When is Chemotherapy indicated in Advanced Luminal Breast Cancer?

Soo-Chin Lee
Head & Senior Consultant
Department of Haematology-Oncology
National University Cancer Institute, Singapore

Senior Principal Investigator
Cancer Science Institute, Singapore
Who still cares about Chemotherapy for Luminal Breast Cancers in this era of CDK4/6 Inhibitors?
What is Luminal Breast Cancer?

**Intrinsic Subtypes by Gene Expression Profiling**

**LUMINAL A**  
**HER2 -**  
ER+/PR+ (high expression)  
Low grade  
Low proliferative index (Ki67)

**LUMINAL B (Heterogeneous group)**

**HER2 -**  
ER/PR+ (low expression)  
ER+/PR- OR ER-/PR+  
High grade/ High proliferative index (Ki67)

**HER2 +**  
ER and/or PR +  
Low/high grade  
Low/high proliferative index

Molecular testing (*e.g.*, PAM50) not routinely done in the clinic
Surrogate markers usually used (**ER, PR, HER2, grade, Ki67**)

**Concordance between surrogate markers vs gene expression profiling ~60-80%**

*Perou et al. PNAS 2001, 98(19): 10869-74*
Systemic Treatment Options for Luminal Breast Cancers

**LUMINAL A**
- HER2 -
- ER+/PR +
- Low grade
- Low proliferative index (Ki67)

**LUMINAL B**
- HER2 -
- ER/PR+ (low expression) OR ER+/PR- OR ER-/PR+
- High grade/ High proliferative index
- HER2 +
- ER and/or PR +
- Low/high grade
- Low/high proliferative index

- Endocrine Therapy*
- Chemotherapy

**Endocrine Therapy**
- Chemotherapy
- Anti-HER2 Therapy

*+-/- biological agent (CDK4/6 inhibitors, mTOR inhibitors)
General Principles in Treatment of Metastatic Breast Cancer

**Treatment goals (non-curative):**
- Prolong overall survival if possible
- Relieve symptoms, preserve quality of life

Treatment with higher **response rate** is preferred if tumor burden is high (to treat or prevent crisis)

Sequential treatment in metastatic breast cancer

- Treatment 1
- Treatment 2
- Treatment 3
- Treatment 4
- Treatment 5

**Treatment that prolongs overall survival** is preferentially given (usually in early line)

If none of the available treatment options improves overall survival, then the **least toxic effective regimen** is preferred
Chemotherapy vs Endocrine Therapy in Advanced Luminal Breast Cancers

1. Does chemotherapy confer a survival advantage (compared to endocrine therapy)?

2. Is there a subset of luminal breast cancers for which chemotherapy confers survival advantage?

3. Does chemotherapy have higher response rate than endocrine therapy to be a better choice when there is an impending crisis?

4. Is the tumor (still) sensitive to endocrine therapy?
Chemotherapy alone vs Endocrine Therapy alone for Metastatic Breast Cancer

Cochrane review; 10 trials (1963-1995)
OS data in 6 trials (n=692)

More toxicities with chemotherapy

Wilcken et al. Cochrane Library 2003
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HR+, HER2+ Metastatic Breast Cancer

Anti-HER2 + Endocrine Therapy improved PFS but not OS

**HER2+, HR+ MBC (TAnDEM)**

N=207 (Phase 3 randomized)

No prior chemo; prior hormonal therapy allowed

- **Trastuzumab + Anastrozole**
- **Letrozole**
- **Lapatinib + Letrozole**

**PFS**

<table>
<thead>
<tr>
<th>Events</th>
<th>Median PFS</th>
<th>95% CI</th>
<th>Hazard Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>87</td>
<td>4.8 months</td>
<td>3.7 to 7.0</td>
<td>0.63</td>
<td>.0016</td>
</tr>
<tr>
<td>99</td>
<td>2.4 months</td>
<td>2.0 to 4.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.8 vs 2.4 months  
P=0.0016

**OS**

28.5 vs 23.9 months, p=0.325

HER2+ Metastatic Breast Cancer

Anti-HER2 + Chemotherapy improved PFS and OS

**HER2+ MBC, First-line**
N=469, ~60% HR+

- Paclitaxel or anthracyclines
- Paclitaxel or anthracyclines
- Trastuzumab

**CLEOPATRA, HER2+ MBC**
First-line; N=808, ~50% HR+

- Trastuzumab + Docetaxel
- Trastuzumab + Docetaxel
- Pertuzumab

**Survival Analysis**

Median OS 20.3 vs 25.1 months, p=0.046

- Chemo + Trastuzumab
- Chemo

OS

40.8 vs 56.5 months
HR 0.68
P<0.001

Impact of First-line Treatments on Survival of HER2+ Metastatic Breast Cancer

Overall survival

- **Pertuzumab + trastuzumab + docetaxel (any HR), 56 months**
  
  *(CLEOPATRA, ~50% HR+)*

- **Trastuzumab + Endocrine (HR+), ~30 months**
- **Endocrine Therapy alone (HR+), ~30 months**
- **Trastuzumab + Chemo (any HR), 25 months**
- **Chemotherapy alone (any HR), 20 months**

*No trials comparing anti-HER2 agent + chemotherapy vs anti-HER2 agent + endocrine therapy for HR+/HER2+ MBC*

**Anti-HER2 therapy + chemotherapy is the preferred initial treatment in HER2+ luminal breast cancer in view of overall survival benefit**

*Exception:* older patient with limited life expectancy from other co-morbidities, very low disease burden (e.g., bone only), highly endocrine sensitive
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Chemotherapy alone vs Endocrine Therapy alone for Metastatic Breast Cancer

Cochrane review; 10 trials (1963-1995)
Treatment response data in 8 trials (n=817)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>endocrine therapy</th>
<th>chemotherapy</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed 95% CI</td>
<td></td>
<td>M-H,Fixed 95% CI</td>
</tr>
<tr>
<td>Coldenberg 1975</td>
<td>2/35</td>
<td>8/40</td>
<td>0.29 [0.06, 1.26]</td>
<td>7.0 %</td>
<td>0.29 [0.06, 1.26]</td>
</tr>
<tr>
<td>Clavel 1982</td>
<td>4/30</td>
<td>10/34</td>
<td>0.45 [0.16, 1.30]</td>
<td>8.8 %</td>
<td>0.45 [0.16, 1.30]</td>
</tr>
<tr>
<td>Taylor 1986</td>
<td>33/95</td>
<td>43/99</td>
<td>0.80 [0.56, 1.14]</td>
<td>39.3 %</td>
<td>0.80 [0.56, 1.14]</td>
</tr>
<tr>
<td>Tashiro 1990</td>
<td>14/26</td>
<td>10/30</td>
<td>1.62 [0.87, 3.00]</td>
<td>8.7 %</td>
<td>1.62 [0.87, 3.00]</td>
</tr>
<tr>
<td>Dixon 1992</td>
<td>7/30</td>
<td>4/30</td>
<td>1.75 [0.57, 5.36]</td>
<td>3.7 %</td>
<td>1.75 [0.57, 5.36]</td>
</tr>
<tr>
<td>ANZBCTG 1986</td>
<td>51/113</td>
<td>25/113</td>
<td>2.04 [1.37, 3.05]</td>
<td>23.4 %</td>
<td>2.04 [1.37, 3.05]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>374</strong></td>
<td><strong>393</strong></td>
<td><strong>100.0 % 1.25 [1.01, 1.54]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Tumor Response Rate**

Very old trials
HER2 status not known
ER/PR status may not be known

Wilcken et al. Cochrane Library 2003
## Chemotherapy vs Endocrine-based Therapy

### ER+ Breast Cancer (Neoadjuvant)

<table>
<thead>
<tr>
<th>Phase II randomized, N=239</th>
<th>ORR</th>
<th>Time to response</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal, ER+, Neoadjuvant</td>
<td>Letrozole or Exemestane x 3 months</td>
<td>64%</td>
<td>57 days</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin/Paclitaxel x 4 cycles</td>
<td>64%</td>
<td>51 days</td>
</tr>
</tbody>
</table>

### UNICANCER-NeoPAL Study

<table>
<thead>
<tr>
<th>ORR</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letrozole + palbociclib x 19 weeks</td>
<td>75%</td>
</tr>
<tr>
<td>FEC x 3</td>
<td>Docetaxel x 3</td>
</tr>
</tbody>
</table>

Chemotherapy vs Endocrine therapy
- No difference in survival
- Higher response rate
- Shorter time to respond

*Semiglazov et al. Cancer 2007;110(2):244-54; Cottu et al. ESMO 2017*
Patients whose tumors express any level of hormone receptors should be offered endocrine therapy, unless there is immediately life-threatening disease (ASCO) or visceral crisis (NCCN), in which case chemotherapy would be indicated.

Sequential endocrine therapy is recommended in the absence of endocrine resistance.

Patridge et al. JCO 2014; 32: 3307-3329
Rugo et al. JCO 2016, 34: 3069-3103
Chemotherapy vs Endocrine Therapy in Advanced Luminal Breast Cancers

1. Does chemotherapy confer a survival advantage (compared to endocrine therapy)?

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Types of Endocrine Resistance

IMPACT trial
Post-menopausal ER+, n=330

Tamoxifen x 12 weeks
Anastrozole x 12 weeks
Tamoxifen + Anastrozole x 12 weeks

Serial biopsy at baseline, 2 weeks and 12 weeks to assess Ki67 (Ki67 is a marker of response to endocrine therapy)

Key Questions about Endocrine Resistance in Metastatic Breast Cancer

DE NOVO RESISTANCE

How common is this? Can these patients be reliably identified before treatment?

ACQUIRED RESISTANCE (all patients, a matter of time)

When is the patient considered endocrine resistant (or refractory) such that further endocrine-based therapies will be futile?
How common is De Novo Endocrine Resistance in Metastatic Breast Cancer?

<table>
<thead>
<tr>
<th>First-Line ER+, HER2-CDK4/6i Trials</th>
<th>Treatment</th>
<th>No Clinical Benefit Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PALOMA-2</strong></td>
<td>Letrozole</td>
<td>30%</td>
</tr>
<tr>
<td>N=666</td>
<td>Letrozole + Palbociclib</td>
<td>15%</td>
</tr>
<tr>
<td><strong>MONALEESA-2</strong></td>
<td>Letrozole</td>
<td>30%</td>
</tr>
<tr>
<td>N=668</td>
<td>Letrozole + Ribociclib</td>
<td>27%</td>
</tr>
<tr>
<td><strong>MONARCH-3</strong></td>
<td>Letrozole or Anastrozole</td>
<td>28%</td>
</tr>
<tr>
<td>N=493</td>
<td>Letrozole or Anastrozole + Abemaciclib</td>
<td>22%</td>
</tr>
</tbody>
</table>

De novo resistance
~30% endocrine therapy
~20% endocrine + CDK4/6i

According to the guidelines*, only <5-10% of patients will be given first-line chemotherapy, but de novo resistance occurs in 20-30% of patients (i.e., progress within 3 months).

*Start with endocrine therapy in the absence of life threatening disease

Finn et al. NEJM 2016; 375: 1925-36; Hortobagyi et al NEJM 2016; 375: 1738-48
Choosing the Wrong Treatment may result in Loss of Opportunity for Further Treatment

After failure of first-line therapy, a proportion of patients cannot undergo second-line therapy due to rapid disease progression.

<table>
<thead>
<tr>
<th>Study</th>
<th>2nd line</th>
<th>3rd line</th>
<th>4th line</th>
<th>5th line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dufresne et al, 2008</td>
<td>100%</td>
<td>56%</td>
<td>25%</td>
<td>11%</td>
</tr>
<tr>
<td>Tacca et al, 2009</td>
<td>100%</td>
<td>68%</td>
<td>43%</td>
<td>23%</td>
</tr>
<tr>
<td>Bernardo et al, 2010</td>
<td>100%</td>
<td>82%</td>
<td>36%</td>
<td>11%</td>
</tr>
<tr>
<td>Planchat et al, 2014</td>
<td>100%</td>
<td>76%</td>
<td>56%</td>
<td>37%</td>
</tr>
<tr>
<td>Jackish et al, 2014</td>
<td>100%</td>
<td>70%</td>
<td>46%</td>
<td>27%</td>
</tr>
</tbody>
</table>

About **one-third of patients** stop their treatment with each new line of therapy.

Can Primary Endocrine Resistance be reliably predicted?

Endocrine sensitivity is a continuum, influenced by multiple factors

<table>
<thead>
<tr>
<th>High</th>
<th>ER/PR EXPRESSION (percentage/intensity)</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>GRADE</td>
<td>High</td>
</tr>
<tr>
<td>Low</td>
<td>PROLIFERATIVE INDEX (E.G., KI67)</td>
<td>High</td>
</tr>
</tbody>
</table>

**Loss of PR**

First-line endocrine therapy alone

- ER+/HER2-: median PFS ~14 months
- ER+/HER2+: median PFS ~3 months

**HER2+**

HIGH ENDOCRINE SENSITIVITY LOW

**ORR to 1st-line therapy**

- AI: ~40%
- AI + CDK4/6i: ~55%

If there is accessibility/affordability, AI + CDK4/6i is a good alternative to chemotherapy in this setting

If the predicted endocrine sensitivity is low, and the patient has a high tumor burden (not amounting to a crisis), chemotherapy may be warranted

Real world use of Chemotherapy vs Endocrine Therapy in HR+ Advanced Breast Cancers

Global Oncology Monitor (physician-based syndicated patient record database)
Post-menopausal, HR+/HER2- advanced/metastatic breast cancers
5 European countries (France, Germany, Italy, Spain, UK) and USA, Jan 2012 to Dec 2014
N = 1272-1740 in Europe and 2225-2760 in USA (every 3 months)

Europe
FIRST-LINE THERAPY

USA

Characteristics of patients given first-line chemotherapy:
Younger, less co-morbidity, more than bone metastases, more liver metastases, more prior adjuvant systemic therapy

Andre et al. Cur Med Res and Opinion, 2014; 30(6); Caldeira et al. Oncol Ther 2016; 4(1); 189-97
Predicting Endocrine Resistance from Prior Treatment Response

**Trial of therapy** may be one of the most reliable ways to determine endocrine sensitivity

**IMPACT (n=158)**; neoadjuvant tamoxifen or AI or combination

**Post-treatment Ki67 at 2 weeks** predicts endocrine sensitivity better than baseline Ki67

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**Baseline Ki67 (tertiles)**

**Post-treatment Ki67 at 2 weeks (tertiles)**

*Dowsett et al. JNCI 2007; 99: 167-70*
Predicting Endocrine Resistance from Prior Treatment Response

Prior Adjuvant Endocrine Therapy

**ADJUVANT ENDOCRINE THERAPY (5-10 years)**

- **Relapse within 2 years**
  - **PRIMARY RESISTANCE** (remote chance of response)

- **Relapse after the first 2 years**
  - **ACQUIRED RESISTANCE** (low chance of response)

- **Relapse ≤12 months of completing adjuvant endocrine therapy**
  - **ACQUIRED RESISTANCE** (some chance of response)

- **Relapse >12 months of completing adjuvant endocrine therapy**
  - **ENDOCRINE SENSITIVE** (good chance of response)

**PALLIATIVE ENDOCRINE THERAPY**

- **Progress within 3 months**
  - **PRIMARY RESISTANCE** (remote chance of response)

- **Progress between 3-6 months**
  - **PRIMARY RESISTANCE** (low chance of response)

- **Progress after 6 months**
  - **ACQUIRED RESISTANCE** (some chance of response)

- **Progress after 12 months**
  - **ACQUIRED RESISTANCE** (good chance of response)

2016 ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer
Special Imaging to Predict Endocrine Resistance

$^{18}$F-FES-PET

N=90 ER+, HER2- breast cancers
For endocrine therapy (63% AI, 22% AI + fulvestrant, 15% others)
FDG-PET and FES-PET ($16\alpha[^{18}F]$fluoro-17$\beta$-estradiol) imaging prior to endocrine therapy

3 kinds of tumor lesions
- FDG low (indolent)
- **FDG high, FES high** (likely endocrine sensitive)
- FDG high, FES low (likely endocrine resistant)

Special Blood Tests (circulating tumor DNA [ctDNA]) to Track Endocrine Resistance

N=83 Metastatic breast cancer, first-line aromatase inhibitor
3-monthly collection of **plasma for ctDNA**, until progression
- digital droplet PCR and enhanced tagged amplicon sequencing

*ESR1* mutations were detectable in plasma
median 6.7 months before clinical progression

Treatment Algorithm for Advanced Luminal Breast Cancers

MOST LUMINAL BREAST CANCERS

Best 1st line Endocrine +/- Biological agent

Best 2nd line Endocrine Tx (+/- Biological agent)

3rd/4th/5th line Endocrine Tx

Chemotherapy

Delay chemotherapy as long as possible with novel therapeutic strategies to overcome endocrine resistance

Her2+ Luminal Breast Cancer (for overall survival benefit)
Visceral Crisis/Life Threatening Disease (for response)
Predicted relative endocrine resistance + narrow window of opportunity to treat (for response)

Start with Chemotherapy
Sequential Endocrine Therapies +/- Biological agent until endocrine resistance
Chemotherapy

Determining endocrine resistance
Prior response to endocrine therapy
Tumor factors (degree of ER/PR expression, HER2, grade, Ki67, etc)
Future special tests (e.g., FES imaging, ctDNA)

Start chemotherapy when endocrine resistance develops
Start chemotherapy when endocrine resistance develops
Start chemotherapy when endocrine resistance develops

Start chemotherapy when endocrine resistance develops

Start chemotherapy when endocrine resistance develops

Start chemotherapy when endocrine resistance develops

Start chemotherapy when endocrine resistance develops

Start chemotherapy when endocrine resistance develops
Good old chemotherapy can still be counted upon in advanced luminal breast cancer!