Systemic adjuvant treatment in invasive lobular breast cancer

P. Neven, H. Wildiers, P. Berteloot, O. Brouckaert, R. Paridaens,
On behalf of MBC, UZ Leuven
• Introduction
  – ILA: Particular but heterogeneous subtype.
  – Should we treat ‘lobular’ type differently (ER-pos non-ILA)?
    • NCCN → No; > 3cm or LN+ “consider” chemo
    • St. Gallen 2011 → No; treat ~ biological behaviour > risk

• UZ Leuven policy for adjuvant R/ in ER-positive breast cancer

• Controversies regarding adjuvant CT in luminal breast cancer
  – classical lobular type
Lobular type is a particular but heterogeneous disease

Most breast carcinomas develop from Terminal Ductulo-Lobular Unit

ALSO LOBULAR BREAST CANCERS

* Most frequent ‘specific type’ breast cancer (5-15%)
* Proportion ILA/ non-ILA is increasing (Age, HST-use, Better Pathol)
  * Older, Larger, more LN-pos, Bilateral, Multifocal, HER-2 neg
* Clinic & imaging → ‘suspicious’ for ILA (mammo, less palpable→ less desmoplastic reaction, PET-neg)
Lobular and non-lobular breast cancers differ regarding axillary lymph node metastasis: a cross-sectional study on 4,292 consecutive patients

T. Vandorpe · A. Smeets · B. Van Calster · K. Van Hoorebeke · K. Leumen · F. Amand · Ph. Moerman · K. De Naeyer · O. Brouckaert · S. Van Huffel · H. Wildiers · M. R. Christiaens · P. Neven

Fig. 1 Multivariable logistic regression: probability of ALN involvement versus tumor size. Full and dashed plot lines are model predictions for, respectively, non-ILC and ILC tumors with the following fixed characteristics: grade II, unifocal, ER+, PR+, and HER-2− for age 58
ILAs are a heterogeneous group with deletion in E-cadherine expression (also exists in non-ILA).

**CLASSIC ILA:**
- aCGH: VEA, grade 1 DCIS, VEA, ITA

**NON-CLASSIC**
- A different disease

Classic (>50%), Alveolar, Solid, Histiocytoid, Pleiomorphic, Mixed, …

Grade 3, Triple Negative, HER-2 positive ILA’s do exist

~ prognostic significance
Proportion patients ~ OncDx RS/ Subtype

Data on file GH

Proportion Patients at Risk

LN-neg & LN-pos

Ductal carcinoma, NOS (n = 82,784)
Lobular carcinoma, classic type (n = 79,568)
Lobular carcinoma, mixed pattern (n = 28,956)
Lobular carcinoma, solid or alveolar type (n = 352)
Pheomorpho-lobular carcinoma (n = 608)
Tubular carcinoma (n = 777)
Cribriform carcinoma (n = 209)
Mucinous carcinoma (n = 2965)
Micropapillary carcinoma (n = 208)
Atypical medullary carcinoma (n = 462)
Papillary carcinoma (n = 459)

▲ ILA
4% High
▲ pILA 8% High
▲ ILA 12% High

Low Risk (RS < 18)  Intermediate Risk (RS 18-30)  High Risk (RS ≥ 31)
UZ Leuven database

01/01/2000 – 31/12/2009

Primary operable (n=4318)

Primary metastatic (n=228)

Male (n=28)

Extern (n=530)

Neo-adjuvant (n=407)

Missing

Surrogate breast cancer subtype available (n=4220)

Endocrine therapy (11)

Chemotherapy (20)

Radiotherapy (16)

Detection mode (84)

559 Lobular type
3401 Ductal type NOS


UZL Database: n= 3960 (IDA-nos + ILA): 6.5 yrs mean FU

767 ILA’s [15 CT- trials (pN0=28%)!]

559 Consecutive ILA’s (pN0=57%)

ILA tend to relapse a bit later than non-ILA


767 ILA’s from 15 chemo trials!

pN+ ILA: 231, 58% CT
pN+ non-ILA: 1365, 64% CT

72% pN+ 78% CT

559 ILA’s from 1 Center (pN0=57%)!

43% pN+ ILA: 559, 33% CT
43% pN+ non-ILA: 3401, 42% CT

pN- ILA: 308, 13% CT
pN- non-ILA: 2245, 25% CT

UZ Leuven data: n= 3960 (IDA-nos + ILA): 6.5 yrs mean FU
Should we treat ILC differently?

Treat Target: Endocrine Responsiveness > Risk

ILC = IDA-nos

ER: predictive
PgR: prognostic
HER-2: both
Grade: ?
Ki-67: ?
LN: Both
...

Adjuvant Treatment
THE ST. GALLEN CONFERENCES
SHIFTED TOWARD NEW PHILOSOPHY
OF TAILORED ADJUVANT TREATMENT

1990-2005
Responsiveness
RISK

2005-....*
Risk to assess trade-off between efficacy and toxicity
RESPONSIVENESS (check target)
### St. Gallen 2011: “Shorthand” Determination of Breast Cancer Subtypes

<table>
<thead>
<tr>
<th>Intrinsic Subtype</th>
<th>Surrogate Definition</th>
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<tbody>
<tr>
<td>Luminal A</td>
<td>ER and/or PgR(+), HER2(-)</td>
</tr>
<tr>
<td></td>
<td>Ki-67 low (&lt;14%)*</td>
</tr>
<tr>
<td>Luminal B1</td>
<td>ER and/or PgR(+), HER2(-)</td>
</tr>
<tr>
<td></td>
<td>Ki-67 high</td>
</tr>
<tr>
<td>Luminal B2</td>
<td>ER and/or PgR(+), HER2(+)</td>
</tr>
<tr>
<td></td>
<td>Any Ki-67</td>
</tr>
<tr>
<td>HER2 over-expression</td>
<td>ER and PgR absent, HER2(+)</td>
</tr>
<tr>
<td>Basal-like</td>
<td>Triple negative ductal (not medullary, adenoid cystic)</td>
</tr>
</tbody>
</table>

* Using PAM50 cutpoint from Cheang et al. JNCI 2009

Annals Oncol 2011
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<td></td>
</tr>
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<td>‘Special histological types’*</td>
<td>Endocrine therapy Cytotoxics</td>
<td>Medullary and apocrine carcinomas may not require any adjuvant cytotoxics (if node negative).</td>
</tr>
</tbody>
</table>
Efficacy adjuvant endocrine therapy in ILC = Efficacy adjuvant chemo in ER-positive luminal breast cancers
Adjuvant hormonal therapy
ER positive breast cancer:
The Leuven guidelines

1. Pre-menopausal & < 45 yrs (TAM + OS 2yrs if <35)
2. Post-menopausal or > 52 yrs (TAM/ AI/ TAM-AI/AI-TAM)
3. Between 45-52 yrs (peri-menopausal)

Definition* menopause (12mths amenorrhea) differs from WHO definition!
At low risk tumours = pT1 & grade 1 & PR+ & HER-2-

Aromatase Inhibitor is a good alternative

- Proven allergy to tamoxifen (Does exist!)
- High risk of thrombosis (Anamnesis!!)
  - Hereditary thrombogenic disease,
  - Positive lupus anticoagulant;
  - Documented history DVT,
  - CVA, not if ischemic,
- Endometrial polyps
  - With or without the presence of atypical cells.
Postmenopausal & > 52y at diagnosis

pN0 en PR neg
pN2-3
≥2 risk factors (pT2-4, grade 3, HER-2+, LVI+ of pN1)

Sometimes tamoxifen (ev. reversed switch*) in case of:
- arthralgia, osteoporosis, fracture, CV-disease

*Until now 5y AI = 2y Tam → 3y AI = 2y Al → 3y Tam
* 5y TAM suboptimal

Bone density & if osteoporosis:
Bisphosphonates/ Denosumab
• Tam → switch if CT-amenorrhea
  – Amenorrhea 12 m ≠ Menopause (Tam, AI)
    • Contraception!
    • Switch to AI
  – FSH, Oestradiol, AMH are very variable
    » AI and high FSH and low E2 = temporary

Tamoxifen
FSH: 37.8 IU/L
FSH: 8 IU/L*
Estradiol 8 ng/L

» Tam: “low” FSH, low E2 could be menopause
→ *Hypogonadotroph hypo-oestrogenic amenorrhea

Aromasin
FSH: 99.2 IU/L
Estradiol 32 ng/L

» Exemestane gives false-positive E2 and Prog
→ High FSH and elevated E2 meaning: more than likely menopause

Femara
FSH: 99.2 IU/L
Estradiol <5 ng/L
Efficacy adjuvant endocrine therapy in ILC

= Efficacy adjuvant chemo in ER-positive luminal breast cancers

No data from RCT on value of adjuvant

Patients can die from
- underuse of CT
- overuse of CT
Efficacy adjuvant CT in ER-pos ILC =
Efficacy adjuvant CT in ER-pos negative luminal breast cancers

Strong ER-pos: High benefit from new schedules of anti-E / Extended ET
Less benefit from CT (pCR ~ 4-6%)
- Doesn’t mean they are resistant to CT
- Lack of pCR doesn’t mean poor prognosis

Age: Age-dependent benefit from CT is → was proven…

Time to Relapse: ER-pos > ER-neg/
ILC slightly later non-ILC
Primary Metastatic Classic Lobular Breast Cancer Bone, Stomach, Ascites, Ovarian, … involvement

Tamoxifen

Classic ILA not completely chemo-resistant

Letrozole  Fulvestant  FEC-75 q3w
48 yrs Premenopausal Primary Metastatic Classic Lobular ER-Pos HER-2 Neg Breast Cancer Visceral Crisis (liver M*)

Classic ILA not completely chemoresistant

Chemotherapy
Taxol qW 18x
~Amenorrhea

Consolidation
Anastrazole
Aromasin

EFECT trial
Fulvestrant

FEC-75
Navelbine
We don’t see such a response to CT within the classic metastatic ILA’s.
Adjuvant Treatment

Should we treat ILC differently?
Treat Target: Endocrine Responsiveness > Risk

ILC = IDA-nos

{ ER: predictive
PgR: prognostic
HER-2: both
Grade: ?
Ki-67: ?
LN: Both
...}
IBCSG VII and 12-93 Postmenopausal N+

**Graph 1:**
- **Chemoendocrine Therapy**
- **Endocrine Therapy**

<table>
<thead>
<tr>
<th>N</th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>589</td>
<td>346</td>
<td>0.81 (0.68-0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>304</td>
<td>192</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Graph 2:**
- **Median ER (fmol/mg cytosol protein) in subpopulations**

P-value = 0.07

IBCSG IX: 13-Year DFS according to ER Values by STEPP

S8814 ER+N+: No DFS Benefit from CAF+T vs Tam if Central IHC HER2- and ER Level High

*Interaction p=0.052; if add mitotic grade, p=0.024

Albain et al. Lancet Oncology 2010
21 Gene Recurrence Score Assay: Strongly Predictive in NSABP B-20 (ER+ N0)

Benefit from CT in ER-pos BrCa ~Risk

Benefit from CT

Distant Recurrence at 10 Years

Recurrence Score

Minimal, if any, Chemo Benefit

Clear Chemo Benefit

Sparano, TBCI San Antonio, 2005; Paik JCO 2006
TransATAC: Rate of Distant Recurrence Increases with Number of Positive Nodes for All Recurrence Score® Values

Low Recurrence Score suggests a low risk of recurrence for patients with 1-3 positive nodes.

Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials

10 yrs outcome

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)
Published online December 6, 2011 in The Lancet

DOI:10.1016/S0140-6736(11)61625-5
ER+ Anthra/CMF plus ET vs ET Control

Age < 55

Age 55-69

2 Mythes Put Into Discussion

EBCTCG 2012

Benefit > Yr 5

Benefit ~ Age
## Anthracyclines vs No Chemotherapy by Subsets of ER+

<table>
<thead>
<tr>
<th>Category</th>
<th>Deaths/Women Allocated anth.</th>
<th>Deaths/Women Allocated control</th>
<th>Anth. deaths Logrank Variance of O-E</th>
<th>Ratio of annual death rates Anth.: Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subsets of ER+</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+, chemo+end. vs end. only †</td>
<td>659/2622 (25.1%)</td>
<td>853/2675 (31.9%)</td>
<td>−56.2, 247.0</td>
<td>0.80 (SE 0.06)</td>
</tr>
<tr>
<td>ER10–99 fmol/mg</td>
<td>416/1371 (30.3%)</td>
<td>544/1442 (37.7%)</td>
<td>−35.3, 162.5</td>
<td>0.80 (SE 0.07)</td>
</tr>
<tr>
<td>ER100+ fmol/mg</td>
<td>274/1146 (23.9%)</td>
<td>337/1160 (29.1%)</td>
<td>−20.6, 95.6</td>
<td>0.81 (SE 0.09)</td>
</tr>
<tr>
<td>ER+, age &lt; 55</td>
<td>250/845 (29.6%)</td>
<td>316/943 (33.5%)</td>
<td>−19.4, 102.4</td>
<td>0.83 (SE 0.09)</td>
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<tr>
<td>ER+, 55 – 69</td>
<td>542/2071 (26.2%)</td>
<td>677/2055 (32.9%)</td>
<td>−53.9, 215.3</td>
<td>0.78 (SE 0.06)</td>
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<td>ER+, poorly differentiated</td>
<td>100/461 (21.7%)</td>
<td>120/477 (25.2%)</td>
<td>−12.2, 45.8</td>
<td>0.77 (SE 0.13)</td>
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<td>ER+, moderately/well</td>
<td>228/985 (23.1%)</td>
<td>286/1026 (27.9%)</td>
<td>−27.8, 112.8</td>
<td>0.78 (SE 0.08)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1416/4754 (29.8%)</td>
<td>1701/4733 (35.9%)</td>
<td>−139.9, 581.3</td>
<td>0.786 (SE 0.037)</td>
</tr>
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</table>

- 99% or ←— 95% confidence intervals

Global heterogeneity: $\chi^2 = 5.8; p = 0.4$

Treatment effect 2p $< 0.00001$

EBCTCG Lancet Dec 6, 2011
Even in strongly ER+ disease, chemotherapy did at least somewhat affect outcome, though not to the same extent as in less strongly ER+ disease, with one large trial demonstrating heterogeneity.
- S8814 does have significant interaction terms in the original and EBCTCG analyses
- While we don’t have strong evidence in the overview studies currently, heterogeneity cannot be ruled out
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<td>St Gallen Ann Oncol 2011</td>
</tr>
<tr>
<td>A. Endocrine responsive</td>
<td></td>
<td>St Gallen Ann Oncol 2011</td>
</tr>
<tr>
<td>B. Endocrine non responsive</td>
<td></td>
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</table>

"Only rare variants of lobular carcinoma require cytotoxic agents"
Who chemo?

Guidelines UZ-Leuven

- Always CT: from pT1c onwards (unless CI)
  - Triple negative
  - HER2 pos
  - <35y
- ER-pos HER-2 neg: + CT prior to ET?
- Luminal A-like
  - If many positive lymph nodes
- Luminal B-like
  - ≥2 bad factors:
    - <50 yrs;
    - LVI/pN1a (mi);
    - pT2-4;
    - Multifocal;
    - ER+PR<13/16;

Ki-67 (pN0 & pN1a)
  - grade 2 lesions
  - grade 1/3 lesions if low mitotic score
Luminal A-like = Ki-67 < 14%
Luminal B-like = Ki-67 > 14%
• HER-2 negative:
  • 3x FEC100 ⇒ 3x docetaxel 100
  • 4x TC (docetaxel-cyclophosphamide) as alternative supposing anthracyclines are not indicated.

• HER-2 positive:
  • 3x FEC100 ⇒ 3x docetaxel 100 + trastuzumab

Alternative 6x TCH
# ILA vs non-ILA

## By Chemotherapy

UZ Leuven data: cumulative events in 3392 consecutive operable BC
ER-pos ILA/non-ILA ~ added benefit of CT (2000-2009)
6.5 yrs FU
(CT: chemotherapy/ET: endocrine therapy)

CT in ER + PR pos pts only young/ high grade/over 3 pos LN

<table>
<thead>
<tr>
<th>n,%</th>
<th>Distant metastatic relapse</th>
</tr>
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<tr>
<td></td>
<td>CT+ET (=1087)</td>
</tr>
</tbody>
</table>
| TREATMENT |     |                      | -31.7%  
| Non-ILA (n=2882) | 94/916 (10.3%) | 104/1966 (5.3%) | -33.5% |
| ILA (n=510) | 25/171 (14.6%) | 21/339 (6.2%) | |

<table>
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<tr>
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<th>Breast cancer specific death</th>
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<td>Non-ILA</td>
<td>53/916 (5.8%)</td>
</tr>
<tr>
<td>ILA</td>
<td>12/171 (7.0%)</td>
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<tr>
<td>Non-ILA</td>
<td>67/916 (7.3%)</td>
</tr>
<tr>
<td>ILA</td>
<td>16/171 (9.4%)</td>
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The Future: Search for Targets

• Predictive markers Anthracyclines/ Taxanes:
  – ILC lack \textit{topoisomerase-IIa} gene amplification
  – ILC frequently high kinase activity through the mutated PIK3CA pathway
  • resistance to cytotoxic agents as taxanes.
  • endocrine agents + targeted agents (mAB & nib’ s)
• Molecular profiling for risk & prediction of CT-benefit
  – Tailor X
  – Mindact
EORTC-BIG MINDACT TRIAL DESIGN

6,000 Women with Node-Negative Breast Cancer

Evaluate Clinical-Pathological Risk and 70-Gene Signature Risk

N=3300

Clinical-pathological and 70-gene both HIGH risk

55%

Discordant cases

Clin-Path HIGH 70-gene LOW

Clin-Path LOW 70-gene HIGH

35%

Clinical-pathological and 70-gene both LOW risk

10%

N=600

R1

N=2100

Use Clin-Path risk to decide Chemo or not

Use 70-gene risk to decide Chemo or not

Chemotherapy

Endocrine therapy

Potential CT sparing in 20-28% pts
If you still give adjuvant CT in low proliferative high risk ILC (luminal A-like)
Conclusion

• Treatment of ILC ~ biological features > “lobular” subtype.
  – A classical ILC & high Ki-67, rare, needs more than ET alone.
  – HER-2, if amplified in classical ILC → a focus with other morphology (ductal or pleomorphic); heterogeneity of HER2 status does exist.

*The added value of adjuvant CT in strong ER-pos breast cancers with a low proliferation rate (even if LN+) is currently being studied in an ongoing RCT → Most classic ILC belong to this group! Question added value!!

*If high proliferation & high risk: UZ Leuven – data: Selected patients for CT with ILA seem to do worse than non-ILA (benefit proven in both groups but might be less comparing ILA vs non-ILA.

→ Each decision needs individually discussed
SOFT [IBCSG 24-02, BIG 2-02]
Premenopausal, ER and/or PgR ≥ 10%

Patients who remain premenopausal within 8 months after CT, or receive tamoxifen alone as adequate treatment.

<table>
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<th>Strata</th>
<th>Treatment</th>
</tr>
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<tr>
<td>Any CT</td>
<td>Tamoxifen x 5y</td>
</tr>
<tr>
<td>No CT</td>
<td>OFS + Tamoxifen x 5y</td>
</tr>
<tr>
<td></td>
<td>OFS + Exemestane x 5y</td>
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OFS (ovarian function suppression) = triptorelin x 5y, oophorectomy or ovarian RT

Reporting in 2013/2014
Proposed Design: Everolimus Adjuvant Trial

Node-positive HR-positive and HER2-negative breast cancer

Number of positive nodes?

1-3 positive

Patients consent to study-sponsored RS testing if not already done

RECURRENCE SCORE evaluated

RS > 25

RS ≤ 25

Low risk 1-3 positive nodes and RS ≤ 25

Randomization

Chemotherapy vs. No Chemotherapy

Chemotherapy; endocrine therapy

No Chemotherapy; endocrine therapy

Current RxPONDER trial

New everolimus trial

Adjuvant or neoadjuvant chemotherapy

Randomization

Post-chemotherapy (stratification by risk group and timing of chemotherapy)

Everolimus vs. Placebo

Everolimus + Endocrine Therapy

Placebo + Endocrine Therapy

A SWOG Proposal
Genomic grade adds prognostic value in invasive lobular carcinoma

1/9 HG3 down-graded
21/125 HG1,2 up-graded
31/165 equivocal (16/31HG2)