Breast Cancer Research Worldwide: Quo Vadis?

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Breast International Group (BIG aisbl), Chair
Disclosures

- **Board member**: PharmaMar

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

- **Research grants to my Institute**: most companies

- **Speakers bureau/stock ownership**: none
The « guardian » ensuring that patients’ needs remain top priority in randomized clinical trials
The only chance to beat an enemy that relies on a highly complex, adaptable network for its survival...

... is through the building of a similarly STRONG, interconnected network of research groups!

55 groups covering 5 continents

1996: the «BIG» concept is born
1999: BIG becomes an international non-profit organisation
BIG in 2015: 55 BIG member groups worldwide

EU: 27 COUNTRIES + Switzerland, Norway, Iceland, Macedonia, Turkey

INIA PAKISTAN

ASIA-PACIFIC
AUSTRALIA
JAPAN
NEW ZEALAND
TAIWAN
China
Korea
Singapore

National GROUPS or International GROUPS / centres

Large multinational trials e.g. HERA, ALTTO, (NEO)ALTTO, APHINITY, MINDACT

ARGENTINA
BRAZIL
CHILE
PERU
URUGUAY

CANADA

RUSSIA

EGYPT
ISRAEL

NIGERIA
SOUTH AFRICA
BIG
CONSTRUCTION
years: 1999 – 2013
Focus = early breast cancer

Large registration trials of new drugs in the adjuvant setting
Successes and failures in designing, setting up and conducting international pivotal clinical trials

The BIG experience

« SUCCESES »

- Maintaining the trial alive after reaching its endpoints
- Recruiting pts at a much higher rate than expected
- Moving away from the « one strategy fits all » approach
- Fighting the fragmentation in clinical trials

« FAILURES »

- Performing the most efficient translational research
- Moving away from the « one strategy fits all » approach
Successes and failures in designing, setting up and conducting international pivotal clinical trials
The BIG experience
Moving away from the “one strategy fits all approach”

BIG 1-98 Overall Design

Breast Cancer Events

Letrozole 2y followed by tam 3y appears as good as letrozole 5y

This matters for patients!
Successes and failures in designing, setting up and conducting international pivotal clinical trials
The BIG experience

Activating trials across continents and recruiting at high speed

**Single HER2 blockade vs observation**
- Trastuzumab

**Dual HER2 blockade vs single HER2 blockade**
- Trastuzumab + Lapatinib
- Trastuzumab + Pertuzumab

**HERA**
- 5102 Pts in 43 months

**ALTTO**
- 8381 Pts in 49 months

**APHINITY**
- 4223 Pts in 18 months (still recruiting pts)

Europe 3850 (75%)
North America 160 (3%)
South America 284 (6%)
Australasia 808 (16%)

Europe 4470 (54%)
North America 959 (11%)
South America 444 (5%)
Australasia 2508 (30%)

Europe 2450 (58%)
North America 614 (14%)
South America 119 (3%)
Australasia 1040 (25%)
Successes and failures in designing, setting up and conducting international pivotal clinical trials

The BIG experience

Moving away from the “one strategy fits all approach”

HERA TRIAL DESIGN
Accrual 2001 – 2005 (n=5102)

- Women with locally determined HER2-positive invasive early breast cancer
- Surgery + (neo)adjuvant CT ± RT
- Centrally confirmed IHC 3+ or FISH+
- and LVEF ≥ 55%

Randomization

Observation n=1998

1 year Trastuzumab
8 mg/kg – 8 mg/kg
3 weekly schedule n=1703

2 years Trastuzumab
8 mg/kg – 6 mg/kg
3 weekly schedule n=1701

After A SCO 2005, option of switch to Trastuzumab

CT, chemotherapy; RT, radiotherapy

This arm was inserted by Academia

Trastuzumab (T) for 2y is not better than T for 1y

OS is improved with 1y trastuzumab

O.S. is improved with 1y trastuzumab

<table>
<thead>
<tr>
<th>Median follow-up (%)</th>
<th>OS benefit</th>
<th>No. of deaths 1 year trastuzumab vs observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 (8%)</td>
<td>0.76</td>
<td>29 vs 37 P=0.26</td>
</tr>
<tr>
<td>2006 (4.1%)</td>
<td>0.86</td>
<td>59 vs 90 P=0.0115</td>
</tr>
<tr>
<td>2005 (20.8%)</td>
<td>0.85</td>
<td>182 vs 213 P=0.1087</td>
</tr>
<tr>
<td>2012 (45.5%)</td>
<td>0.76</td>
<td>279 vs 350 P=0.0005</td>
</tr>
</tbody>
</table>

Favours 1 year trastuzumab: 1, Favours observation: 2

HR (95% CI)

Overall Survival (%)

No. at risk

Trastuzumab 2 years
Trastuzumab 1 year
Successes and failures in designs…
The BIG experience
What about translational research?

VERY SLOW and INEFFICIENT biomarker discovery process

Trastuzumab Yes or No
N > 10,000
Hera + NSABP B3 + NCCTG 9381…

Trastuzumab + Lapatinib
(ALTTO)

Trastuzumab + Pertuzumab
(APHINITY)

Missed opportunity
to identify patients « cured » w/o trastuzumab and pts resistant to trastuzumab

ALTTO and APHINITY:
All patients receive trastuzumab!
ALTTO STUDY DESIGN

Anti-HER2 therapy: 4 groups assigned by randomization

Trastuzumab (T) x 52 weeks
Lapatinib (L) x 52 weeks
T x 12 wks ↔ L x 34 weeks (6 weeks)
Trastuzumab and Lapatinib x 52 weeks

3 modalities of adjuvant CT administration per physician’s choice

Design 1
Chemotherapy
Anti-HER2 therapy
12 to 18 weeks ↔ 52 weeks

Design 2a
Anthracycline
Taxane
9 to 12 weeks ↔ 12 weeks ↔ 52 weeks

Design 2b
Docetaxel + Carboplatin
18 weeks ↔ 52 weeks

*R: refers to the timing of randomization
2011: Closure of L alone arm

2014: ASCO presentation

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

Protocol amendment after the closure of the lapatinib alone arm
years: 1999 – 2013
Focus = early breast cancer

Big Construction

Large registration trials on new drugs in the adjuvant setting

Early proof of concept trials in the neoadjvtt setting
NEOADJUVANT SETTING: AN ATTRACTIVE MODEL FOR CLINICAL / TRANSLATIONAL RESEARCH

**Diagnosis**
- Biopsy
- Fine molecular characterization
  - + Molecular imaging
  - + Blood

**Preoperative therapy**
- Intermediate by Early read-out of efficacy
  - + Molecular imaging
  - + Blood

**Surgery**

**Postoperative therapy**
- Pathology at Sx
  - Mid-term read-out of efficacy

*In vivo assessment of response + Easy access to tissue + Short-term surrogate endpoints!*
Identifying clinically useful biomarkers of response

Predicting the success of new targeted drugs

Predicting the success of cytotoxic/endocrine agents or fine-tuning their schedule of administration

Yet to be proven!

True at least for
- Aromatase inhibitors
- Taxanes

- True for Trastuzumab
- Not true for Lapatinib
- Not true for Bevacizumab
### Key questions

**Preoperative trials**

- **Docetaxel in sequence with anthracycline or anthracycline?**
  - Aberdeen
  - $N=162$
  - Many adjuvant trials
  - $N \sim 44,000$

- **Paclitaxel q3wks or weekly?**
  - MD Anderson
  - $N=258$
  - ECOG 1199 trial
  - $N=5,000$

- **Aromatase inhibitor or tamoxifen?**
  - M. Ellis / M. Dowsett
  - $N=324$ / $N=330$
  - Many adjuvant trials
  - $N>40,000$
Predicting the success of new targeted agents
Using the neoadjuvant model

**Key questions**

1. **Trastuzumab** combined or not with chemo in HER2+ BC?
   - **Preoperative trials**:
     - **NOAH trial**: Strong positive signal in terms of pCR, DFS, OS for trastuzumab arm
   - **Postoperative trials**: Almost all adjuvant trials «positive»: (B31, Hera, NCCTG-9831, BCRIG006) N>13000

2. **Lapatinib** alone... comparable to trastuzumab in HER2+ BC?
   - **Preoperative trials**: NeoALTTO trial: pCR lapatinib arm close to pCR trastuzumab arm
   - **Postoperative trials**: ALTTO trial: (N=8381) Lapatinib alone arm closed by IDMC!

3. **Bevacizumab** combined or not with chemo in HER2- BC?
   - **Preoperative trials**: Geparquinto trial: N=1948 with strongest Signal in triple – BC (pCR 32 → 39%)
   - **Postoperative trials**: Beatrice trial: N = 2591 ... negative at 32 months fup
Early signal in TNBC

- EC-D+ Bevacizumab
- EC-D

All BC Subtypes (N = 1925)
- pCR* %
  - EC-D+ Bevacizumab: 18.4
  - EC-D: 14.9

TNBC (N = 663)
- pCR* %
  - EC-D+ Bevacizumab: 39.3
  - EC-D: 27.9

P = 0.04
P = 0.003

*pCR = breast + LN

The BEATRICE trial in triple negative BC

Primary endpoint: IDFS$^a$

- Median duration of follow-up, months: CT (N=1290) 31.5, CT + BEV (N=1301) 32.0
- Events, n (%): CT 205 (15.9), CT + BEV 188 (14.5)
- 3-year IDFS rate, % (95% CI): CT 82.7 (80.5–85.0), CT + BEV 83.7 (81.4–86.0)
- Stratified HR (95% CI): 0.87 (0.72–1.07)
- Log-rank p-value: 0.1810

No. at risk:

<table>
<thead>
<tr>
<th></th>
<th>CT + BEV</th>
<th>CT</th>
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<tbody>
<tr>
<td>0</td>
<td>1301</td>
<td>1290</td>
</tr>
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<td>6</td>
<td>1244</td>
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<td>12</td>
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<td>48</td>
<td>4</td>
<td>2</td>
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<tr>
<td>54</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

$^a$Intent to treat, not censored for non-protocol therapy

D. Cameron – SABCS 2012
BIOMARKER RESEARCH: Disappointing stories in early breast cancer

<table>
<thead>
<tr>
<th>Biomarker of benefit in the neoadjuvant setting</th>
<th>? Validated in the adjuvant setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aromatase inhibitor « tailoring »</td>
<td>HER2+++</td>
</tr>
<tr>
<td>Taxane « tailoring »</td>
<td>Low tau mRNA</td>
</tr>
<tr>
<td>Trastuzumab a/o pertuzumab « tailoring »</td>
<td>No biomarker found beyond HER2 in an hypothesis driven approach examining isolated biomarkers</td>
</tr>
</tbody>
</table>
Tumor infiltrating lymphocytes (TILs)

- TILs
- Immune gene expression signatures

Present mostly in HER2+ and TNBC

+ Good prognosis TNBC and HER2+

+ Higher pCR rates to neoadjuvant chemotherapy in TNBC and HER2+ breast cancer

References:
FinHER: Only LPBC benefit from addition of trastuzumab

Conflicting results

N9831: Only non-LPBC benefit from addition of trastuzumab
TWO SISTER TRIALS

**NEO-ALTTO**
- 450 women with \( \geq 2\)cm HER2 positive breast cancer
- Randomization
  - Trastuzumab x 6 weeks
  - Trastuzumab + paclitaxel x 12 weeks
  - Lapatinib x 6 weeks
  - Lapatinib + paclitaxel x 12 weeks
  - Trastuzumab + Lapatinib x 6 weeks
  - Trastuzumab + Lapatinib + paclitaxel x 12 weeks
- Surgery
  - FEC
  - FEC
  - FEC
  - FEC
- Chemotherapy
  - Trastuzumab x 34 weeks
  - Lapatinib x 34 weeks
  - Trastuzumab + Lapatinib x 34 weeks
- Design 1 = sequential administration
- Design 2 = concomitant administration
- Biopsy
  - Week 2: Biopsy (PET Scan)
  - pCR rate
- pCR x 2 with dual HER2 blockade

**ALTTO**
- 8000 women with HER2 positive breast cancer
- Design 1 = sequential administration
  - Trastuzumab x 1y
  - Lapatinib x 1y
  - Trastuzumab ↓ then lapatinib
- Design 2 = concomitant administration
  - Trastuzumab combined with lapatinib
- Negative DFS results in early 2014

Biomarker discovery...? Biomarker validation...?
Neo-ALTTO Study (N = 455 women)

**Biological Window**

- **Randomize**
  - 6 weeks
  - + 12 weeks
  - Biopsies
  - L **apatinib**
  - P **aclitaxel**
  - T **rastuzumab**
  - P **aclitaxel**
  - L **apatinib**
  - T **rastuzumab**
  - P **aclitaxel**

**Surgery**

- **pCR**
  - 24.7%
  - 29.5%
  - 51.3%

J. Baselga, SABCS 2010
# Neoadjuvant trials testing dual HER2 blockade

<table>
<thead>
<tr>
<th>Trials</th>
<th>N° pts</th>
<th>chemo</th>
<th>Single blockade pCR (trastuzumab)</th>
<th>Dual blockade pCR</th>
<th>pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>NeoSphere</td>
<td>417</td>
<td>Docetaxel</td>
<td>29%</td>
<td>46%</td>
<td>0.0141</td>
</tr>
<tr>
<td>NeoAltto</td>
<td>455</td>
<td>Paclitaxel</td>
<td>29%</td>
<td>51%</td>
<td>0.0001</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CALGB 40601</td>
<td>305</td>
<td>Paclitaxel</td>
<td>46%</td>
<td>56%</td>
<td>0.12 (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>NSABP-B41</td>
<td>529</td>
<td>AC/paclitaxel</td>
<td>52%</td>
<td>62%</td>
<td>0.095</td>
</tr>
</tbody>
</table>
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.
Can neoadjuvant trials provide reassuring «proof of concept» prior to the launch of large, pivotal adjuvant trials?
**BIG’s neoadjuvant program of Pi3K inhibitors**

**HER2-positive BC**
- PiK3 CA mutant
  - Trastuzumab
  - Trastuzumab + paclitaxel
- PiK3 CA wild type
  - Trastuzumab + Pi3K inh
  - Trastuzumab + Pi3K inh + paclitaxel

**Luminal BC**
- Genotyping
  - PiK3 CA Mutant/WT
    - L + Pi3K inh
    - L + placebo

**Stopped prematurely**

**6 wk biological window**

« Success » = Increase in pCR by 18% in either subgroup
N = 220

« Success » = Increase in RR (MRI) by 21% and/or Increase in pCR by 13%
N ≈ 330
Although the model generates considerable enthusiasm on both sides (Academia & Pharma)

1. Optimal design and statistical considerations require lengthy discussions
2. Safety issues for truly « early » compounds need to be adequately addressed
3. The trial may be « killed in utero » if, meanwhile, the new drug performs poorly in other solid tumors
BIG CONSTRUCTION
years: 1999 – 2013
Focus = early breast cancer

- Large registration trials on new drugs in the adjuvant setting
- Early proof of concept trials in the neoadjuvant setting
Big Construction

Years: 1999 – 2013
Focus = early breast cancer

- Large registration trials on new drugs in the adjuvant setting
- Early proof of concept trials in the neoadjuvant setting
- Non-drug or «cheap drug» oriented trials
Successes and failures in designing, setting up and conducting international pivotal clinical trials
The BIG experience
Non drug or “cheap” drug oriented trials

BIG 02-05
« ACTION »
UK led trial
CT or NoCT in older ER- pts
Expected accrual : 1000
Actual accrual : 4
Stopped permanently

BIG 01-05
« CASA »
IBCSG led trial
PLD or metronomic « CM » or observation in older pts
Expected accrual : 1296
Actual accrual : 77
Stopped permanently

BIG « SUPREMO»
UK led trial
Chest wall irradiation in intermed risk post mastectomy
Expected accrual : 1600
Actual accrual : 1688
« Success » : only thanks to huge academic efforts to obtain multiple grants

BIG « DCIS»
TROG led trial
DCIS : radiation doses & fractionation schedules
Expected accrual : 1600
Actual accrual : 1060
years: 1999 – 2013
Focus = early breast cancer

- Large registration trials on new drugs in the adjuvant setting
- Early proof of concept trials in the neoadjuvant setting
- Non drug or « cheap drug » oriented trials

Translational Research Initiatives
Translational Research in Breast Cancer

• Small, “proof of concept” studies

• Large, clinical-practice changing studies
  - MINDACT
  - AURORA
age is associated with ▼ in RANKL expression independent of BC subtype and stage

<table>
<thead>
<tr>
<th>Function</th>
<th>Untreated cohort (cohort 1, n = 1,188)</th>
<th>Treated cohort (cohort 2, n = 2,334)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Genes</td>
<td>Gene sets</td>
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<tr>
<td>Apoptosis related</td>
<td>FAS</td>
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<td></td>
<td>CASP3</td>
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<tr>
<td></td>
<td>BAD</td>
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<tr>
<td>MAP kinase related</td>
<td>MAPK</td>
<td></td>
</tr>
<tr>
<td>mTOR/PI3K related</td>
<td>PDK1</td>
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<td>PIK3CA-GS</td>
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<td>BRCA related</td>
<td>BRCA1</td>
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<td>Luminal progenitor</td>
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<td>c-kit</td>
</tr>
<tr>
<td>Luminal progenitor</td>
<td></td>
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</tr>
</tbody>
</table>

Azim HA Jr et al., Clin Cancer Research 2012
RANKL beyond Bone Metastases

RANKL mediates the effect of hormone signaling on Mammary stem cell function

Asselin-Labat M et al; Nature 2010
Collectively this data suggest that the effect on RANKL inhibition may go far beyond its osteoclastic actions.

Development of a window study to evaluate the role of RANKL on newly diagnosed breast cancer patients
D-BEYOND
Denosumab Biological Effects in Young Women Diagnosed with Breast Cancer

Key eligibility:
- Pre-menopausal
- Tumor size >1.5
- M0

PI: [S. Loi, M. Piccart, C. Sotiriou, H. Azim]

EudraCT number: 2011-006224-21

(Erasmus, IJB, Leuven, Mons, Namur + Melbourne)
DEVELOPMENT OF A PROGNOSTIC SIGNATURE

tumour samples of known clinical outcome

Unbiased full genome gene expression analysis

Prognosis reporter genes

distant metastases group

no distant metastases group

70 prognosis genes

Courtesy of R. Bernards
MINDACT: CURRENT STATUS

Enrolled: 6694 women, all evaluated according to clinical-pathological risk (adjvt on line) and the 70gene signature.

- High risk by both methods: $N = 1873 \ (28.0\%)$
- Discordant risk: $N = 2187 \ (32.7\%)$
- Low risk by both methods: $N = 2634 \ (39.3\%)$

[Predicted 30%]

Supported by EU 6th framework program
Evaluate Clinical-Pathological risk and 70-gene signature risk

EORTC-BIG MINDACT TRIAL DESIGN
6,000 Node - & 1-3 N+ women

Clinical-pathological and 70-gene both HIGH risk

N=1873

Clinical-pathological and 70-gene both LOW risk

N=2634

Discordant

<table>
<thead>
<tr>
<th>Clinical-pathological</th>
<th>70-gene</th>
<th>Risk Status</th>
<th>N</th>
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</thead>
<tbody>
<tr>
<td>Clin-Path HIGH</td>
<td>70-gene LOW</td>
<td>72%</td>
<td>1497</td>
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<tr>
<td>Clin-Path LOW</td>
<td>70-gene HIGH</td>
<td>28%</td>
<td>690</td>
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Use Clin-Path risk to decide Chemo or not

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Clin-Path High</td>
<td>70-gene Low: CTx</td>
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<tr>
<td>Clin-Path Low</td>
<td>70-gene High: no CTx</td>
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</table>

Use 70-gene risk to decide Chemo or not

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<th>70-gene</th>
<th>Risk Status</th>
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<tr>
<td>Clin-Path High</td>
<td>70-gene Low: no CTx</td>
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<tr>
<td>Clin-Path Low</td>
<td>70-gene High: CTx</td>
<td>344</td>
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</table>

* Hypothesis: DMFS ≥ 92% at 5 y → results in 2015!
MINDACT: A GOLDMINE FOR FUTURE RESEARCH!!!

FROZEN TUMOR SAMPLES (remaining after RNA extraction for MINDACT)

PARAFFIN-EMBEDDED TUMOR SAMPLES (after TMA construction)

SERUM & BLOOD SAMPLES

Independent biological materials bank
Policy for access to samples and/or data
Survival in Patients With Metastatic Recurrent Breast Cancer After Adjuvant Chemotherapy

Little Evidence of Improvement Over the Past 30 Years

Distant recurrence from interval

Metastatic BC by year of diagnosis

Amye J. Tevaarwerk et al, Cancer 2013;119:1140-8
ECOG data base (N = 13785 pts entered in adjt trials between 1978-2002 of whom 3447 (25%) became metastatic
The landscape of genomic alterations in metastatic Breast Cancer

"Early" Breast Cancer

Adjuvant therapy

Metastatic relapse

Sequential systemic therapies

Clone 1
Clone 2
Clone 3
Clone 4
Clone 5

“Clonal” evolution

Dynamics of the subdonal tumor architecture over time

Relative importance of “driver” mutations in the “trunk” or in the branches

Can “driver” mutations be captured by plasma tumour DNA

Which clones are going to play a major role in the lethal evolution of the disease

TGS RNA seq
Primary tumor

TGS RNA seq
Metastatic lesions

Plasma ctDNA
Plasma ctDNA
Plasma ctDNA
Plasma ctDNA
The AURORA Program

A prospective, longitudinal study of 1,300 women with Metastatic Breast Cancer recruited at 81 centers across 15 European countries

Secured budget as of 2014: 11 million euros

- Improved understanding of the "clonal evolution" of the disease
- Can "driver" mutations be captured by plasma tumour DNA?
- Dynamics of the subdonal tumor architecture over time
- Relative importance of "driver" mutations in the "trunk" or in the branches
- Which clones are going to play a major role in the lethal evolution of the disease?
- Up-scaling of the number of MBC patients candidate for clinical trials with new targeted therapies

BCRF - Breast Cancer Research Foundation
Fondation Cancer - NIF Trust
BIG against breast cancer
Newly diagnosed or 1st Line MBC Patients

N=1,300

Screening Failure n=300

Timeline

Entry in DCT
Cycle 1
Cycle 2
Cycle 3
Cycle X
Disease Progression

‘Actionable’ Mutation(s) (n~300)

Downstream Targeted Clinical Trials as first or second line

‘Non-Actionable’ Mutations (n~700)

Standard of Care

Clinical Outliers (Exceptional Responders and Rapid Progressors) to be subjected to WES

Timeline:
- Entry in DCT
- Cycle 1
- Cycle 2
- Cycle 3
- Cycle X (Continue until disease progression)
- Disease Progression

Metastatic Lesion:
- Biopsy – TGS (real time) and RNAseq (on batches)

Primary Tumour:
- Archival – TGS (real time) and RNAseq (on batches)

Blood:
- TGS (real time)

Plasma/Serum:
- Collection every 6 months – up to 10 years

Clinical Outcome Information:
- Collection every 6 months – up to 10 years