Current Optimal Sequence and Duration of Endocrine Treatment

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Honoraria:
AstraZeneca, Novartis, and Chugai, Pfizer, Taiho, Eisai, Kyowa Hakko Kirin

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Chugai, Daiichi-Sankyo, and Taiho.
Although significant advances have been made in some areas of breast cancer research resulting in improvements in therapies and outcomes over the last few decades, other areas have not benefited to the same degree. This article summarizes the 12 clinical research needs in breast cancer deemed as priorities by a panel of experts, in an attempt to focus and accelerate future research in the most needed areas.
Research needs in breast cancer

1. de-escalate breast cancer therapies in early breast cancer without sacrificing outcomes
2. explore optimal adjuvant treatment durations
3. develop better tools and strategies to identify patients with genetic predisposition
4. improve care in young patients with breast cancer
5. develop tools to speed up drug development in biomarker-defined populations
6. identify and validate targets that mediate resistance to chemotherapy, endocrine therapy and anti-HER2 therapies
7. evaluate the efficacy of local-regional treatments for metastatic disease
8. better define the optimal sequence of treatments in the metastatic setting
9. evaluate the clinical impact of intra-patient heterogeneity (intra-tumor, inter-tumor and inter-lesion heterogeneity)
10. better understand the biology and identify new targets in triple-negative breast cancer
11. better understand immune surveillance in breast cancer and further develop immunotherapies
12. increase survivorship research efforts including supportive care and quality of life

Current Optimal Sequence and Duration of Endocrine Treatment

• Early breast cancer

• Advanced breast cancer
Risk of recurrence and subtype

Median follow-up time among 3,726 eligible patients was 14.8 years.

Late recurrence

Kennecke H et al. JCO 2010;28:3271-3277
Optimal sequence and duration of endocrine therapy (ET)

- Optimal duration of tamoxifen (1, 2, 5 years)
- Optimal drug and sequence for 5 years
  - Tamoxifen *versus* Aromatase inhibitor (AI)
  - Tamoxifen *vs* Tamoxifen → AI
  - Tamoxifen → AI *vs* AI
- Optimal duration after 5 years ET
  - 10 years tamoxifen
  - Extended AI after 5 years tamoxifen
  - Extended AI after 5 years ET
Optimal sequence and duration of endocrine therapy (ET)

• Optimal duration of tamoxifen (1, 2, 5 years)
• Optimal drug and sequence for 5 years
  • Tamoxifen versus Aromatase inhibitor (AI)
  • Tamoxifen vs Tamoxifen → AI
  • Tamoxifen → AI vs AI
• Optimal duration
  • 10 years tamoxifen
  • Extended AI after 5 years tamoxifen
  • Extended AI after 5 years ET
Duration of tamoxifen for 37,000 women in 55 trials
Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)

Recurrence

Mortality

<table>
<thead>
<tr>
<th></th>
<th>1 year</th>
<th>2 years</th>
<th>5 years</th>
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<tbody>
<tr>
<td>Recurrence</td>
<td>21</td>
<td>29</td>
<td>47</td>
</tr>
<tr>
<td>Mortality</td>
<td>12</td>
<td>17</td>
<td>26</td>
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</tbody>
</table>

Optimal sequence and duration of endocrine therapy (ET)

- Optimal duration of tamoxifen (1, 2, 5 years)
- Optimal drug and sequence for 5 years
  - Tamoxifen versus Aromatase inhibitor (AI)
  - Tamoxifen vs Tamoxifen → AI
  - Tamoxifen → AI vs AI
- Optimal duration after 5 years ET
  - 10 years tamoxifen
  - Extended AI after 5 years tamoxifen
  - Extended AI after 5 years ET
Tamoxifen versus AI for 5 years

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) 9,885 women

RR=0.80 (95%CI0.73-0.88)
10-year gain 3.6%
Log-rank 2p<0.00001

RR=0.85 (95%CI0.72-0.96)
10-year gain 2.1%
Log-rank 2p=0.009

Lancet. 2015;386(10001):1341-1352
Tamoxifen vs tamoxifen → AI

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) 11,798 women

Recurrence (%)

RR=0.82 (95% CI 0.75-0.91)
10-year gain 2.0%
Log-rank 2p<0.0001

Breast mortality (%)

RR=0.84 (95% CI 0.72-0.96)
10-year gain 1.5%
Log-rank 2p<0.01

Lancet. 2015;386(10001):1341-1352
Tamoxifen → AI vs AI

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) 12,799 women

RR = 0.90 (95% CI 0.81-0.99)
7-year gain 0.7%
Log-rank 2p = 0.045

RR = 0.89 (95% CI 0.78-1.03)
7-year gain 1.1%
Log-rank 2p = 0.11

Lancet. 2015;386(10001):1341-1352
Optimal sequence and duration of endocrine therapy (ET)

- Optimal duration of tamoxifen (1, 2, 5 years)
- Optimal drug and sequence for 5 years
  - Tamoxifen versus Aromatase inhibitor (AI)
  - Tamoxifen vs Tamoxifen → AI
  - Tamoxifen → AI vs AI
- Optimal duration after 5 years ET
  - 10 years tamoxifen
  - Extended AI after 5 years tamoxifen
  - Extended AI after 5 years ET including AI
10 versus 5 years of adjuvant tamoxifen

**ATLAS**

- **5-9y:RR** 0.90 (0.79-1.02)
- **≥10y:RR** 0.75 (0.62-0.90)
- All yes: log-rank p = 0.002

- **5-9y:RR** 0.97 (0.79-1.02)
- **≥10y:RR** 0.71 (0.62-0.90)
- All yes: log-rank p = 0.01

# Extended Aromatase inhibitor after 5 years tamoxifen

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study arms</th>
<th>No. of patients</th>
<th>DFS (RFS)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA. 17</td>
<td>5 y Letrozole vs Placebo after 5y tam</td>
<td>5157</td>
<td>HR 0.58 [0.45-0.84] (p&lt;0.001)</td>
<td>HR 0.82 [0.57-1.19] (P=0.3)</td>
</tr>
<tr>
<td>NSABP B-33</td>
<td>5 y Exemestane vs Placebo after 5y tam</td>
<td>1598</td>
<td>RR 0.68 (P=0.07)</td>
<td></td>
</tr>
<tr>
<td>ABCSG 6a</td>
<td>3 yrs anastrozole vs No therapy after 5y tam</td>
<td>856</td>
<td>HR 0.62 [0.40-0.96] (P=0.031) (RFS)</td>
<td>HR 0.89 [0.59-1.34] (P=0.57)</td>
</tr>
</tbody>
</table>

Extended Aromatase inhibitor after 5 years endocrine therapy including AI

<table>
<thead>
<tr>
<th>Study</th>
<th>DFS HR</th>
<th>P-value</th>
<th>OS HR</th>
<th>P-value</th>
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<tbody>
<tr>
<td>MA.17R</td>
<td>0.66</td>
<td>0.01</td>
<td>0.66</td>
<td>0.01</td>
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<tr>
<td>NSABP-B42</td>
<td>0.85</td>
<td>0.048 [NS]</td>
<td>1.15</td>
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<tr>
<td>DATA</td>
<td>0.79</td>
<td>0.07</td>
<td>0.91</td>
<td>0.60</td>
</tr>
<tr>
<td>IDEAL</td>
<td>0.96</td>
<td>0.70</td>
<td>1.08</td>
<td>0.59</td>
</tr>
<tr>
<td>SOLE</td>
<td>1.08</td>
<td>0.31</td>
<td>0.88</td>
<td></td>
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<tr>
<td>SALSA</td>
<td>1.007</td>
<td>0.925</td>
<td>1.007</td>
<td>0.947</td>
</tr>
</tbody>
</table>

Wimmer K et al. Ther Adv Med Oncol 2017, 9: 679-692
Factors predicting late recurrence for ER+ breast cancer
Recurrence after 5 years adjuvant hormone therapy

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) 62,923 women

The risk of distant recurrence was strongly correlated with the original TN status

T1 Stage

T2 Stage

PAM50 Risk of Recurrence Score Predicts 10-Year Distant Recurrence in a Comprehensive Danish Cohort of Postmenopausal Women Allocated to 5 Years of Endocrine Therapy for Hormone Receptor–Positive Early Breast Cancer

Laenkholm AV et al. 2018;36:735-740
Utility of testing as predictive factors
St Gallen Consensus Conference 2015

<table>
<thead>
<tr>
<th>Test</th>
<th>Early recurrence</th>
<th>Late recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncotype DX®</td>
<td>82.9%</td>
<td>43...%</td>
</tr>
<tr>
<td>MammaPrint 70®</td>
<td>81.0%</td>
<td>19.0%</td>
</tr>
<tr>
<td>PAM-50</td>
<td>92.9%</td>
<td>63.2%</td>
</tr>
<tr>
<td>EndoPredict®</td>
<td>70.3%</td>
<td>38.2%</td>
</tr>
<tr>
<td>Breast Cancer Index</td>
<td>58.3%</td>
<td>30...%</td>
</tr>
</tbody>
</table>

Current Optimal Sequence and Duration of Endocrine Treatment

• Early breast cancer

• Advanced breast cancer
Research needs in breast cancer

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12. increase survivorship research efforts including supportive care and quality of life

Goal and treatment for patients with ABC

Goal:
ABC is a treatable but still generally incurable disease. The goal of care is to optimize both length and quality of life.

Treatment:
ER positive ABC is responsive to endocrine therapy, whereas the majority of patients with ABC eventually develop resistance. Recently, promising target therapeutic drugs have been produced to overcome the endocrine resistance.
Treatment strategy for ER+ ABC before the era of target therapy

Hormone-responsive disease and No life-threatening disease

1st line hormonal therapy
- Response then Progression
- No response

2nd line hormonal therapy
- Response then Progression
- No response

3rd line hormonal therapy
- No response

Hormone-unresponsive or life-threatening disease

1st line chemotherapy (AC)
- Progression of disease
- No response

2nd line chemotherapy (Taxanes)
- Progression of disease
- No response

3rd line chemotherapy
- Supportive care

Hortobagyi G  NEJM 339; 974, 1998
CDK4/6i in patients naïve or pre-exposed to ET

**PALOMA 2 (2:1)**
- Median PFS
  - Palbociclib + NSAI: 24.8 m
  - Placebo + NSAI: 14.5 m
- HR (95% CI): 0.58 (0.46, 0.72) \( p \leq 0.000001 \)

**MONALEESA 2 (1:1)**
- Median PFS
  - Ribociclib + NSAI: 25.3 m
  - Placebo + NSAI: 16 m
- HR (95% CI): 0.568 (0.457, 0.704) \( p = 0.000000096 \)

**MONARCH 3 (2:1)**
- Median PFS
  - Abemaciclib + NSAI: not reached
  - Placebo + NSAI: 14.7 m
- HR (95% CI): 0.543 (0.409, 0.723) \( p = 0.000021 \)

CDK4/6i in patients previously exposed to ET

**PALOMA 3**

HR (95% CI): 0.46 (0.36, 0.59)

p = < 0.0001

**MONARCH 2**

HR (95% CI): 0.55 (0.45, 0.68)

p = < 0.001


BOLERO-2 (exemestane + evelorimus)

**Progression free survival**

- **HR = 0.45 (95% CI, 0.38-0.54)**
- **Log-rank *P* < 0.0001**
- Kaplan-Meier medians:
  - **EVE+EXE**: 7.8 mo
  - **PBO+EXE**: 3.2 mo

**Overall survival**

- **HR = 0.89 (95% CI, 0.73-1.10)**
- **Log-rank *P* = 0.14**
- Kaplan-Meier medians:
  - **EVE+EXE**: 30.96 months
  - **PBO+EXE**: 26.55 months

Yardley et al, Adv Ther 2013; Baselga et al, NEJM 2012
ASCO Guideline: Postmenopausal HR+ ABC

No prior adjuvant endocrine therapy

Prior adjuvant endocrine therapy

Prior treatment with tamoxifen

Early relapse (≤ 12 months since adjuvant therapy)
- Al, nonsteroidal preferred
- Al + fulvestrant
- Al + palbociclib

Late relapse (> 12 months since adjuvant therapy)
- Al (nonsteroidal)
- Fulvestrant
- Al + palbociclib
- Al (nonsteroidal) + palbociclib, Tam

Prior treatment with an Al

Early relapse (≤ 12 months since adjuvant therapy)
- Fulvestrant + palbociclib
- Al + everolimus

Late relapse (> 12 months since adjuvant therapy)
- Al (nonsteroidal)
- Fulvestrant
- Al + palbociclib

Depending on prior therapy:
- Fulvestrant ± palbociclib
- Al + everolimus
- Al (steroidal), Tamoxifen

Sequential therapy based on prior exposure and response to hormone therapy
- Estradiol (2 mg three times per day)
- Megestrol acetate
- Fluoxymesterone
- Reintroduction of prior therapy

Bridging the gap

- Too little attention
- Few therapeutic standards
- No international consensus guidelines
- Treatable, but Incurable
The optimal sequence of endocrine-based therapy is uncertain. It depends on which agents were previously used (in the (neo)adjuvant or advanced settings), the burden of the disease, patients’ preference, costs and availability.
The preferred 1st line ET depends on type and duration of adjuvant ET as well as time elapsed from the end of adjuvant ET; it can be an aromatase inhibitor, tamoxifen or fulvestrant.

Total votes: (44)

- **84.0% (37)**
- **9.0% (4)**
- **6.8% (3)**

The addition of a CDK4/6 inhibitor to an aromatase inhibitor, in patients naïve or pre-exposed to ET, provided a significant improvement in median PFS (~10 months), with an acceptable toxicity profile, and is therefore one of the preferred treatment options*. Patients relapsing < 12 months from the end of adjuvant AI were not included in the published studies and may not be suitable for this combination.

OS results are still awaited. QoL was comparable to that with ET alone.
The addition of a CDK4/6 inhibitor to Fulvestrant, in patients previously exposed to ET, provided significant improvement in median PFS (6 to 7 months) as well as improvement of QoL, and is one of the preferred treatment options, if a CDK4/6 inhibitor was not previously used.

OS results are awaited.
Many trials in ER+ ABC have not included pre-menopausal women. Despite this, we recommend that young women with ER+ ABC should have adequate ovarian suppression or ablation (OS/OA) and then be treated in the same way as post-menopausal women with endocrine agents with or without targeted therapies.

Future trials exploring new endocrine-based strategies should be designed to allow for enrollment of both pre- and post-menopausal women.
At present, no validated predictive biomarker other than hormone receptor status exists to identify patients who will/will not benefit from the addition of a targeted agent (i.e. CDK4/6 inhibitor, mTOR inhibitor) to endocrine therapy and none of the studied biomarkers is ready for use in clinical practice. Research efforts must continue.
Treatment strategy? (48y.o. premenopausal woman)

Left invasive breast cancer (3cm), cN0, bone metastasis (scalp, rib, lumbal), Stage IV, ER+/PgR+/,/HER2-, Ki67 10%, NG1

LHRHa+Tam → LHRHa+Al → ChemoTx

LHRHa+Tam → LHRHa+Flu +CDK4/6i → ChemoTx

LHRHa+Al → LHRHa+Tam/Al → ChemoTx
Treatment strategy？（58y.o. post-menopausal woman）

Left invasive breast cancer（3cm）、cN0、bone metastasis（scalp、rib、lumbal）、Stage IV、ER+/PgR+、HER2-、Ki67 10%、NG1
Optimal timing and Optimal drug for ER+HER2-ABC (before targeting therapy Era)
Optimal timing and Optimal drug for ER+HER2-ABC (targeting therapy Era)

- Endocrine monotherapy
- Hormone + targeting therapy
- Chemotherapy

Hormone sensitivity

Tumor burden

Bone
Lung
Liver
The value of any new therapeutic strategy or treatment is determined by the magnitude of its clinical benefit balanced against its cost. Value considerations have become increasingly important in an era of rapid expansion of new, expensive cancer medicines.
### Evidence Blocks (NCCN guideline)

<table>
<thead>
<tr>
<th></th>
<th>E</th>
<th>S</th>
<th>Q</th>
<th>C</th>
<th>A</th>
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<tbody>
<tr>
<td>5</td>
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</tbody>
</table>

- **E** = Efficacy of Regimen/Agent
- **S** = Safety of Regimen/Agent
- **Q** = Quality of Evidence
- **C** = Consistency of Evidence
- **A** = Affordability of Regimen/Agent

Evidence Blocks for each regimen/drug

Anastrozole/Letrozole

- Everolimus + exemestane

Tamoxifen

- Palbociclib + letrozole
- Ribociclib + letrozole

fulvestrant

- Palbociclib + fulvestrant

Summary

• Early breast cancer
  • Physicians take a number of factors into account when deciding whether to recommend that a patient extend adjuvant hormone therapy.
  • These factors include the patient’s age and nodal status, existing comorbidities, bone mineral density, and overall AI tolerance during her initial 5 years of therapy.

• Advanced breast cancer
  • Endocrine therapy is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance.
  • Tremendous progress in new potential agents to improve response to hormone therapy, such as CDK4/6 inhibitors and mTOR inhibitor.
  • The optimal sequence of endocrine-based therapy is uncertain.
  • It depends on which agents were previously used (in the (neo)adjuvant or advanced settings), the burden of the disease, patients’ preference, costs and availability.
  • Biomarkers to identify tumors most likely to benefit is essential.
HOPE

Thank you for your attention.