Luminal Breast Cancer (LBC) – (Neo) Adjuvant Chemotherapy

Multidisciplinary management, standards of care, therapeutic targets and future perspectives

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Specialist in Medical Oncology & Hon. Clinical Assistant Professor
Li Ka Shing Faculty of Medicine, The University of Hong Kong
Founding Convenor, Hong Kong Breast Oncology Group (HKBOG)
27th November, 2018

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DISCLOSURES

Consultant or Advisory Role:

AstraZeneca, Aptus, Astellas, De Novo, Eisai, Foundation Medicine, Nanostring, Novartis, Pfizer & Roche

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(Neo)adjuvant Chemotherapy for Luminal Breast Cancer

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Breast cancer was initially thought as a strictly *local* disease...

Based on **William Stewart Halsted** (1852-1922)’s theory: Breast cancer is a strictly local disease, only curable by radical surgery...

Early breast cancer used to be managed exclusively by surgeons...
Breast cancer was then thought as a systemic disease...

The work of Bernard Fisher, breast surgeon & chairman of the National Surgical Adjuvant Breast & Bowel Project (NSABP) in the 1960s has led to the development of breast cancer being a systemic disease...

Leading to a paradigm shift in breast cancer management with the introduction of adjuvant therapy...

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Personalized treatment of breast cancer started in the 1960s...

Professor Elwood V. Jensen, first identified the Estrogen receptor (ER) in 1958...

Introduction of TAMOXIFEN as a first “targeted agent” in the 1970s...
Breast cancer subtypes

All Breast Cancers

ER+ 65-75%

HER2+ 15-20%

TN 15%

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Classical prognostic & predictive factors

- Age
- Tumour size
- Grade
- Histological subtypes
- ER/PR and HER2 status
- Presence of lymphovascular invasion
- High proliferative index (Ki-67)
- Tumor margins
Changing Portraits of Breast Cancer
Intrinsic Subtypes

Perou et al., Nature, 2000
Sorlie et al., PNAS, 2003
Cheang et al., CCR 2008
Cheang et al., JNCI 2009
Parker et al., JCO, 2009
Nielsen et al., CCR 2010
Cheang et al., CCR 2012
Dowsett et al., JCO 2013
Hoadley et al., Cell, 2014
Carey et al., JCO 2015

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

EBCTCG Lancet, 2012

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### The EBCTCG Overview - Subgroup Analyses

#### Deaths/women

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Deaths/women</th>
<th>Adjusted CHF</th>
<th>Adjusted anthracycline</th>
<th>Ratio of overall survival</th>
<th>Adjusted anthracycline CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Discrepancy in anthracycline exposure, if breast cancer is present in at most one woman</td>
<td>40/160 (25%)</td>
<td>160/229 (21%)</td>
<td>1.5</td>
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<td>B. Cyclophosphamide CHF and cyclophosphamide in 4% to 15% (N = 12)</td>
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<td>D. Egg age, defined as (menopause at 45-59 years)</td>
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<td>120/139 (23%)</td>
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<td>E. Menstrual status (menopause at 45-59 years)</td>
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<td>F. All status (menopause at 45-59 years)</td>
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<td>2.5</td>
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### The EBCTCG Overview - Subgroup Analyses

**Subgroup analysis of breast cancer mortality in ER positive patients by HER2, age and tumour grade**

#### Table 1: Subgroup Analyses of Breast Cancer Mortality in ER Positive Patients

<table>
<thead>
<tr>
<th></th>
<th>Deaths/women</th>
<th>Anthracycline deaths</th>
<th>Ratio of overall/anthracycline deaths</th>
<th>Log rank D=0</th>
<th>Variance of D</th>
<th>Anthracycline/D=0</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td><strong>A</strong></td>
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</tr>
<tr>
<td>Adjuvant tamoxifen (AT) (Y/N)</td>
<td>383 (202/181)</td>
<td>570 (265/205)</td>
<td>-9.0 58.6</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td></td>
</tr>
<tr>
<td>Adjuvant chemotherapy (C)</td>
<td>341 (143/198)</td>
<td>518 (238/280)</td>
<td>-4.1 78.4</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td></td>
</tr>
<tr>
<td>No chemotherapy (NC)</td>
<td>279 (102/177)</td>
<td>403 (182/221)</td>
<td>0.0 100.0</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
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<tr>
<td><strong>B</strong></td>
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</tr>
<tr>
<td>Chemotherapeutic drugs (CD)</td>
<td>426 (177/249)</td>
<td>591 (262/329)</td>
<td>-9.4 52.4</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td></td>
</tr>
<tr>
<td>No chemotherapy (NC)</td>
<td>381 (139/242)</td>
<td>559 (238/321)</td>
<td>-4.4 68.3</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td></td>
</tr>
<tr>
<td>No chemotherapy (NC)</td>
<td>300 (102/198)</td>
<td>409 (187/222)</td>
<td>0.0 100.0</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
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<tr>
<td><strong>C</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Concurrent endocrine therapy (CET)</td>
<td>423 (172/251)</td>
<td>588 (260/328)</td>
<td>-9.5 53.3</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td></td>
</tr>
<tr>
<td>No endocrine therapy (NET)</td>
<td>380 (140/240)</td>
<td>553 (237/316)</td>
<td>-4.4 68.7</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td></td>
</tr>
<tr>
<td>No endocrine therapy (NET)</td>
<td>300 (101/199)</td>
<td>408 (188/220)</td>
<td>0.0 100.0</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
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<tr>
<td>Age group (years)</td>
<td>75 (28/47)</td>
<td>108 (52/56)</td>
<td>-3.2 80.1</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td></td>
</tr>
<tr>
<td>45-54 years</td>
<td>720 (279/441)</td>
<td>957 (410/547)</td>
<td>-8.6 57.5</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td></td>
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<tr>
<td>55-64 years</td>
<td>75 (28/47)</td>
<td>104 (49/55)</td>
<td>-2.3 95.7</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td></td>
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<tr>
<td>65-74 years</td>
<td>75 (32/43)</td>
<td>103 (42/61)</td>
<td>-0.9 100.0</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
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<td><strong>E</strong></td>
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<tr>
<td>Histological grade (HG)</td>
<td>573 (226/347)</td>
<td>783 (336/447)</td>
<td>-9.6 55.4</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
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<tr>
<td>HG 1</td>
<td>300 (101/199)</td>
<td>408 (188/220)</td>
<td>0.0 100.0</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td></td>
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<tr>
<td>HG 2</td>
<td>300 (102/218)</td>
<td>409 (187/222)</td>
<td>0.0 100.0</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td></td>
</tr>
<tr>
<td>HG 3</td>
<td>300 (102/198)</td>
<td>409 (187/222)</td>
<td>0.0 100.0</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
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<tr>
<td><strong>F</strong></td>
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<td></td>
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<tr>
<td>ER status (ER+)</td>
<td>426 (177/249)</td>
<td>591 (262/329)</td>
<td>-9.4 52.4</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
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<tr>
<td>ER negative</td>
<td>381 (140/240)</td>
<td>553 (237/316)</td>
<td>-4.4 68.7</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
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<td>ER negative</td>
<td>300 (101/199)</td>
<td>408 (188/220)</td>
<td>0.0 100.0</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td></td>
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<tr>
<td><strong>G</strong></td>
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<tr>
<td>Subgroups of ER+</td>
<td>420 (176/244)</td>
<td>587 (252/335)</td>
<td>-9.3 53.1</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td></td>
</tr>
<tr>
<td>ER -low (15% or less)</td>
<td>420 (176/244)</td>
<td>587 (252/335)</td>
<td>-9.3 53.1</td>
<td>0.0 0.0</td>
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Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials

Figure 6: Subgroup analyses of breast cancer mortality (mortality with recurrence, by log-rank subtraction) for any anthracycline-based regimen versus no chemotherapy

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The EBCTCG Overview: Bottom-line Message

- Anthracycline/taxane-based regimens reduce breast cancer mortality by, on average, about one-third.
- Proportional benefits in the ER positive population do not seem to be affected by age, HER2 status or tumour grade.

**Interpretation**

10-year gains from a one-third breast cancer mortality reduction depend on absolute risks without chemotherapy (which, for oestrogen-receptor-positive disease, are the risks remaining with appropriate endocrine therapy). Low absolute risk implies low absolute benefit, but information was lacking about tumour gene expression markers or quantitative immunohistochemistry that might help to predict risk, chemosensitivity, or both.

**Funding**

Cancer Research UK; British Heart Foundation; UK Medical Research Council.

EBCTCG Lancet, 2012
Who responds to anthracycline better?

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The Chemosensitivity of Individual Breast Cancer Depends on Multifactorial Factors…

In favor of adjuvant chemotherapy
- ER negative
- Ductal histology
- Grade 3
- High proliferation
- High uPA and PAI1
- Basal and HER2 positive
- High MammaPrint® or Oncotype DX® or GGI

Against adjuvant chemotherapy
- ER positive
- Lobular histology
- Grade 1
- Low proliferation
- Low uPA and PAI1
- Luminal A
- Low MammaPrint® or Oncotype DX® or GGI
(Neo)adjuvant Chemotherapy for *Luminal A-like vs Luminal B-like*
An exploratory analysis to test sensitivity to different chemotherapy regimens by luminal subtype


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An exploratory analysis to test sensitivity to different chemotherapy regimens by luminal subtype


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When cytotoxic chemotherapy is indicated for luminal disease:

- the specific choice of regimen depends on the position within the spectrum of degree of endocrine responsiveness and risk of relapse.
- On average, for ‘luminal B-like’ tumors, the Oxford overview supports the inclusion of both an anthracycline and a taxane.
- while in ‘luminal A-like’ tumors, there is little evidence of an advantage compared with older regimens such as AC and CMF.
- If given, chemotherapy for ‘luminal B-like’ disease should not extend beyond four courses of the same treatment, especially, for patients with a lower burden of disease.
- The addition of taxanes should be considered for patients with more extensive disease burden.
- A slim majority considered that there was a high-risk group for which dose-dense therapy with G-CSF support should be preferred.
Adjuvant Chemotherapy

The St. Gallen vote on adjuvant chemotherapy focused on patients who might have a prognostic benefit from postoperative chemotherapy and should therefore receive chemotherapy postoperatively.

When considering patients without lymph node involvement (pN0), their prognosis as well as the decision for or against adjuvant chemotherapy should be based on immunohistochemical assessment of the tumor biology, which can be supplemented by multigene expression testing in cases of ambiguous staining. Relative indications for adjuvant chemotherapy are poorly differentiated G3 tumors, lymph node involvement (pN+), high Ki-67 proliferation index, very young patient age (<35 years) and low hormone receptor (HR) expression (<10%). The German experts agree with the St. Gallen panelists and add that, based on these criteria, it is important to consider the risk-benefit-ratio.

The majority of St. Gallen panelists also considered extensive lymphovascular tumor invasion a relative indication for adjuvant chemotherapy. The German experts refer to the current AGO guidelines and state that lymphovascular tumor invasion is not an indication for chemotherapy. From the German point of view chemotherapy is not necessarily indicated, if there are no additional risk factors.

Luminal B-like breast cancer without HER2 overexpression

For patients with luminal B-like breast cancer, a common question in clinical practice is whether adjuvant chemotherapy is indicated in addition to endocrine therapy. Adjuvant chemotherapy is indicated if there is an increased risk of recurrence. The German experts agree with the majority of St. Gallen panelists that adjuvant chemotherapy should be recommended to patients with early luminal B-like breast cancer and prognostically unfavorable tumor biology confirmed by immunohistochemistry, irrespective of lymph node status. The German experts point out that in patients with no lymph node involvement tumor size should also be taken into account for treatment decisions. If the primary tumor is very small (<T1a pN0), and there are no additional negative criteria.
Initial Treatment of Patients with Primary Breast Cancer: Evidence, Controversies, Consensus

Spectrum of Opinion of German Specialists at the 15th International St. Gallen Breast Cancer Conference (Vienna 2017)

Michael Ulrich, Jens Huebner, Christian Jackisch, Andreas Schneweis, Gero P. Becker, Feihm, Bernd Garber, Wolfgang Jarek, Thordens Kihlin, Diana Lüthi, Thomsen, Nadia Harbeck, and Carola Liedtke

Author information Articlenotes Copyrigth and License information

Abstract

The St. Gallen International Consensus Conference

Adjuvant Chemotherapy

The St. Gallen vote on chemotherapy and show

When considering patients, chemotherapy should be expressed testing in case lymph node involvement expression (<10%). The consider the risk-benefit.

The majority of St. Gallen chemotherapy. The consideration of chemotherapy: indication for chemotherapy risk factors.

Luminal B-like breast cancer

For patients with luminal B-like breast cancer in addition to endocrine therapy. Adjuvant chemotherapy is indicated if there is an increased risk of recurrence. The German experts agree with the majority of St. Gallen panelists that adjuvant chemotherapy should be recommended to patients with early luminal B-like breast cancer and pathologically unfavorable tumor biology confirmed by immunohistochemistry, irrespective of lymph node status. The German experts point out that in patients with no lymph node involvement tumor size should also be taken into account for treatment decisions. If the primary tumor is very small (pT1a or pN0) and there are no additional negative criteria, adjuvant chemotherapy is not indicated from the German point of view.

The St. Gallen panelists and the German experts confirm again that multigene expression analysis can be an effective method in patients with luminal B-like breast cancer to determine whether the patient has an increased 10-year risk of metastasis and chemotherapy is therefore indicated. The majority of St. Gallen panelists voted that adjuvant chemotherapy is not necessary if RS is low as long as there is no lymph node involvement or if less than three nodes are involved. The German experts agree with this opinion and refer to the prospective data collected in the TAILORx trial which had a follow-up of five years. The findings of this study have been confirmed by recent data from the West German Study Group (WSP) Phase III Plan B trial, which also had a follow-up of just under five years.

The findings referred specifically to low-risk patients with an RS of less than 11 and no lymph node involvement or fewer than three involved lymph nodes and a follow-up of five years. If the RS score is intermediate, the St. Gallen panelists and the German specialists agree that avoiding adjuvant chemotherapy should only be considered in individual cases. For the final assessment (adjuvant chemotherapy indicated yes/no) it is necessary to wait until data on patients with intermediate scores are available from the TAILORx trial.

Initial prospective data on patients with 1-3 involved lymph nodes with a follow-up of just under five years are now also available for the MP score. Based on preliminary data, adjuvant chemotherapy is not required for patients with 1-3 involved lymph nodes with a risk profile as low according to MP score. No prospective data are available yet for SOR and EP. However, according to retrospective data from prospective studies with EP, the cumulative risk of metastasis for low-risk node-negative patients (just under 20% of patients) who receive only endocrine therapy is about 5%. This means that chemotherapy is not necessary in this patient population.

The St. Gallen panelists and the German experts agree that adjuvant chemotherapy should be anthracycline-based and taxane-based for patients with luminal B-like (HER2-negative) breast cancer.
Current Status...

- No strong evidence in favour of anthracycline or taxane-based regimens in Luminal A-like breast cancer – lack of robust data.
- Anthracycline/taxane-based regimens seem to be the most appropriate treatment choice in Luminal B-like tumour.
ESMO Clinical Practice Guideline for Primary Breast Cancer…

clinical practice guidelines

Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

E. Senkus1, S. Kyriakides2, S. Ohno3, F. Penault-Llorca4,5, P. Poortmans6, E. Rutgers7, S. Zackrisson8 & F. Cardoso9, on behalf of the ESMO Guidelines Committee*

1Department of Oncology and Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland; 2Europa Donna Cyprus, Nicosia, Cyprus; 3Breast Oncology Center, Cancer Institute Hospital, Tokyo, Japan; 4Department of Pathology, Centre Jean Perrin, Clermont-Ferrand; 5EA 4677 Université d’Auvergne, Clermont-Ferrand, France; 6Radboud University Medical Center, Nijmegen, The Netherlands; 7Department of Surgery, Netherlands Cancer Institute, Amsterdam, The Netherlands; 8Department of Diagnostic Radiology, Lund University, Malmö, Sweden; 9Breast Unit, Champalimaud Clinical Center, Lisbon, Portugal

incidence and epidemiology

In 2012, the estimated age-adjusted annual incidence of breast cancer in Europe was 488 per 100,000 and the mortality reduction benefit in the age group of 50–69 years and is recommended by the European Union and numerous individual countries [8]. The evidence for effectiveness of mammography
**Table 2. Surrogate definitions of intrinsic subtypes of breast cancer according to the 2015 St Gallen Consensus Conference** and also recommended by the ESMO Clinical Practice Guidelines

<table>
<thead>
<tr>
<th>Intrinsic subtype</th>
<th>Clinicopathologic surrogate definition</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>Luminal A</td>
<td>Luminal A-like’ ER positive HER2-negative Ki67 low* PgR high**</td>
<td>*Ki-67 scores should be interpreted in the light of local laboratory values: as an example, if a laboratory has a median Ki-67 score in receptor-positive disease of 20%, values of 30% or above could be considered clearly high, those of 10% or less clearly low. **Suggested cut-off value is 20%; quality assurance programmes are essential for laboratories reporting these results.</td>
</tr>
<tr>
<td>Luminal B</td>
<td>Luminal B-like (HER2-negative) ER positive HER2-negative and either Ki67 high or PgR low high-risk molecular signature (if available)</td>
<td></td>
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<tr>
<td></td>
<td>Luminal B-like (HER2-positive) ER positive HER2 positive any Ki67 any PgR</td>
<td></td>
</tr>
<tr>
<td>HER2 overexpression</td>
<td>HER2-positive (non-luminal) HER2-positive ER and PgR absent</td>
<td></td>
</tr>
<tr>
<td>Basal-like</td>
<td>Triple-negative (ductal) ER and PgR absent HER2-negative</td>
<td>There is ~80% overlap between ‘triple-negative’ and intrinsic ‘basal-like’ subtype, but ‘triple-negative’ also includes some special histological types such as (typical) medullary and adenoid cystic carcinoma with low risks of distant recurrence.</td>
</tr>
</tbody>
</table>

ER, oestrogen receptor; HER2, human epidermal growth factor 2 receptor; PgR, progesterone receptor.
If preoperative systemic therapy is planned:

1) **a core needle biopsy** is mandatory to ensure a diagnosis of invasive disease and assess biomarkers [III, A].
2) A **marker** (e.g. surgical clip, carbon) should be placed into the tumour at biopsy, to ensure surgical resection of the correct site [V, A].
3) As a minimum, **ultrasound-guided fine needle aspiration or core biopsy of suspicious lymph nodes** should be carried out [III, A].
4) In patients with clinically and imaging negative axilla, **the best timing** to carry out sentinel lymph node biopsy (SLNB), i.e. before or after preoperative systemic therapy, **remains controversial** [II, C].
5) The recently published **SENTINA and ACOSOG Z1071 studies** demonstrated lower detection rates and higher rates of false-negatives when SLNB is carried out after systemic therapy, compared with SNLB that is carried out before neoadjuvant chemotherapy.

---

**Figure 2.** (Neo)adjuvant systemic treatment choice by biomarker expression and intrinsic phenotype. ER, estrogen receptor; HER2, human epidermal
Precision Medicine for (Neo)adjuvant Chemotherapy Luminal EBC
Predictive Marker vs Prognostic Marker

**Predictive Marker** ↔ Treatment Response (Treatment Sensitivity)

**Prognostic Marker** ↔ Risk of Recurrence or Risk of Relapse

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Ongoing studies – Idea Trial...

Eligible patients

- ER+, LUM A or LUM B
- pre/post
- candidate to chemotherapy according to the treating doctor

“soft” chemo → optimal HT
(CMF, AC, TC, weekly paclitaxel)

“intensive” chemo → optimal HT
(A → T for ± 6 months)

Separate analysis for LUM A and LUM B cohorts

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Even within ER+ subtype – a heterogeneous population
Not just luminal BC disease...
A considerable proportion of EBC not receiving adjuvant systemic chemotherapy actually do not relapse...

Bonadonna G et al, BMJ 2005

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Current Limitations or Challenges…

- There is no specific biomarkers to predict which patient is of high risk disease besides the histopathological status.
- There is no predictive biomarkers for specific chemotherapy regimen.
- Prognostic value of molecular subtypes.
## Individualized Test Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Selection</strong></td>
<td>HER2 (Anti-HER-2 targeted agents) ER+ (Tamoxifen/Aromatase Inhibitors)</td>
</tr>
<tr>
<td><strong>Drug Dosage</strong></td>
<td>• Not yet available</td>
</tr>
<tr>
<td><strong>Drug Efficacy</strong></td>
<td>• Not yet available</td>
</tr>
<tr>
<td><strong>Disease Status</strong></td>
<td>• Not yet available</td>
</tr>
</tbody>
</table>
| **Recurrence Risk**| • Mammaprint/Oncotype Dx  
|                   | • Prosigna (PAM50)/Endopredict  
|                   | • Multivariate analysis  
|                   | • uPA/PAI-1 (node negative)  |
| **Predisposition**| • BRCA-1/2                                                              |

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- 6,600 pts < 70
  - FEB 2007-AUG 2011
  - 11,291 registered pts
  - 6,673 enrolled (59.1%)
The MINDACT population: CT assignment according to a “Clinical” vs a “Genomic” strategy

Whole population N = 6,693

- N=2745 clinical Low/ genomic Low
- N=592 clinical Low/ genomic High
- N=1550 clinical High/ genomic Low
- N=1806 clinical High/ genomic High

«Clinical» strategy
CT to 1550 + 1806 = 3,356 pts = 50 %

«Genomic» strategy
CT to 592 + 1806 = 2,398 pts = 36 %

14% reduction

F. Cardoso, NEJM 2016
The MINDACT population: CT assignment according to a “Clinical” vs a “Genomic” strategy

**Population N = 6,693**

Please refer to the super excellent lecture by Professor Fatima Cardoso yesterday Day 1 (26\(^{th}\) November, 2018) on “Prognostic and predictive markers for breast cancer management” (Module 2).

![Image of Professor Fatima Cardoso with text](image)

---

F. Cardoso, NEJM 2016

---

CT to 592 + 1806 = 2,398 pts = 36 %

---

14% reduction
GENOMIC TESTS IN ALL OR ONLY SELECTED BREAST CANCER CASES?

TRIPLE NEGATIVE (ER-, PR-, HER-2 neg) → CT indispensable

LUMINAL ER+ HER-2 neg → “Clear” indication from classical factors

All LOW risk: high levels ER, PR, grade 1, node negative, low proliferation
All HIGH risk: low levels ER, PR, grade 3, node positive, high proliferation

“No Clear” indication from classical factors; some high & some low risk

CRUCIAL IMPORTANCE OF HIGH QUALITY PATHOLOGY

HT alone → CT → HT

HER-2 POSITIVE → CT + anti-HER indispensable

GENOMIC TEST

Courtesy of Professor Fatima Cardoso, ESMO 2017

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Neoadjuvant Chemotherapy for Luminal Breast Cancer
Efficacy of Neoadjuvant Chemotherapy ⇔ Adjuvant Chemotherapy

Wolmark, JNCI Mongr 2001, Maurl JNCI 2005

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Objectives of Neoadjuvant Chemotherapy (NACT)
Also known as “Primary Systemic Therapy”

- For technically inoperable primary breast tumour to become technically operable
- For tumour only deemed for mastectomy to become also eligible for BCT
- Down-size thus down-staging the disease
- Control occult metastases
- To assess treatment response with serial monitoring (*In vivo* chemosensitivity test)
- Information on prognosis –no residual cancer after NACT correlates with good prognosis
- To achieve better outcome esp high chance of complete pathological response, e.g. *HER2* positive and *triple negative disease*.
Those with G3 tumour, ER and PgR negative and TNC do better…
I-SPY: Neoadjuvant Chemotherapy for Breast Cancer and Biomarker Analysis

I-SPY: study to identify biomarkers of response to neoadjuvant CT

<table>
<thead>
<tr>
<th></th>
<th>ER (P &lt; .0001)</th>
<th>PgR (P &lt; .0001)</th>
<th>HER2 (P = .02)</th>
<th>Ki67 Index (P &lt; .0001)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+ (n = 115)</td>
<td>- (n = 88)</td>
<td>+ (n = 95)</td>
<td>- (n = 107)</td>
</tr>
<tr>
<td></td>
<td>- (n = 95)</td>
<td>+ (n = 28)</td>
<td>+ (n = 28)</td>
<td>Low (n = 50)</td>
</tr>
<tr>
<td></td>
<td>+ (n = 137)</td>
<td>- (n = 137)</td>
<td></td>
<td>Int (n = 62)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High (n = 70)</td>
</tr>
<tr>
<td>pCR*</td>
<td>16%</td>
<td>44%</td>
<td>12%</td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td>43%</td>
<td>39%</td>
<td>18%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>16%</td>
<td>16%</td>
<td>43%</td>
<td>43%</td>
</tr>
</tbody>
</table>

- Tumor basal (ER+/PgR-/HER2-) and luminal B (ER+/PgR+/HER2+) and HER2 (ER-/PgR-/HER2+) associated with higher pCR rates
- Luminal A (ER+/PgR+/HER2+) showed low pCR (9%)
- ER-/HER2+ tumors showed higher pCR (88%) compared to ER+/HER2+ tumors (25%)

The implication of pCR in Luminal Breast Cancer…

Cortazar, Lancet 2014
Association between pCR and EFS by BC subtype

Is pCR really important in luminal BC?

- **luminal A tumors**
  - Proportion Disease Free
  - Disease-Free Survival (months)
  - Log-rank
  - pCR (n = 106)
  - no pCR (n = 1,323)
  - Log-rank
  - P = .388

- **luminal B HER2(+) tumors**
  - Proportion Disease Free
  - Disease-Free Survival (months)
  - Log-rank
  - pCR (n = 126)
  - no pCR (n = 925)
  - Log-rank
  - P = .495

6,377 patients treated with neoadjuvant anthracycline-taxane based chemotherapy

 Patients achieving pCR

von Minckwitz, JCO 2012
NCCN Guidelines Version 3.2018
Invasive Breast Cancer

PREOPERATIVE/ADJUVANT THERAPY REGIMENS\textsuperscript{1,2,3,4,5}

HER2-Negative\textsuperscript{6}
- **Preferred regimens:**
  - Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks\textsuperscript{2}
  - Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel\textsuperscript{7}
  - TC (docetaxel and cyclophosphamide)
- **Useful in certain circumstances:**
  - Dose-dense AC (doxorubicin/cyclophosphamide)
  - AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B)
  - CMF (cyclophosphamide/methotrexate/fluorouracil)
  - AC followed by weekly paclitaxel
- **Other recommended regimens:**
  - AC followed by docetaxel every 3 weeks
  - EC (epirubicin/cyclophosphamide)
  - TAC (docetaxel/doxorubicin/cyclophosphamide)

HER2-Positive
- **Preferred regimens:**
  - AC followed by T + trastuzumab\textsuperscript{8}
    - (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules)
  - AC followed by T + trastuzumab + pertuzumab\textsuperscript{8}
    - (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab plus pertuzumab)
  - Paclitaxel + trastuzumab\textsuperscript{8}
  - TCH (docetaxel/carboplatin/trastuzumab)
  - TCH (docetaxel/carboplatin/trastuzumab) + pertuzumab
- **Useful in certain circumstances:**
  - Docetaxel + cyclophosphamide + trastuzumab
- **Other recommended regimens:**
  - AC followed by docetaxel + trastuzumab\textsuperscript{8}
    - (doxorubicin/cyclophosphamide followed by docetaxel plus trastuzumab)
  - AC followed by docetaxel + trastuzumab + pertuzumab\textsuperscript{8}
    - (doxorubicin/cyclophosphamide followed by docetaxel plus trastuzumab plus pertuzumab)

---
\textsuperscript{1}Retrospective evidence suggests that anthracycline-based chemotherapy regimens may be superior to non-anthracycline-based regimens in patients with HER2-positive tumors.
\textsuperscript{2}Randomized clinical trials demonstrate that the addition of a taxane to anthracycline-based chemotherapy provides an improved outcome.
\textsuperscript{3}CMF and radiation therapy may be given concurrently, or the CMF may be given first. All other chemotherapy regimens should be given prior to radiation therapy.
\textsuperscript{4}Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy.
\textsuperscript{5}Nab-paclitaxel may be substituted for paclitaxel or docetaxel due to medical necessity (e.g., hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of nab-paclitaxel should not exceed 125 mg/m\textsuperscript{2}.
\textsuperscript{6}The regimens listed for HER2-negative disease are all category 1 (except where indicated) when used in the adjuvant setting.
\textsuperscript{7}It would be acceptable to change the administration sequence to paclitaxel followed by dose-dense AC.
\textsuperscript{8}Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
\textsuperscript{9}Paclitaxel + trastuzumab may be considered for patients with low-risk T1,N0,I0, HER2 positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities.
Holistic Multidisciplinary Team (MDT) Approach

Breast Cancer Patients

Clinical Oncologists
Supporting Staff
Surgeons
Pathologists
Nurse Specialists
Clinical Psychologists
Medical Social Workers
Physiotherapists
Occupational Therapists
Dietitians

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