relative Risk Meta-analysis plot

Overall survival

Disease Free survival

HERA
B31/N9831
BCIRG006
FinHER

HR=0.66 CI 0.57-0.67

HR=0.62 CI 0.56-0.68

Issa J. Dahabreh, The Oncologist
"First select the target in the tumor based on the biology of the tumor... then think about risk to « fine-tune » adjuvant therapy.
Adjuvant therapy for Luminal Breast Cancers

What did we learn?

✓ Some patients do not need chemotherapy
✓ Consideration for the incorporation of an “AI” in the treatment scheme should be given (in post menopausal women)
✓ Some patients benefit from extended (10y) hormonal treatment
✓ Exemestane+OFS is an emerging option for premenopausal women
✓ Bisphosphonates (mostly zoledronic acid) are to be considered for some women
✓ When chemotherapy is indicated, shorter regimens can be considered in certain circumstances
✓ There is no role for adjuvant Bevacizumab
✓ BC mortality is increased in high BMI premenopausal women
Adjuvant Therapy for HER2+ BC

What did we learn?

✓ HER2+ BC is an heterogeneous disease
✓ There is no role for dual adjuvant blockade using T+L in the presence of aggressive chemotherapy
✓ There is still benefit for delayed adjuvant antiHER2 therapy
✓ For $T_1N_0$ tumors, the Dana Farber regimen offers a very favourable Benefit/Harm ratio
✓ TILs are now accepted as important stratification and prognostic factor in clinical trials for HER2+ BC
✓ There is no role for adjuvant bevacizumab
What chemotherapy should we give (ER+)?

CAN WE OMIT ANTHRACYCLINES?

US Oncology Trial 9735
Docetaxel + Cyclo x4 v Doxorubicin + Cyclo x4:
Overall Survival Benefit with 7-Year Follow-Up

• 1016 women
• 48% N-ve
• Around 70% ER+ve

Jones S et al; JCO 2009
Paclitaxel alone not proven equivalent to AC

N = 3871 (early closure)
Mostly N-2/3 HR+
16% HER2+

AC (mostly q2wk)
4 courses
6 courses
5y RFS
91%
HR 1.26 (p 0.02)

Paclitaxel weekly
4 courses
6 courses
88%

... but more « toxic » deaths on AC (7 AML/MDS, 2 cardiac)

L.Shulman, CALGB 40101, JCO 2014
CAN WE OMIT Taxanes?
Exploratory pooled analysis (4 trials) on the role of Ki67% in predicting benefit of adjuvant taxanes in ER+ patients

High Ki67

<table>
<thead>
<tr>
<th>Study</th>
<th>TE</th>
<th>seTE</th>
<th>Hazard Ratio</th>
<th>HR</th>
<th>95%-CI W(fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACS01</td>
<td>-0.67</td>
<td>0.350</td>
<td>0.51</td>
<td>0.26; 1.01</td>
<td>7.2%</td>
</tr>
<tr>
<td>BCIRG001</td>
<td>-0.42</td>
<td>0.185</td>
<td>0.66</td>
<td>0.46; 0.95</td>
<td>25.8%</td>
</tr>
<tr>
<td>WSG-AGO</td>
<td>-0.97</td>
<td>0.390</td>
<td>0.38</td>
<td>0.18; 0.82</td>
<td>5.8%</td>
</tr>
<tr>
<td>BIG 02-98</td>
<td>-0.23</td>
<td>0.120</td>
<td>0.79</td>
<td>0.63; 1.00</td>
<td>61.2%</td>
</tr>
</tbody>
</table>

Fixed effect model
Heterogeneity: I-squared=33%, tau-squared=0.0235, p=0.2146

DFS

0.2 0.5 1 2 5

P<0.001

Low Ki67

<table>
<thead>
<tr>
<th>Study</th>
<th>TE</th>
<th>seTE</th>
<th>Hazard Ratio</th>
<th>HR</th>
<th>95%-CI W(fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACS01</td>
<td>0.03</td>
<td>0.207</td>
<td>1.03</td>
<td>0.69; 1.55</td>
<td>49.9%</td>
</tr>
<tr>
<td>BCIRG001</td>
<td>-0.36</td>
<td>0.490</td>
<td>0.70</td>
<td>0.27; 1.83</td>
<td>8.9%</td>
</tr>
<tr>
<td>WSG-AGO</td>
<td>0.26</td>
<td>0.513</td>
<td>1.30</td>
<td>0.48; 3.55</td>
<td>8.1%</td>
</tr>
<tr>
<td>BIG 02-98</td>
<td>-0.08</td>
<td>0.254</td>
<td>0.92</td>
<td>0.58; 1.52</td>
<td>33.1%</td>
</tr>
</tbody>
</table>

Fixed effect model
Heterogeneity: I-squared=0%, tau-squared=0, p=0.8273

DFS

0.5 1 2

P=0.89

Benefit of taxanes appears to be restricted to highly proliferative tumors

But...

Heterogeneity in the design of these trials and different Ki67% cut-offs

Sonnenblick A, ESMO 2014
PALOMA-1: Progression-Free Survival (ITT) Part 1 and Part 2

<table>
<thead>
<tr>
<th>Part 1</th>
<th>PAL + LET (N=34)</th>
<th>LET (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Events (%)</td>
<td>15 (44)</td>
<td>25 (78)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>26.1 (11.2, NR)</td>
<td>5.7 (2.6, 10.5)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.299 (0.156, 0.572)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Part 2</th>
<th>PAL + LET (N=50)</th>
<th>LET (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Events (%)</td>
<td>26 (52)</td>
<td>34 (69)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>18.1 (13.1, 27.5)</td>
<td>11.1 (7.1, 16.4)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.508 (0.303, 0.853)</td>
<td>0.0046</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0046</td>
<td></td>
</tr>
</tbody>
</table>

Encouraging results... but randomized phase II, not III

RS Finn et al, AACC 2014
Phase 3 trials in breast cancer inhibiting PI3K-Akt

Belle-2
buparlisib plus fulvestrant in HR+/HER2− advanced breast cancer (NCT01610284)

Belle-3
buparlisib plus fulvestrant in HR+/HER2− advanced breast cancer previously treated with AI and mTOR inhibitor (NCT01633060)

Many other drugs are in earlier phases
GDC-0032, GSK2636771, GDC-0941
Platinum benefit- in GeparSixto

N=595 centrally confirmed TNBC or HER2-positive breast cancer

PM

PMCb

R

Paclitaxel 80 mg/m² q1w

Non-pegylated liposomal doxorubicin 20 mg/m² q1w

Carboplatin AUC 1.5* q1w

Trastuzumab 6(8) mg/kg q3w (for 1 year) + Bevacizumab 15 mg/kg q3w

Lapatinib 750 mg/d 18 wks

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

G. Von Minckwitz, Lancet Oncology 2014
Does carboplatin add benefit to neoadjuvant CT with paclitaxel and non-pegylated doxorubicin given weekly? (+ bevacizumab in TNBC; + trastuzumab and lapatinib in HER2+ BC)

**TNBC**

- Chemotherapy (N = 157)
- Chemotherapy + carbo** (N = 138)

| pCR* rates | 38% | 58% |

P < .05

**HER2+**

- Chemotherapy (N = 136)
- Chemotherapy + carbo** (N = 137)

| pCR rates | 36% | 33% |

* Strict definition: in situ not allowed
** Carboplatin weekly x 18 at AUC 1.5

G. Von Minckwitz, Lancet Oncology 2014
Predictive tools in TNBC

Neoadjuvant setting

Platinum benefit in GeparSixto

TILs, better than immune mRNAs, predict for ↑ pCR and carboplatin benefit

BRCA status and family history predict carboplatin effect with 25% absolute ↑ pCR

Denkert S1-06 SABCC 2013, Von Minckwitz 1005 ASCO 2014
BRCA germline testing: in all TNBC below 60y!

N = 186 unselected women with TNBC in the Kansas City area are submitted to BRCA (Myriad) testing

All comers BRCA mutation frequency 14%

- ≤ 50y: 23%
- 51-60y: 12%
- > 61y: 2%

If SFHx or age < 50y were the only criteria used ≈ one third of mutation carriers would have been missed!

P. Sharma, abst 1026, ASCO 2013
Olaparib data in breast cancer:

- **Tutt et al 2010**: Ph II monotherapy olaparib in patients with *BRCA1* or *BRCA2* mutations and with advanced breast cancer (doses: 100mg BD or 400mg BD); Median 3 prior lines of chemotherapy. ORR for 400mg BD 41% (11/27)

- **Gelmon et al 2011**: Ph II monotherapy Olaparib in patients with *BRCA1* or *BRCA2* mutations and with advanced breast cancer or ovarian cancer (dose 400mg BD) Median 3 prior lines of chemotherapy overall – breast cancer patient more heavily pretreated. No RECIST responses for breast cancer patients – 38.5% had SD

- **Kauffman et al 2013**: Ph II monotherapy olaparib in patients (multiple tumours) with *BRCA1* or *BRCA2* mutations (dose 400mg BD). 62 breast cancer patients with median number of 6 prior lines of chemo. ORR for breast cancer patients = 12.9% (8/62), At 4 mo, disease control in 37% (23/62)

"Olympia" is currently open in the adjuvant setting: Olaparib for BRCAg TNBC
Why do we fail to incorporate new targeted drugs in the adjuvant setting?
**Recent Negative trials with new targeted drugs in the adjuvant setting**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>BC subtype</th>
<th>N status</th>
<th>End point</th>
<th>Needed Events</th>
<th>Actual Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEATRICE</td>
<td>Bevacizumab</td>
<td>TNBC</td>
<td>63% N-</td>
<td>3y IDFS: 82.7 VS 83.7 HR: 0.87 p=0.18</td>
<td>388</td>
<td>393/2591</td>
</tr>
<tr>
<td>BETH</td>
<td>Bevacizumab</td>
<td>HER2+</td>
<td>48% N-</td>
<td>38m IDFS: <strong>92% Vs 92%</strong> HR: 1 p=0.9</td>
<td>296</td>
<td><strong>116/3509</strong></td>
</tr>
<tr>
<td>E5103</td>
<td>Bevacizumab</td>
<td>ER+ 64%</td>
<td>26% N-</td>
<td>47.5m IDFS 77% Vs 80% HR: 0.87 p=0.17</td>
<td>426</td>
<td>430/3008 (arm A vs C)</td>
</tr>
<tr>
<td>ALTTO</td>
<td>Lapatinib</td>
<td>HER2+</td>
<td>40% N-</td>
<td>4.5y IDFS <strong>88% Vs 86%</strong> HR: 0.84 p=0.048</td>
<td>850</td>
<td>555/6281</td>
</tr>
</tbody>
</table>

HER2 control arms did extremely well!