Module 7: Luminal Breast Cancer (LBC)

Defining a role for chemotherapy in early LBC

Dr. Janice Tsang
MBBS, MRCP(UK), FRCP(Lond.), FRCP (Edin.), FHKCP, FHKAM(Medicine)
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)
26th November, 2019

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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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Defining a role for chemotherapy in early 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** (23 August, 1918 – 16 October, 2019), 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...
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%
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

Table 2. Surrogate definitions of intrinsic subtypes of breast cancer [23]

<table>
<thead>
<tr>
<th>Intrinsic subtype</th>
<th>Clinicopathological surrogate definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>'Luminal A-like' ER-positive</td>
</tr>
<tr>
<td></td>
<td>HER2-negative</td>
</tr>
<tr>
<td></td>
<td>Ki67 low&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>PgR high&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Low-risk molecular signature (if available)</td>
</tr>
<tr>
<td>Luminal B</td>
<td>'Luminal B-like (I HER2-negative)' ER-positive</td>
</tr>
<tr>
<td></td>
<td>HER2-negative</td>
</tr>
<tr>
<td></td>
<td>and either Ki67 high or PgR low</td>
</tr>
<tr>
<td></td>
<td>High-risk molecular signature (if available)</td>
</tr>
<tr>
<td></td>
<td>'Luminal B-like (I HER2-positive)' ER-positive</td>
</tr>
<tr>
<td></td>
<td>HER2-positive</td>
</tr>
<tr>
<td></td>
<td>Any Ki67</td>
</tr>
<tr>
<td></td>
<td>Any PgR</td>
</tr>
<tr>
<td>HER2</td>
<td>'HER2-positive (non-luminal)'</td>
</tr>
</tbody>
</table>

Cardoso F. Annals of Oncology 2019
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

EBCTCG Lancet, 2012

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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>
<thead>
<tr>
<th>(A)</th>
<th>Cumulative anthracycline doses, if dose per cycle is at least AUC/2 (tried 3.0 to 2: p=0.035)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated anthracycline</td>
</tr>
<tr>
<td>Age of enrolment</td>
<td>30% (45)</td>
</tr>
<tr>
<td></td>
<td>50% (34)</td>
</tr>
<tr>
<td></td>
<td>15% (38)</td>
</tr>
<tr>
<td></td>
<td>10% (20)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(B)</th>
<th>Cytochalasan/thalidomid/CMF (or) (1.5 x 3.0, 3.0, 3.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cytosar A</td>
</tr>
<tr>
<td></td>
<td>80% (34)</td>
</tr>
<tr>
<td></td>
<td>40% (34)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(C)</th>
<th>Concurrent endocrine therapy (E+D+C) (1.5 x 3.0, 3.0, 3.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>57% (34)</td>
</tr>
<tr>
<td></td>
<td>43% (34)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(D)</th>
<th>History age (50 years) (1.5 x 3.0, 3.0, 3.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>45+ years</td>
</tr>
<tr>
<td></td>
<td>60% (34)</td>
</tr>
<tr>
<td></td>
<td>40% (34)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(E)</th>
<th>Histological type (1.5 x 3.0, 3.0, 3.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Invasive</td>
</tr>
<tr>
<td></td>
<td>60% (34)</td>
</tr>
<tr>
<td></td>
<td>40% (34)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(F)</th>
<th>Subtypes of ER+ (1.5 x 3.0, 3.0, 3.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ER+=20%</td>
</tr>
<tr>
<td></td>
<td>60% (34)</td>
</tr>
<tr>
<td></td>
<td>40% (34)</td>
</tr>
</tbody>
</table>

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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

(F) ER status ($\chi^2=0.1; 2p=0.7; \text{NS}$)

<table>
<thead>
<tr>
<th>ER Status</th>
<th>$n$</th>
<th>$95%$ CI</th>
<th>$n$</th>
<th>$95%$ CI</th>
<th>Difference</th>
<th>SE 0.07</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER-poor</td>
<td>403/1095 (36.8%)</td>
<td>464/1043 (44.5%)</td>
<td>-40.5</td>
<td>180.4</td>
<td>0.80 (SE 0.07)</td>
<td></td>
</tr>
<tr>
<td>ER+</td>
<td>831/3100 (26.8%)</td>
<td>1063/3177 (33.5%)</td>
<td>-84.6</td>
<td>328.5</td>
<td>0.77 (SE 0.05)</td>
<td></td>
</tr>
<tr>
<td>ER unknown</td>
<td>182/559 (32.6%)</td>
<td>174/513 (33.9%)</td>
<td>-14.9</td>
<td>72.3</td>
<td>0.81 (SE 0.11)</td>
<td></td>
</tr>
</tbody>
</table>

Subsets of ER+

- ER+, chemotherapy + endocrine vs endocrine
- ER 10–99 fmol/mg
- ER $\geq$100 fmol/mg
- ER+, age $<$55 years
- ER+, age 55–69 years
- ER+, poorly differentiated
- ER+, moderately/well differentiated

Total

| Total               | 1416/4754 (29.8%) | 1701/4733 (35.9%) | -139.9 | 581.3 | 0.786 (SE 0.037) |

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.
Who responds to anthracycline better?

3452 patients: CMF vs anthracyclins

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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

Bedard & Cardoso. Nature Reviews Clinical Oncology 2011 8(272-279)
(Neo)adjvant 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 uncertainty. *Relative* indications for adjuvant chemotherapy are poorly differentiated G3 tumors, lymph node involvement (pN+), a 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 1. 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 1. 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 decision. If the primary tumor is very small (≤1cm pN0) and there are no additional negative criteria...
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; 4Breast Unit, Champalimaud Clinical Center, Lisbon, Portugal

incidence and epidemiology

In 2012, the estimated age-adjusted annual incidence of breast cancer in 40 European countries was 94.3/100,000 and the mortality rate was 18.8/100,000 women [8]. Mammography screening has been shown to reduce mortality in the general population at risk of breast cancer and is recommended for women aged 50-70 years in the UK and USA, the European Union and numerous individual countries [9]. The evidence for effectiveness of mammography is strongest for women aged 50-69 years and is weaker for women aged 70 years or over [3,9].
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.

![Image](image_url)
Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. Cardoso1, S. Kyriakides2, S. Ohno3, F. Penault-Llorca4,5, P. Poortmans6,7, I. T. Rubio8, S. Zackrisson9 & E. Senkus10, on behalf of the ESMO Guidelines Committee*

1Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal; 2Europa Donna Cyprus, Nicosia, Cyprus; 3Breast Oncology Center, Cancer Institute Hospital, Tokyo, Japan; 4Department of Pathology, Centre Jean Perrin, Clermont-Ferrand; 5UMR INSERM 1240, IMaST Université d’Auvergne, Clermont-Ferrand; 6Department of Radiation Oncology, Institut Curie, Paris; 7Paris Sciences & Lettres – PSL University, Paris, France; 8Breast Surgical Oncology Unit, Clínica Universidad de Navarra, Madrid, Spain; 9Department of Translational Medicine, Diagnostic Radiology, Lund University and Skåne University Hospital Malmö, Malmö.
**Figure 1.** Early breast cancer treatment algorithm.

- Biology that requires ChT (TNBC, HER2-positive, luminal B-like), to assess response and prognosis and eventually decide on postoperative therapies, should preferentially receive preoperative ChT.
- Aggressive phenotypes: TNBC or HER2-positive breast cancer.
- If ChT is planned, it should all be given as neoadjuvant.
- Concomitant postoperative RT, postoperative ET and anti-HER2 therapy.
- BCS, breast-conserving surgery; ChT, chemotherapy; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; RT, radiotherapy; TNBC, triple-negative breast cancer.
Defining a role for chemotherapy depends on...

- **Tumour burden**
  - Tumour size
  - Grade
  - Histological subtypes
  - ER/PR and HER2 status
  - Presence of lymphovascular invasion
  - Proliferation (Ki-67)

- **Presumed responsiveness to endocrine therapy**

- **Patient’s preference**

Cardoso F. Annals of Oncology 2019
<table>
<thead>
<tr>
<th>Subtype</th>
<th>Recommended therapy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A-like</td>
<td>ET alone in the majority of cases</td>
<td>Consider ChT if high tumour burden (≥ 4 LNs, T3 or higher)</td>
</tr>
<tr>
<td>Luminal B-like (HER2-negative)</td>
<td>ChT followed by ET for the majority of cases</td>
<td>If contraindications for the use of ChT, one may consider ET + anti-HER2 therapy, although no randomised data exist</td>
</tr>
<tr>
<td>Luminal B-like (HER2-positive)</td>
<td>ChT + anti-HER2 followed by ET for all patients</td>
<td></td>
</tr>
<tr>
<td>HER2-positive (non-luminal)</td>
<td>ChT + anti-HER2</td>
<td></td>
</tr>
<tr>
<td>Triple-negative (ductal)</td>
<td>ChT</td>
<td></td>
</tr>
</tbody>
</table>

For special histological types, the authors recommend following the St Gallen recommendations [23] that propose ET for endocrine-responsive histologies (cribriform, tubular and mucinous), ChT for high-risk endocrine-nonresponsive histologies (medullary, metaplastic) and no systemic therapy for low-risk endocrine nonresponsive histologies (adenoid cystic and apocrine).

ChT, chemotherapy; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; LN, lymph node.
Precision Medicine for (Neo)adjuvant Chemotherapy Luminal EBC
Figure 2. (Neo)-adjuvant systemic treatment choice by marker expression and intrinsic phenotype.

*With possible exception of selected cases with very low risk T1abN0.

1 Anti-HER2: trastuzumab ± pertuzumab.

2 Adenoid cystic or apocrine, secretory carcinoma, low-grade metaplastic carcinoma.

3 Depending on level of ER and PgR expression, proliferation, genomically assessed risk, tumour burden and/or patient preference.

4 Except for very low-risk patients T1abN0 for whom ET/anti-HER2 therapy alone can be considered.

ChT, chemotherapy; ER, oestrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; N0, node-negative; PgR, progesterone receptor; TNBC, triple-negative breast cancer.
Predictive Marker vs Prognostic Marker

**Predictive Marker**

Treatment Response (Treatment Sensitivity)

**Prognostic Marker**

Risk of Recurrence or Risk of Relapse
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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Breast Cancer is a heterogeneous disease...

- Breast cancer is a *heterogeneous* disease comprised of different molecular subtypes based on gene/protein expression profiling.

---

Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications

Therese Soerlie\(^{a,b}\), Charles M. Perou\(^{c,d}\), Robert Tibshirani\(^{e}\), Turid Aas\(^{a}\), Stephanie Geisler\(^{f}\), Hilde Johnsen\(^{g}\), Trevor Hastie\(^{e}\), Michael B. Eisen\(^{b}\), Matt van de Rijn\(^{h}\), Stefanie S. Jeffrey\(^{i}\), Thor Thorsen\(^{h}\), Hanne Quist\(^{j}\), John C. Matses\(^{k}\), Patrick O. Brown\(^{l}\), David Botstein\(^{m}\), Per Eystein Lønning\(^{n}\), and Anne-Lise Berresem-Dalh\(^{m}\)

Departments of \(^{a}\)Genetics and Surgery, The Norwegian Radium Hospital, Montebello, N-0319 Oslo, Norway; \(^{b}\)Department of Genetics and Linebøgner Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC 27599; Departments of \(^{c,d}\)Health Research and Policy and Statistics, \(^{e}\)Genetics, Pathology, Surgery, and \(^{f}\)Biochemistry and Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, CA 94305; Departments of \(^{g}\)Medical Genetics and \(^{h}\)Biochemical Endocrinology, Haukeland University Hospital, N-5021 Bergen, Norway; and \(^{i}\)Life Sciences Division, Lawrence Orlando Berkeley National Laboratories, and \(^{j}\)Department of Molecular and Cellular Biology, University of California, Berkeley, CA 94720

Contributed by David Botstein, July 17, 2001

The purpose of this study was to classify breast carcinomas based on variations in gene expression patterns derived from cDNA microarrays and to correlate tumor characteristics to clinical outcome. A total of 85 cDNA microarray experiments representing 78 cancers, three fibroadenomas, and four normal breast tissues were analyzed by hierarchical clustering. As reported previously, the cancers could be classified into a basal epithelial-like group, an ESR12-overexpressing group, and a normal breast-like group based on unsupervised hierarchical clustering. Several studies show that the correlations between gene expression patterns and clinically relevant parameters. We found that classification of tumors based on gene expression patterns can be used as a prognostic marker with respect to overall and relapse-free survival in a subset of patients that had received uniform therapy. One finding was the separation of estrogen receptor (ER)-positive tumors into at least two distinctive groups with characteristic gene expression profiles and different prognoses.
Changing Portraits of Breast Cancer over the past decades...

claudin low
Lum A  Lum B  Basal  Her2
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
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.
PROGNOSTIC VALUE OF SUBTYPES IHC SURROGATES

CRUCIAL ROLE OF HIGH-QUALITY PATHOLOGY (and also cost-effective!)
PATIENT SELECTION (individualized treatment): HOW?

2 MAIN QUESTIONS TO BE ANSWERED

WHO NEEDS TREATMENT?

WHICH TREATMENT IS BEST?

TREATMENT CHOICES

AVOID UNDER AND OVER TREATMENT

INDIVIDUALIZE TREATMENT

New/better PROGNOSTIC FACTORS

New/better PREDICTIVE FACTORS

Courtesy of Professor Fatima Cardoso, ESMO ASIA 2019
### Individualized Test Categories

| Drug Selection          | HER2 (Anti-HER-2 targeted agents)  
<table>
<thead>
<tr>
<th></th>
<th>ER+ (Tamoxifen/Aromatase Inhibitors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Dosage</td>
<td>Not yet available</td>
</tr>
<tr>
<td>Drug Efficacy</td>
<td>Not yet available</td>
</tr>
<tr>
<td>Disease Status</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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Avoiding unnecessary medical care can save your life.
# Clinical Implementation of Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th></th>
</tr>
</thead>
</table>
| **Analytical Validation**  | • Accuracy and prediction in measurement of the analytes  
                             | • Robustness                 |
| **Clinical Validation**    | • Correlation of score/classifier with clinical state or outcome |
| **Clinical Utility**       | • Actionable (could affect treatment)  
                             | • Use results for patient benefit |

Courtesy F. Penault-Llorca
## Diagnostic Breast Cancer Assay: Comparative Chart

<table>
<thead>
<tr>
<th></th>
<th>Prosigna PAM50</th>
<th>RT-qPCR</th>
<th>Microarray</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Company</strong></td>
<td>nanoString</td>
<td>GHI</td>
<td>MammaPrint</td>
</tr>
<tr>
<td><strong>CE/FDA Cleared</strong></td>
<td>Yes/Yes 510K</td>
<td>No/No</td>
<td>Agendia</td>
</tr>
<tr>
<td><strong>Model</strong></td>
<td>Decentralized</td>
<td>Centralized</td>
<td>Centralized</td>
</tr>
<tr>
<td><strong>Genes measured</strong></td>
<td>50 + 8 reference</td>
<td>16 + 5 reference</td>
<td>80</td>
</tr>
<tr>
<td><strong>Patient Type</strong></td>
<td>Postmenopausal, HR+, node – or +, early stage</td>
<td>Pre or Post, ER+, HER2 - , node – or +, early stage; DCIS</td>
<td>Pre or Post, HR+, node-, early stage, tumor &lt;5cm (node + outside US)</td>
</tr>
<tr>
<td><strong>Classification</strong></td>
<td>Low, Intermediate, High</td>
<td>Low, Intermediate, High</td>
<td>Low, High</td>
</tr>
<tr>
<td><strong>Intrinsic Subtype</strong></td>
<td>Ex-US: Luminal A, B, HER2-Enriched, Basel-Like</td>
<td>No</td>
<td>Requires Blueprint</td>
</tr>
<tr>
<td><strong>Sample</strong></td>
<td>FFPE</td>
<td>FFPE CNB accepted</td>
<td>FFPE, Frozen</td>
</tr>
<tr>
<td><strong>Turnaround time</strong></td>
<td>As few as 3 days</td>
<td>7-10 days</td>
<td>10 days</td>
</tr>
<tr>
<td><strong>Guideline Inclusion</strong></td>
<td>ASCO, NCCN, ESMO</td>
<td>ASCO, NCCN, ESMO</td>
<td>ASCO, ESMO, St. Gallen</td>
</tr>
<tr>
<td><strong>Microarray</strong></td>
<td>MammaPrint</td>
<td>Agendia</td>
<td>Agendia</td>
</tr>
<tr>
<td></td>
<td>BluePrint</td>
<td>No/No</td>
<td>NA</td>
</tr>
</tbody>
</table>
Trial Assigning Individualized Options for Treatment (TAILORx):

Phase III trial of chemoendocrine therapy versus endocrine therapy alone in hormone receptor-positive, HER2-negative, node-negative breast cancer and an intermediate prognosis 21-gene recurrence score


on behalf of the TAILORx Investigators

Canadian Cancer Trials Group
ECOG-ACRIN Cancer Research Group
National Cancer Institute
SWOG
Alliance for Clinical Trials in Oncology
Reshaping the future of patient care

Presented at: 2018 ASCO Annual Meeting
Presented by: Joseph A. Sparano, MD
TAILORx Methods: Treatment Assignment & Randomization
Accrued between April 2006 – October 2010

Preregister - Oncotype DX RS (N=11,232)
⇒ Register (N=10,273)

- ARM A: Low RS 0-10 (N=1629 evaluable)
  ASSIGN
  Endocrine Therapy (ET)

- Mid-Range RS 11-25 (N=6711 evaluable)
  **RANDOMIZE**
  Stratification Factors: Menopausal Status, Planned Chemotherapy, Planned Radiation, and RS 11-15, 16-20, 21-25

  - ARM B: Experimental Arm (N=3399)
    ET Alone

  - ARM C: Standard Arm (N=3312)
    ET + Chemo

- ARM D: High RS 26-100 (N=1389 evaluable)
  ASSIGN
  ET + Chemo

PRESENTED AT: 2018 ASCO ANNUAL MEETING
#ASCO18
PRESENTED BY: Joseph A. Sparano, MD

ECOG-ACRIN
Cancer Research Group
Reshaping the future of patient care
**TAILORx Results - ITT Population: All Arms (A,B,C & D)**

**9-Year Event Rates**

- **RS 0-10 (Arm A)**
  - 3% distant recurrence with ET alone

- **RS 11-25 (Arms B & C)**
  - 5% distant recurrence rate overall
  - ≤ 1% difference for all endpoints
    - IDFS (83.3 vs. 84.3%)
    - DRFI (94.5 vs. 95.0%)
    - RFI (92.2 vs. 92.9%)
    - OS (93.9 vs. 93.8%)

- **RS 26-100 (Arm D)**
  - 13% distant recurrence despite chemo + ET

---

**Number at risk**

<table>
<thead>
<tr>
<th>Months</th>
<th>Arm A</th>
<th>Arm B</th>
<th>Arm C</th>
<th>Arm D</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1619</td>
<td>3399</td>
<td>3312</td>
<td>1389</td>
</tr>
<tr>
<td>12</td>
<td>1568</td>
<td>3293</td>
<td>3204</td>
<td>1291</td>
</tr>
<tr>
<td>24</td>
<td>1523</td>
<td>3194</td>
<td>3104</td>
<td>1174</td>
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<td>36</td>
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<td>3081</td>
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<td>48</td>
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<td>60</td>
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<td>2741</td>
<td>2645</td>
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</tr>
<tr>
<td>72</td>
<td>1153</td>
<td>2431</td>
<td>2335</td>
<td>463</td>
</tr>
<tr>
<td>84</td>
<td>867</td>
<td>1859</td>
<td>1781</td>
<td>329</td>
</tr>
<tr>
<td>96</td>
<td>511</td>
<td>1197</td>
<td>1130</td>
<td>187</td>
</tr>
<tr>
<td>108</td>
<td>213</td>
<td>537</td>
<td>523</td>
<td>77</td>
</tr>
</tbody>
</table>

---

**IDFS Probability**

- P < 0.001

**DFS Probability**

- RS 0-10: Assigned to ET Alone
- RS 11-25: Randomized to ET Alone
- RS 11-25: Randomized to CHEMO + ET
- RS 25-100: Assigned to CHEMO + ET
TAILORx Results - ITT Population: Potential Chemotherapy Benefit in Women ≤ 50 Years (N=2216) in RS 11-25 Arms

- **RS 16-25 - some chemo benefit**
  - **RS 16-20**: 9% fewer IDFS events, including 2% fewer distant recurrences
  - **RS 21-25**: 6% fewer IDFS events, mainly consisting of fewer distant recurrences

- **RS 0-15 - good prognosis with endocrine therapy**
  - 3% distant recurrence with ET alone
  - no evidence for chemo benefit in RS 11-15
TAILORx Results: Association between Continuous RS 11-25 and 9-Year Distant Recurrence Rate by Treatment Arms Stratified by Age (<\=50 vs. >50 Years)

\[
\begin{align*}
\text{\leq 50 years (N=2216)} & \\
\text{\geq 50 years (N=4495)} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Adjusted for tumor size and grade} & \\
\end{align*}
\]

RS modeled with a natural spline with 2 degrees of freedom, adjusted for tumor size and grade
TAILORx Results: Summary

**Primary conclusions**

- **RS 11-25**: ET was non-inferior to chemotherapy + ET (primary endpoint - ITT)

- **RS 0-10**: Distant recurrence rates very low (2-3%) with ET alone at 9 years

- **RS 25-100**: Significantly higher event rates, driven by more recurrences despite adjuvant chemo plus ET

**Other observations**

- **Age – RS – Chemo treatment interaction:**
  - Some chemo benefit in women 50 or younger with a RS 15-25
  - Greatest impact on distant recurrence with RS 21-25
PlanB:
Recurrence Score by (central) Ki-67

RS result
- >30
- 26-30
- 19-25
- 12-18
- 0-11

Ki-67
0-9 n = 509
10-19 n = 910
20-29 n = 592
30-39 n = 160
>39 n = 99

Courtesy of Nadia Harbeck
WSG GmbH
Gluz et al. JCO 2016
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=1806 clinical High/ genomic High
- N=592 clinical Low/ genomic High
- N=1550 clinical High/ genomic Low

«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
Practical use of Mammaprint® in the clinic based on evidence from the MINDACT trial

HR+ tumor: Define clinical risk

Clinical “low” risk*
- Treatment according to guidelines

Clinical “high” risk
- Discuss with patient if she would value a 1.5% gain in DMFS with adjuvant chemotherapy
  - No
    - Order Mammaprint
  - Yes
    - Proceed with chemotherapy

* Courtesy M. Piccart
Recommends clinician may use PAM50/Prosigna in conjunction with other clinicopathologic variables, to guide decisions on adjuvant systemic therapy for women with Node-negative ESBC.

An overview of the Early Breast Cancer Trialists Collaborative Group suggested that the reduction of risk of recurrence (ROR) with adjuvant chemotherapy is at least 30%. Therefore, adjuvant chemotherapy would improve a patient’s odds of distant, incurable recurrence by approximately 15% to 20% (one-third of the 5% to 60% initial risk). Several studies have suggested that the odds of fatal, life-threatening, or permanent life-changing toxicities are at least 2% to 3% in healthy women who participate in prospective trials.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Evidence Characteristics</th>
<th>OncotypeDx (RS)</th>
<th>Prosigna (PAM50 ROR)</th>
<th>EndoPredict (EPClin)</th>
<th>Mammaprint</th>
<th>Breast Cancer Index</th>
<th>IHC4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Node-Negative</strong></td>
<td><strong>Type</strong></td>
<td>Evidence</td>
<td>Evidence</td>
<td>Evidence</td>
<td>Evidence</td>
<td>Evidence</td>
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</tr>
<tr>
<td></td>
<td><strong>Evidence Quality</strong></td>
<td>High</td>
<td>High</td>
<td>Intermediate</td>
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<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Strength of</strong></td>
<td>Strong</td>
<td>Strong</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
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</tr>
<tr>
<td></td>
<td><strong>Recommendation</strong></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td><strong>ER/PgR-positive, Her2-negative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Node-Positive</strong></td>
<td><strong>Type</strong></td>
<td>Evidence</td>
<td>Evidence</td>
<td>Evidence</td>
<td>Evidence</td>
<td>Consensus</td>
<td></td>
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<tr>
<td></td>
<td><strong>Evidence Quality</strong></td>
<td>Intermediate</td>
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<td>Insufficient</td>
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<td>Insufficient</td>
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<tr>
<td></td>
<td><strong>Strength of</strong></td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Strong</td>
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<tr>
<td></td>
<td><strong>Recommendation</strong></td>
<td></td>
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<tr>
<td><strong>ER/PgR-positive, Her2-negative</strong></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

HK$ 40000 (US$ 5130)  HK$ 35000 (US$ 4500)  HK$ 22000 (US$ 2820)  HK$ 25000 (US$ 3200)  Not A/V  Not A/V

*Mammaprint achieved recommendations for subsets of N0 and N1 patients based on MindACT in 2017 ASCO Biomarker Guideline update


This is the intellectual property of Dr. Janice Tsang. Please contact her at jwhtsang@hku.hk for permission to reprint and/or distribute.
DO GENOMIC TESTS REPLACE CLASSICAL PROGNOSTIC FACTORS OR ADD TO THEM?

Genomic

Clinico-pathological

Risk factors:  
- poor-vs-good  
- grade (2+3 vs 1)  
- ER-negative  
- node-positive  
- size >2cm  
- age >50y

Hazard ratio:  
- 3e-05  
- 1e-06  
- 0.05  
- 1e-07  
- 0.002  
- 0.5

P-value:  
- 0.004  
- 0.03  
- 0.9  
- 0.2  
- 0.006  
- 0.5

untivar. multivar.

Clinico-pathological

Risk factors:  
- poor-vs-good  
- grade (2+3 vs 1)  
- ER-negative  
- node-positive  
- size >2cm  
- age >50y

Hazard ratio:  
- 2e-09  
- 2e-09  
- 0.0003  
- 6e-07  
- 1e-05  
- 0.3

P-value:  
- 9e-05  
- 0.1  
- 0.01  
- 1e-06  
- 0.003  
- 0.2

untivar. multivar.

Untreated  

Treated

C. Sotiriou et al
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

HER-2 POSITIVE
- CT + anti-Her indispensable

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

CRUCIAL IMPORTANCE OF HIGH QUALITY PATHOLOGY

HT alone
- CT → HT
- GENOMIC TEST

Courtesy of Professor Fatima Cardoso, ESMO 2017

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**SYSTEMIC ADJUVANT TREATMENT: NODE-NEGATIVE - HORMONE RECEPTOR-POSITIVE - HER2-NEGATIVE DISEASE**

<table>
<thead>
<tr>
<th>Tumor ≤0.5 cm</th>
<th>pN0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider adjuvant endocrine therapy&lt;sup&gt;aa,bb&lt;/sup&gt; (category 2B)</td>
<td></td>
</tr>
<tr>
<td>Adjuvant endocrine therapy&lt;sup&gt;aa,bb&lt;/sup&gt; or Adjuvant chemotherapy&lt;sup&gt;cc,dd&lt;/sup&gt; followed by endocrine therapy&lt;sup&gt;aa,bb&lt;/sup&gt; (category 1)</td>
<td></td>
</tr>
<tr>
<td>Not done</td>
<td></td>
</tr>
<tr>
<td>Recurrence score &lt;26&lt;sup&gt;ii&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Adjuvant endocrine therapy&lt;sup&gt;aa,bb,ij&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Recurrence score 26–30</td>
<td></td>
</tr>
<tr>
<td>Adjuvant endocrine therapy&lt;sup&gt;aa,bb&lt;/sup&gt; or Adjuvant chemotherapy&lt;sup&gt;cc,dd&lt;/sup&gt; followed by endocrine therapy&lt;sup&gt;aa,bb&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Recurrence score ≥31</td>
<td></td>
</tr>
<tr>
<td>Adjuvant endocrine therapy&lt;sup&gt;aa,bb&lt;/sup&gt; + adjuvant chemotherapy&lt;sup&gt;cc,dd&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

---

<sup>d</sup> See Principles of HER2 Testing (BINV-A).

<sup>y</sup> See Special Considerations for Breast Cancer in Men (BINV-J).

<sup>z</sup> Mixed lobular and ductal carcinoma should be graded based on the ductal component and treated based on this grading. For metaplastic carcinoma, the prognostic value of the histologic grading is uncertain. However, when a specific histologic subtype of metaplastic carcinoma is present and accounts for more than 10% of the tumor, the subtype is an independent prognostic variable.

<sup>aa</sup> Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving endocrine therapy.

<sup>bb</sup> Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. See Adjuvant Endocrine Therapy (BINV-K).

<sup>cc</sup> Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable. See Adjuvant Endocrine Therapy (BINV-K) and Chemotherapy in Breast Cancer (BINV-I).

<sup>dd</sup> There are limited data to make chemotherapy recommendations for those >70 y of age. See NCCN Clinical Practice Guidelines for Older Adult Oncology.

<sup>HH</sup> Other prognostic multigene assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy. See Multigene Assays for Consideration of Addition of Adjuvant Systemic Chemotherapy to Adjuvant Endocrine Therapy (BINV-N).

<sup>ii</sup> Patients with T1b tumors with low-grade histology should be treated with endocrine monotherapy as the TAILORx trial did not include patients with such tumors.

<sup>ii</sup> Consider the use of adjuvant chemotherapy in women 50 years of age or younger with a recurrence score of 16–25 based on an exploratory analysis from the TAILORx study demonstrating lower distant recurrences in women 50 years of age.
SYSTEMIC ADJUVANT TREATMENT: NODE-POSITIVE - HORMONE RECEPTOR-POSITIVE - HER2-NEGATIVE DISEASE

- **pN1mi (≤2 mm axillary node metastasis) or N1kk (less than 4 nodes):**
  - Patient not a candidate for chemotherapy → Adjuvant endocrine therapy

- **Initial decision-making for adjuvant systemic chemotherapy based on:**
  - Clinical characteristics
  - Tumor stage
  - Pathology

- **Patient is a candidate for chemotherapy:**
  - Consider multigene assay to assess prognosis and determine chemotherapy benefit

- **Patient is a candidate for chemotherapy and multigene assay not available:**
  - Use clinical and pathologic features for decision-making

- **Adjuvant chemotherapy followed by endocrine therapy** (category 1)

- **Adjuvant endocrine therapy or Adjuvant chemotherapy followed by endocrine therapy** (category 1)

- **Follow-Up (BINV-17)**

---

**Histology:**
- Ductal
- Lobular
- Mixed
- Metaplastic

**Node positive (4 or more ipsilateral metastases >2 mm):**

---

See Principles of HER2 Testing (BINV-A).

See Special Considerations for Breast Cancer in Men (BINV-J).

Mixed lobular and ductal carcinoma should be graded based on the ductal component and treated based on this grading. For metaplastic carcinoma, the prognostic value of the histologic grading is uncertain. However, when a specific histologic subtype of metaplastic carcinoma is present and accounts for more than 10% of the tumor, the subtype is an independent prognostic variable.

Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant therapy.

Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. See Adjuvant Endocrine Therapy (BINV-K).

Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable. See Adjuvant Endocrine Therapy (BINV-K) and Preoperative/Adjuvant Therapy.

There are limited data to make chemotherapy recommendations for those >70 y of age. See NCCN Clinical Practice Guidelines for Older Adult Oncology.

In N1mi and N1, multigene assays are prognostic and not proven to be predictive of chemotherapy benefit but can be used to identify a low-risk population that when treated with proper endocrine therapy may derive little absolute benefit from chemotherapy. Regarding the 21-gene RT-PCR assay, a secondary analysis of a prospective trial suggests that the test is predictive for women 1–3 involved ipsilateral axillary lymph nodes. Other multigene assays have not proven to be predictive of chemotherapy benefit.

See Multigene Assays for Consideration of Addition of Adjuvant Systemic Chemotherapy to Adjuvant Endocrine Therapy (BINV-N).

There are few data regarding the role of multigene assays in women with four or more ipsilateral axillary lymph nodes. Decisions to administer chemotherapy in these patients should be made based on clinical judgment.
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. \( \text{HER2 positive} \) and \( \text{triple negative disease} \).
Those with G3 tumour, ER and PgR negative and TNC do better…

Huober, BCRT 2010
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 = 95)</td>
<td>+ (n = 28)</td>
<td>Low (n = 50)</td>
</tr>
<tr>
<td></td>
<td>16%</td>
<td>12%</td>
<td>39%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>- (n = 88)</td>
<td>- (n = 107)</td>
<td>- (n = 137)</td>
<td>Int (n = 62)</td>
</tr>
<tr>
<td></td>
<td>44%</td>
<td>43%</td>
<td>18%</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High (n = 70)</td>
</tr>
</tbody>
</table>

- Tumor basal (ER⁻/PgR⁻/HER2⁻), 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?

6,377 patients treated with neoadjuvant anthracycline-taxane based chemotherapy
### PREOPERATIVE/ADJUVANT THERAPY REGIMENS

**HER2-Negative**

<table>
<thead>
<tr>
<th>Preferred regimens:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks</td>
<td></td>
</tr>
<tr>
<td>Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel</td>
<td></td>
</tr>
<tr>
<td>TC (docetaxel and cyclophosphamide)</td>
<td></td>
</tr>
<tr>
<td>If triple-negative breast cancer and residual disease after preoperative therapy with taxane-, alkylator-, and anthracycline-based chemotherapy: capecitabine</td>
<td></td>
</tr>
</tbody>
</table>

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)
Our Future Directions…

**Young Patients**

“Quantity of life” – to strive to live longer

Family and social obligations – independent, and staying at home

**Oncologist’s perspective**

Investigations and Treatment
- RECIST
- NCI CTC V 4.0
- Survival (DFS, PFS, OS)
- “Fast-Moving” world

“Molecular Portrait”

**Elderly Patients**

“Quality of life” – to strive to live better

**Geriatrician’s perspective**

Diagnosis
- QoL
- functional status
- nutrition

“Global Portrait” – aging population

**GEP**

- Identifying individual patient who can be spared or benefitted from chemo (systemic therapy)

**CGA**

- Identifying individual elderly patient who will benefit from systemic therapy

**Genomic Defect**

- Targeted Therapy

**CGA Defect**

- Targeted Geriatric Intervention
Holistic Multidisciplinary Team (MDT) Approach

Breast Cancer Patients

DECISION MAKING TEAM

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

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