Neoadjuvant therapy for ER-positive breast cancers

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European Institute of Oncology
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Neoadjuvant therapy for ER-positive breast cancers

Primary goals – treatment choice for women with early breast cancer:

- Integrate tumor biology and tumor extent into an estimate of responsiveness to treatment and outcome
- Utilize tumor biology, host biology and disease extension to obtain an optimal management strategy
Neoadjuvant therapy for ER-positive breast cancers

Trials are conducted to compare treatments

Often the results indicate that one treatment is better than the other, on average...

Degree of consensus on the specific treatment to use for “niche” of patients or the individual patient is low...
Limits of studies focusing on Neoadjuvant therapy for ER-positive breast cancers

Studies designed in an era when preoperative therapies were prescribed according to stage
Different cut-off and methodology in the definition of predictive features
Reliable histopathological assessment (P024 study: on central laboratory ER testing 12% of patients had ER- tumors)
Different adjuvant treatments
Studies not enough powered for the outcome questions
Follow-up too short (Patients with endocrine responsive disease continue to relapse after several years of diagnosis)
Neoadjuvant therapy for ER-positive HER2-negative breast cancers

Questions to be debated

- End points (pCR, Ki67, PEPI score)
- Patterns requiring chemotherapy
- Genomic signatures
- Selection of treatment according to subtypes
- Duration
- Endocrine therapy for premenopausal pts with ER+ disease
- Endocrine therapy for postmenopausal pts with ER+ disease
- Combination with Targeted agents
- Concurrent chemo-endocrine therapy
- Luminal “special type”
The definition of pCR should be based on histopathologic assessment, including absence of invasive cancer in both breast and lymph nodes. Patients with complete response in the breast but positive lymph nodes in the axilla have a far worse prognosis than patients with true pCR. The presence, extent, and classification of ductal carcinoma-in situ (DCIS) should be reported separately.

Ann Surg Oncol 2012; 19:1508-16
End points

Likelihood of pCR in Neoadjuvant chemotherapy

- **Higher likelihood:**
  - Age: < 40 years
  - Tumor size: < 2 cm
  - Histology: ductal
  - Grade: high (G3)
  - Proliferation: high Ki-67
  - ER: negative
  - Intrinsic subtype: Basal-like or HER2-enriched

- **Lower likelihood:**
  - Age: ≥ 60 years
  - Tumor size: > 4 cm
  - Histology: lobular
  - Grade: low (G1)
  - Proliferation: low Ki-67
  - ER: positive
  - Intrinsic subtype: luminal A

Ann Surg Oncol 2012;19:1508-16

www.esmo2012.org
End points

Neoadjuvant Chemotherapy: degree of endocrine responsiveness and pCR

End points

IMPACT study: Objective response rate versus ER H score, by quartiles

J Clin Oncol 2005; 23:5108-5116

P .02
End points

P024 study Clinical response rate versus ER Allred score

% of cases in each category

J Clin Oncol 2001; 19:3808-3816
End points

pCR: a reliable marker of outcome?

pCR after preoperative chemotherapy has been shown to correlate with survival.

An optimal definition of pCR (including axillary nodal status) is critical.

Pathologist Challenge

Relationship not perfect with the outcome of interest (DFS, OS); it can depend on both tumor subtype and specific therapy.
Prognostic impact of pCR on DFS according to breast cancer intrinsic subtype

End points

Luminal A–like tumors.
ER positive and/or PgR positive, HER2 negative, grade 1 or 2

Luminal B/HER2-negative–like tumors.
ER positive and/or PgR positive, HER2 negative, grade 3

J Clin Oncol 2012; 30:1796-1804
## End points

### The preoperative endocrine prognostic index (PEPI)

<table>
<thead>
<tr>
<th>Pathology, biomarker status</th>
<th>RFS</th>
<th></th>
<th></th>
<th>BCSS</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>HR</td>
<td>Points</td>
<td></td>
<td>HR</td>
<td>Points</td>
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</tr>
<tr>
<td>Pathological tumor size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1/2</td>
<td>—</td>
<td>0</td>
<td></td>
<td>—</td>
<td>0</td>
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</tr>
<tr>
<td>T3/4</td>
<td>2.8</td>
<td>3</td>
<td></td>
<td>4.4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Node status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>—</td>
<td>0</td>
<td></td>
<td>—</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>3.2</td>
<td>3</td>
<td></td>
<td>3.9</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Ki67 level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%–2.7% (0–1†)</td>
<td>—</td>
<td>0</td>
<td></td>
<td>—</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>&gt;2.7%–7.3% (1–2†)</td>
<td>1.3</td>
<td>1</td>
<td></td>
<td>1.4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&gt;7.3%–19.7% (2–3†)</td>
<td>1.7</td>
<td>1</td>
<td></td>
<td>2.0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>&gt;19.7%–53.1% (3–4†)</td>
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<td>2</td>
<td></td>
<td>2.7</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>&gt;53.1% (&gt;4†)</td>
<td>2.9</td>
<td>3</td>
<td></td>
<td>3.8</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>ER status, Allred score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>2.8</td>
<td>3</td>
<td></td>
<td>7.0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>3–8</td>
<td>—</td>
<td>0</td>
<td></td>
<td>—</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*J Natl Cancer Inst 2008; 100: 1380 – 1388*
End points

Relapse-free survival by risk-group in P024 and IMPACT study

J Natl Cancer Inst 2008;100: 1380 – 1388
End points

Recurrence-free survival according to tertiles of tumor Ki67 expression after 2 weeks of treatment

J Natl Cancer Inst 2007; 99:167–70
End points

BIG and NABCG proposals for standard definitions and endpoints in neoadjuvant breast cancer clinical trials

**Ki67:** for patients receiving neoadjuvant endocrine treatment in the context of clinical trials, we recommend assessment of Ki67 on baseline biopsy samples, on biopsy specimens collected during treatment, and on surgical specimens for research purposes.

**PEPI:** we recommend assessment of the PEPI score 12–16 weeks after treatment in neoadjuvant trials using endocrine therapy, for research purposes.

Genomic signatures

Distribution of the continuous genomic grade index (GGI) within response groups defined by the residual cancer burden (RCB) for ER-positive disease

J Clin Oncol 2009; 27:3185-3191
## Performance of Genomic Signatures for Predicting Pathologic Response

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Discovery Cohort (n = 310)</th>
<th>Validation Cohort (n = 198)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>PPV&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Genomic Grade Index, high</td>
<td>301 (29)</td>
<td>36 (30 to 43)</td>
</tr>
<tr>
<td>Genomic subtype classifier, luminal B or basal-like</td>
<td>301 (29)</td>
<td>40 (32 to 48)</td>
</tr>
<tr>
<td>Genomic predictor of pathologic complete response</td>
<td>301 (29)</td>
<td>46 (37 to 55)</td>
</tr>
<tr>
<td>ER-stratified genomic predictor of pathologic complete response/RCB-I&lt;sup&gt;e&lt;/sup&gt;</td>
<td>301 (29)</td>
<td>69 (60 to 77)</td>
</tr>
<tr>
<td>Predictive test, treatment sensitive&lt;sup&gt;e,f,g&lt;/sup&gt;</td>
<td>256 (31)</td>
<td>78 (66 to 88)</td>
</tr>
</tbody>
</table>

JAMA 2011; 305: 1873-1881

www.esmo2012.org
Genomic signatures

ER-positive Analysis of Genomic Predictions in the Validation Cohort

JAMA 2011; 305: 1873-1881
PAM50 analysis identified AI-unresponsive nonluminal subtypes (HER-2 enriched or basal-like) in 3.3% of patients.

Clinical response and surgical outcomes were similar in luminal A (LumA) versus luminal B tumors.

PEPI of 0 (best prognostic group) was highest in the LumA subset (27.1% v 10.7%; P < .004).

J Clin Oncol 2011; 29: 2342-2349
Genomic signatures

Gene expression profiling would not be possible in the direct future for the majority of patients

Lack of a standardized molecular class prediction method

Large number of variables (genes) in small data sets

Still imperfect in the identification of the population which can avoid chemotherapy or candidate to pCR
# Selection of treatment according to subtypes

## Surrogate definitions of intrinsic subtypes of breast cancer

<table>
<thead>
<tr>
<th>Intrinsic Subtype</th>
<th>Clinico-pathologic definition</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Luminal A               | ‘Luminal A’  
ER and/or PgR positive  
HER2 negative  
Ki-67 low (<14%) | Optimal cut-point for Ki-67 labelling index was established by comparison with PAM50 intrinsic subtyping. Local quality control of Ki-67 staining is important |
| Luminal B               | ‘Luminal B (HER2 negative)’  
ER and/or PgR positive  
HER2 negative  
Ki-67 high  
‘Luminal B (HER2 positive)’  
ER and/or PgR positive  
Any Ki-67  
HER2 over-expressed or amplified | Genes indicative of higher proliferation are poor prognostic markers in multiple genetic assays.  
Operationally useful to distinguish ‘luminal B HER2 positive’ as both endocrine and anti-HER2 therapy may be indicated |
| Erb-B2 overexpression   | ‘HER2 positive (non luminal)’  
HER2 over-expressed or amplified  
ER and PgR absent | The majority of HER2 positive tumours are endocrine-receptor negative |
| ‘Basal-like’            | ‘Triple negative (ductal)’  
ER and PgR absent  
HER2 negative | Approximately 80% overlap between ‘triple negative’ and intrinsic ‘basal-like’ subtype but ‘triple negative’ also includes some special histological types such as medullary and adenoid cystic carcinoma |

www.esmo2012.org
The choice of neoadjuvant chemotherapy should be made on the same basis as applied in the selection of postoperative adjuvant treatments (e.g. high histological grade, high proliferation as measured by Ki-67, low hormone receptor status, ...)

Cytotoxic neoadjuvant therapy not supported for tumors with low proliferation or high endocrine responsiveness

Neoadjuvant endocrine therapy is an option for postmenopausal patients with highly endocrine-responsive disease

Duration

For how long the neoadjuvant treatment should be used?

In routine practice, the same regimens should be used for neoadjuvant chemotherapy as in the adjuvant setting (anthracyclines and taxanes concurrently or sequentially for at least 6 cycles or 6 months, respectively) with no chemotherapy regimen preferred.

All chemotherapy should be provided before surgery rather than split into preoperative and postoperative phases.

Neoadjuvant endocrine therapy should be continued for a minimum of 4 months.

Ann Surg Oncol 2012;19:1508-16
Pathologic tumor responses according to estrogen receptor status in NSABP B-27 study

J Clin Oncol 2003; 21:4165-4174
Duration

Association of pCR with treatment characteristics in 7 neoadjuvant German studies

Number of cycles (per 2 additional cycles)
- HER2 -/ HR +: 1.30 (1.02 to 1.65)
- HER2 +/ HR +: 1.42 (1.04 to 1.94)
- HER2 +/ HR -: 1.00 (0.71 to 1.41)
- HER2 -/ HR -: 1.09 (0.88 to 1.35)

Antracycline (high vs low dose)
- HER2 -/ HR +: 1.92 (1.14 to 3.21)
- HER2 +/ HR +: 0.94 (0.31 to 2.85)
- HER2 +/ HR -: 0.72 (0.20 to 2.58)
- HER2 -/ HR -: 1.49 (0.98 to 2.27)

Taxane (high vs low dose)
- HER2 -/ HR +: 1.52 (0.84 to 2.76)
- HER2 +/ HR +: 2.23 (0.75 to 6.61)
- HER2 +/ HR -: 1.87 (0.51 to 6.92)
- HER2 -/ HR -: 1.73 (1.02 to 2.94)

The Breast 2011; S3, S142–S145
Duration

Individual values for % reduction in clinical and ultrasound volume during letrozole between time intervals 0–3 mos, 3–6 mos, 6–12 mos and 12–24 mos

Breast Cancer Res Treat 2009; 113:145–151
Neoadjuvant endocrine therapy for premenopausal pts with ER+ disease

**STAGE STUDY**

**Phase III**
197 Premenopausal breast cancer
T [2–5 cm], N0, M0
ER≥10%
HER2 negative

**Days**
1  28  84  112  140  168

- TAMOXIFEN + Anastrozole placebo
- Anastrozole + Tamoxifen placebo
- Goserelin 3.6 mg every 28 days

**Surgery**

*Lancet Oncol 2012; 13: 345-52*

www.esmo2012.org
Neoadjuvant endocrine therapy for premenopausal pts with ER+ disease

**STAGE study: RESULTS**

<table>
<thead>
<tr>
<th></th>
<th>Anastrozole plus goserelin (n=98)</th>
<th>Tamoxifen plus goserelin (n=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall tumour response</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Calliper</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>12 (12.2%)</td>
<td>7 (7.1%)</td>
</tr>
<tr>
<td>PR</td>
<td>57 (58.2%)</td>
<td>43 (43.4%)</td>
</tr>
<tr>
<td>CR+PR</td>
<td>69 (70.4%)</td>
<td>50 (50.5%)</td>
</tr>
<tr>
<td><strong>Ultrasound</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1 (1.0%)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>56 (57.1%)</td>
<td>42 (42.4%)</td>
</tr>
<tr>
<td>CR+PR</td>
<td>57 (58.2%)</td>
<td>42 (42.4%)</td>
</tr>
<tr>
<td><strong>MRI or CT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>2 (2.0%)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>61 (62.2%)</td>
<td>37 (37.4%)</td>
</tr>
<tr>
<td>CR+PR</td>
<td>63 (64.3%)</td>
<td>37 (37.4%)</td>
</tr>
</tbody>
</table>

Lancet Oncol 2012;13: 345-52
Neoadjuvant endocrine therapy for premenopausal pts with ER+ disease
Summary of the P024, IMPACT and PROACT trials

<table>
<thead>
<tr>
<th></th>
<th>Letrozole P024</th>
<th>IMPACT</th>
<th>PROACT</th>
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<tbody>
<tr>
<td></td>
<td>Postmenopausal women, HT+ breast cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>337</td>
<td>330</td>
<td>451</td>
</tr>
<tr>
<td>HR positivity</td>
<td>ER/PR &gt; 10%</td>
<td>ER &gt; 1%</td>
<td>ER + / PR +</td>
</tr>
<tr>
<td>Neoad ET</td>
<td>L x 4 months T for 4 months</td>
<td>A x 12 weeks A+T x 12 weeks T x 12 weeks</td>
<td>A x 3 months T x 3 months</td>
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<td>Concomitant CT</td>
<td>NO</td>
<td>-</td>
<td>YES</td>
</tr>
<tr>
<td>Response</td>
<td>55% (L) vs 36% (T); p&lt;0.001</td>
<td>37% (A) vs 39% (A+T) vs 36% (T)</td>
<td>39.5% (A) vs 35.4% (T)</td>
</tr>
</tbody>
</table>
Neoadjuvant endocrine therapy for postmenopausal pts with ER+ disease

ACOSOG Z1031 Clinical Response Based on ITT Population

<table>
<thead>
<tr>
<th>Response</th>
<th>Exemestane (n = 124)</th>
<th>Letrozole (n = 127)</th>
<th>Anastrozole (n = 123)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Clinical response at week 16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(WHO criteria with caliper</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>measurements)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>27</td>
<td>21.8</td>
<td>27</td>
</tr>
<tr>
<td>Partial response</td>
<td>51</td>
<td>41.1</td>
<td>68</td>
</tr>
<tr>
<td>No change</td>
<td>28</td>
<td>22.6</td>
<td>20</td>
</tr>
<tr>
<td>Disease progression</td>
<td>8</td>
<td>6.5</td>
<td>6</td>
</tr>
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</table>

J Clin Oncol 2011; 29: 2342-2349
Neoadjuvant endocrine therapy for postmenopausal pts with ER+ disease

ACOSOG Z1031. Mean percentage suppression of Ki67 from baseline by treatment arm

J Clin Oncol 2011; 29:2342-2349
Targeted agents and endocrine therapy

Neoadjuvant aromatase inhibitor and genome-wide somatic mutations. Three on-treatment Ki67 < 10% (top panel) and three on-treatment Ki67 > 10% (bottom panel)

Nature 2012; 486: 353-60
Targeted agents and endocrine therapy

Key cancer pathway components altered in luminal breast tumours

Nature 2012; 486: 353-60

www.esmo2012.org
Targeted agents and endocrine therapy

Everolimus Plus Letrozole Compared With Placebo Plus Letrozole in Patients With ER+ Breast Cancer

<table>
<thead>
<tr>
<th>Response by Evaluation Type</th>
<th>Everolimus + Letrozole (n = 138)</th>
<th>Placebo + Letrozole (n = 132)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Clinical palpation</td>
<td></td>
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<tr>
<td>Complete response</td>
<td>18</td>
<td>13.0</td>
</tr>
<tr>
<td>Partial response</td>
<td>76</td>
<td>55.1</td>
</tr>
<tr>
<td>No change</td>
<td>34</td>
<td>24.6</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>6</td>
<td>4.3</td>
</tr>
<tr>
<td>Not available/not assessable</td>
<td>4</td>
<td>2.9</td>
</tr>
<tr>
<td>Overall response*</td>
<td>94</td>
<td>68.1</td>
</tr>
</tbody>
</table>

95% CI: 60.3 to 75.9            50.7 to 67.5

χ² test P = .0616

Ultrasound

<table>
<thead>
<tr>
<th>Response by Evaluation Type</th>
<th>Everolimus + Letrozole</th>
<th>Placebo + Letrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Complete response</td>
<td>7</td>
<td>5.1</td>
</tr>
<tr>
<td>Partial response</td>
<td>73</td>
<td>52.9</td>
</tr>
<tr>
<td>No change</td>
<td>43</td>
<td>31.2</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>4</td>
<td>2.9</td>
</tr>
<tr>
<td>Not available/not assessable</td>
<td>11</td>
<td>8.0</td>
</tr>
<tr>
<td>Overall response*</td>
<td>80</td>
<td>58.0</td>
</tr>
</tbody>
</table>

95% CI: 49.7 to 66.2            38.5 to 55.5

χ² test P = .0352

J Clin Oncol 2009; 27:2630-2637

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Targeted agents and neoadjuvant chemotherapy

Bevacizumab for HER2 negative breast cancer

NSABP B-40 trial


www.esmo2012.org
Targeted agents and neoadjuvant chemotherapy

Bevacizumab for HER2 negative breast cancer.

GeparQuinto trial

www.esmo2012.org
Concurrent chemo-endocrine therapy

LET vs LET-CYC: Distribution of Disease Response According to Treatment Arm

<table>
<thead>
<tr>
<th></th>
<th>LET</th>
<th></th>
<th>LET-CYC</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Not assessable</td>
<td>1</td>
<td>1.7</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Progressive disease</td>
<td>3</td>
<td>5.3</td>
<td>3</td>
<td>5.3</td>
</tr>
<tr>
<td>Stable disease</td>
<td>12</td>
<td>21.0</td>
<td>4</td>
<td>7.1</td>
</tr>
<tr>
<td>Partial response</td>
<td>18</td>
<td>31.6</td>
<td>25</td>
<td>43.8</td>
</tr>
<tr>
<td>Complete response</td>
<td>23</td>
<td>40.3</td>
<td>25</td>
<td>43.8</td>
</tr>
<tr>
<td>Overall response</td>
<td>41</td>
<td>71.9</td>
<td>50</td>
<td>87.7</td>
</tr>
<tr>
<td>95% CI</td>
<td>60.8% to 83.8%</td>
<td></td>
<td>78.6% to 96.2%</td>
<td></td>
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<tr>
<td>Pathologic response</td>
<td>2</td>
<td>3.5</td>
<td>2</td>
<td>3.5</td>
</tr>
<tr>
<td>Residual in situ carcinoma</td>
<td>1</td>
<td>1.8</td>
<td>1</td>
<td>1.8</td>
</tr>
</tbody>
</table>

J Clin Oncol 2006; 24:3623-3628
Luminal “special types”

Disease-free survival according to histological subtypes for luminal A and luminal B subtypes

Ann Oncol 2012; 23: 1428–1436

www.esmo2012.org
Luminal “special types”

Lobular carcinoma (ILC): a distinct responsiveness

<table>
<thead>
<tr>
<th>Author</th>
<th>Pts</th>
<th>%pCR IDC</th>
<th>%pCR ILC</th>
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<tbody>
<tr>
<td>Cristofanilli</td>
<td>1034</td>
<td>15</td>
<td>3</td>
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Summary

ER-positive, HER-2-negative operable breast cancer represents a mixed group of tumors where the identification of distinct clinical entities is the key achievement for proper management.

Limited information on tailoring Neoadjuvant treatment for an individual patient.
Summary

On the one extreme, patients with ER-positive, HER2-negative disease may have tumors with very low risks of recurrence, where there is little evidence supporting the use of neoadjuvant therapy.

On the other extreme, patients may present with high-risk, highly proliferative disease, where prolonged neoadjuvant chemotherapy appears clearly justified.
Summary

Patients and their physicians must weigh the costs and benefits of all therapeutic options.

Tailored neoadjuvant treatment investigation on specific niches of patients is key to make progress on how to treat individual patients with ER-positive, HER2-negative breast cancer.