Role of Endocrine Therapy in Breast Cancer

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32nd AROI ICRO Teaching Course on Breast Cancer, 27th of July 2019
WHY ENDOCRINE THERAPY IN BREAST CANCER?
"Removal of ovaries reduces size of primary breast cancer"
- George Beatson (1896)

- Stilbestrol
  - Haddow ~ 1930s

- Adrenalectomy
  - Huggins ~ 1940s

- Androgenic steroids
  - 1950s

- Hypophysectomy or ablation
  - Forest ~ 1960s

- TAMOXIFEN 1970s

- Aminoglutethimide and Goserelin
  - 1980s

- AROMATASE INHIBITORS 1990s

- FULVESTRANT / EVEROLIMUS / CDK4/6 inhibitors
Early days

On Treatment of Inoperable Cases of Carcinoma of the Mamma: Suggestions for a New Method of Treatment, with Illustrative Cases.

Beatson G.W. Lancet 1896
A NEW ANTI-OESTROGENIC AGENT IN LATE BREAST CANCER
AN EARLY CLINICAL APPRAISAL OF ICI46474

From the Christie Hospital and Holt Radium Institute, Manchester M20 9BX

Received for publication April 7, 1971

SUMMARY.—An introductory clinical trial of the anti-oestrogenic agent ICI46474 in late or recurrent carcinoma of the breast is described. Forty-six patients have been treated, of whom 10 have shown a good response. This is of the same order as that seen with oestrogens and androgens. The particular advantage of this drug is the low incidence of troublesome side effects.

Anti-oestrogen Therapy for Breast Cancer: A Trial of Tamoxifen at Two Dose Levels

H. W. C. WARD

PRELIMINARY TRIAL OF AMINOGLUTETHIMIDE IN BREAST CANCER

C. THOMAS GRIFFITHS, MD,* THOMAS C. HALL, MD,† ZEINA SABA, MD,‡ JOSEPH J. BARLOW, MD,¶ AND HANS B. NEVINNY, MD∥
Targets and pathways for Endocrine Therapy in Breast Cancer

Hormone Therapy in Breast Ca:
Major determining factors.

- ER
- PR
- HER 2 neu

- Menstrual Status
  - Not a predeterminant for necessity of Hormone therapy.
  - Just a factor for the choice of Hormone.

Ki 67
PI3KCA mutations
Definition of Menopause

EUSOMA Guidelines

• Amenorrhea > 12 months, Irrespective of age

• Amenorrhea > 6 months, Age ≥ 50 years

• Bilateral Oophorectomy at any age

• Already Hysterectomized & age > 55 years

• Hysterectomy, < 55 years if Serum FSH & LH in Post Menopausal Level

Permanent cessation of menses which includes profound decrease in ovarian function.

NCCN Guidelines v 2.2019

• Amenorrhea > 12 months

• Amenorrhea > 6 months, Age ≥ 50 years

• Bilateral Oophorectomy at any age

• Already Hysterectomized & age > 55 years

• Amenorrhea > 12 months, Age > 60 yrs.

• Amenorrhea > 12 months, Age < 60 yrs and amenorrhea for 12 months in absence of CT, HT, Ov Supr and estrogen and FSH in post menopausal range

• If taking Tamoxifen or Toremifene, and age < 60 yrs, then FSH and plasma estradiol in post menopausal ranges.

In women who have become amenorrhetic during chemotherapy or the menopausal status is unsure, serial serum Estradiol & FSH measurements are necessary to establish Menopausal Status.
WHO ARE THE CANDIDATES FOR HORMONE THERAPY IN BREAST CANCER?
• LCIS (ER +ve)

• DCIS (ER +ve)

• Invasive Cancer
  – All ER +ve pts.

  – A subset of these patients may be candidates for ET alone
    • Age > 70 yrs
    • Micro-invasive or pT < 0.6 cm pN0
    • Low grade, no LVSI, strongly ER+

• In ER unknown – Tamoxifen???
| Optimal algorithm for ER/PgR testing | Positive for ER or PgR if finding of ≥ 1% of tumor cell nuclei are immunoreactive. Negative for ER or PgR if finding of < 1% of tumor cell nuclei are immunoreactive in the presence of evidence that the sample can express ER or PgR (positive intrinsic controls are seen). Uninterpretable for ER or PgR if finding that no tumor nuclei are immunoreactive and that internal epithelial elements present in the sample or separately submitted from the same sample lack any nuclear staining. |
Allred Scoring

A  Proportion Score (PS)

0  1→1/100  2 →1/10  3 →1/3  4 →2/3  5 →1

B  Intensity Score (IS)

0 = negative  1 = weak  2 = intermed  3 = strong

Allred Score = PS + IS (range 0-8)
BREAST CANCER - **ONE** DISEASE?
Molecular portraits of human breast tumours

Charles M. Perou*†, Therese Sørlie‡‡, Michael B. Eisen*,
Matt van de Rijn§, Stefanie S. Jeffrey‖, Christian A. Rees*,
Jonathan R. Pollack§, Douglas T. Ross§, Hilde Johnsen‡‡,
Lars A. Akslen#, Øystein Fluge☆, Alexander Pergamenschikov*,
Cheryl Williams*, Shirley X. Zhu§, Per E. Lønning**,
Anne-Lise Børresen-Dale‡‡, Patrick O. Brown††† & David Botstein*

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California 94305, USA
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N-0310 Montebello Oslo, Norway
### Intrinsic Subtype Characteristics

<table>
<thead>
<tr>
<th>Intrinsic Subtype</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| Luminal A         | ER+  PR high  Her2 neu –  
|                   | Ki 67 low  Recurrence risk low                       |
| Luminal B         | ER+  PR low  Her2 neu –  
|                   | Ki 67 high  Recurrence risk high                      |
|                   | ER+  PR any  Her2 neu +  
|                   | Ki 67 any  Recurrence risk any                        |
| Her 2 overexpressed| Her2 neu overexpressed / amplified  ER and PR absent |
| Basal             | ER−  PR−  Her 2 neu –  
|                   | Triple Negative                                       |

*The threshold for cut-off of PR high and low is typically taken as **20%** and for Ki 67 as **14%** respectively.*
CAN WE BETTER PREDICT WHO WILL BENEFIT MOST FROM ENDOCRINE THERAPY?
Tools to better predict candidates for ET alone

Prospective Validation of a 21-Gene Expression Assay in Breast Cancer

Tools to better predict responsiveness to ET
ADJUVANT ENDOCRINE THERAPY IN EARLY BREAST CANCER.
Timing ET: newly diagnosed women

Recurrence rate/year (%)

Time (years)

Early Recurrence
18 – 30 months

Late Recurrence
7 – 9 yrs
And Beyond?

Node +ve

Node -ve

Endocrine therapy is generally not given along with Chemotherapy but can be used concomitantly with Radiotherapy and Her 2 directed therapy.

Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)*

Lancet 2005; 365: 1687-1717

Figure 8: About 5 years of tamoxifen versus not in ER-positive (or ER-unknown) disease: 15-year probabilities of recurrence and of breast cancer mortality
10 386 women: 20% ER-unknown, 30% node-positive. Error bars are ±1SE.
Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)*

Lancet 2005; 365: 1687–1717

Nodal status

Node-negative (7244 women)

5-year gain 9.1% (SE 0.9)
Logrank 2p<0.00001

Node-positive (3126 women)

5-year gain 16.1% (SE 1.8)
Logrank 2p<0.00001

Recurrence (%)

Years

0 1 2 3 4 5

Control
20.1%

About 5 years of tamoxifen 11.0%

Control
40.8%

About 5 years of tamoxifen 24.7%
Which drug to choose?

**Nolvadex-D**
- SERM, Prodrug, CYP2D6
- Hot flushes, thromboembolic events
- Endometrial hyperplasia – a concern

**Arimidex**
- Most mature data yet available
- Long carryover effect
- BMD reduction more; CVS problems less

**Femara**
- Max suppression of estradiol
- ↑OS in node+
- CVS, Thromboembolic events more

**AROMASIN**
- Better in pts. with low BMD & impaired lipid profile
The broad guidelines

• Premenopausal
  – Tamoxifen 20 mg OD for at least 5 years.

• Postmenopausal
  – An AI should be incorporated into the adjuvant endocrine therapy of these women at some point of time.
  – Bisphosphonates should be incorporated into the treatment paradigm of these patients to prevent / reverse AI induced BMD derangements.
ADJUVANT ENDOCRINE THERAPY IN EARLY BREAST CANCER: PREMENOPAUSAL
Adjuvant Tamoxifen 10 vs 5 yrs?

**ATLAS (Adjuvant Tamoxifen Long Against Short):** Randomized trial of 10 versus 5 years of adjuvant tamoxifen among 6,846 women with ER+ / untested Breast cancer.

**aTTom (adjuvant Tamoxifen — To offer more?):** Randomized trial of 10 versus 5 years of adjuvant tamoxifen among 6,934 women with ER+ / untested Breast cancer.

*Figure 3: Recurrence (A) and breast cancer mortality (B) by treatment allocation for 6846 women with ER-positive disease. Bars show SE. Recurrence rates are percentage per year (events/patient-years of follow-up). Death rates (overall rate — rate in women without recurrence) are percentage per year (SE). ATLAS=Adjuvant Tamoxifen: Longer Against Shorter.*
Adjuvant AI + GnRH in Premenopausal women
The TEXT & SOFT trials

**TEXT**
- Premenopausal, HR+ BC
- ≤ 12 wks after surgery
- N = 2672

- *OFS*
  - TEXT: Inj. Triptorelin 3.75 mg IM every 28 days for 6-8 weeks prior to initiation of HT or concurrently with chemotherapy.
  - SOFT: triptorelin, bilateral oophorectomy or Ovarian irradiation

**SOFT**
- Premenopausal HR+ BC
- ≤ 12 wks after surgery (if no chemo) or
- ≤ 8 mos after chemo if premen status confirmed
- N = 3066

<table>
<thead>
<tr>
<th>Tamoxifen 20 mg/day + OFS* (n = 1338)</th>
</tr>
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<tbody>
<tr>
<td>Exemestane 25 mg/day + OFS* (n = 1334)</td>
</tr>
<tr>
<td>Tamoxifen 20 mg/day + OFS* (n = 1024)</td>
</tr>
<tr>
<td>Exemestane 25 mg/day + OFS* (n = 1021)</td>
</tr>
</tbody>
</table>

**Joint Analysis**
- Median follow up: 68 months
- 42% N+
- Neo/Adjuvant chemotherapy: 58%

<table>
<thead>
<tr>
<th>Tamoxifen + OFS*</th>
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</thead>
<tbody>
<tr>
<td>N = 2344</td>
</tr>
<tr>
<td>Exemestane+ OFS*</td>
</tr>
<tr>
<td>N = 2346</td>
</tr>
</tbody>
</table>

Pagani O, et al.  
In premenopausal women with hormone-receptor–positive early breast cancer, adjuvant treatment with exemestane (an AI) plus ovarian suppression, as compared with tamoxifen plus ovarian suppression, significantly reduced recurrence rates. The impact on overall survival was not significantly different.
ADJUVANT ENDOCRINE THERAPY IN EARLY BREAST CANCER: POSTMENOPAUSAL
Aromatase inhibitors as Adjuvant ET in EBC

Two strategies, both superior to tamoxifen alone

I. Al x 5 years
   Upfront

II. Tamoxifen x 2 to 3 years  Al x 2 to 5 years
   Switching

A third strategy looks good as well

III. Tamoxifen x 5 years  Al x 5 years

A fourth strategy tested but not robust enough

IV. Al x 2 years  Tamoxifen x 3 years
Women on adjuvant ET 5 yrs of Tamoxifen vs AI: The Upfront Trials

Recurrence rate/year (%)

Time (years)

Randomisation

Arimonex and Tamoxifen Alone or in Combination (ATAC)
Breast International Group 1-98 (BIG 1-98)

Adapted from EBCTCG. Lancet 1998;352:930-942
The Arimidex™ Alone or in Combination ATAC trial: 10-year analysis

Postmenopausal women with invasive breast cancer (n = 9366)

Surgery ± radiotherapy ± chemotherapy

Randomisation 1:1:1 for 5 years

- Anastrozole (n = 3125)
  - ITT population n = 3125
  - Safety population n = 3092
  - HR+ subpopulation n = 2618
- Tamoxifen (n = 3116)
  - ITT population n = 3116
  - Safety population n = 3094
  - HR+ subpopulation n = 2598

Discontinued following initial analysis as no efficacy or tolerability benefit compared with tamoxifen arm

ITT, intent-to-treat; HR+, hormone receptor-positive

Cuzick et al, Lancet Oncol 2010;11:1135 - 1141
Arimidex, as compared to tamoxifen (in HR+ve patients), significantly:

• improves disease free survival by 14% \(p=0.003\)
• reduces the risk of all recurrences by 21% \(p=0.0002\)
• reduces the risk of distant metastases (recurrence elsewhere in the body) by 15% \(p=0.02\)
• weak evidence of fewer deaths after recurrence with anastrozole by 13% \(p=0.09\)

The absolute differences in time to recurrence between anastrozole and tamoxifen increased over time (2.7% at 5 years and 4.3% at 10 years)

Cuzick et al, Lancet Oncol 2010;11:1135 - 1141
BIG 1-98 Overall Design

4-Arm Option

- A: Tamoxifen
- B: Letrozole
- C: Tamoxifen + Letrozole
- D: Letrozole + Tamoxifen

N=8,010*

*ITT: excludes 18 patients who withdrew consent and did not receive study treatment

Enrolled 1999-2003

N=6,182

Previous Analyses:

- Is 5 years Let superior to 5 years Tam as initial therapy?
- Primary Core Analysis (PCA), Median follow-up 26 months
- Monotherapy Arm Analysis, Median follow-up 51 months

Stratify
- Institution
- CT (Adjuvant/Neoadjuvant)
  - Prior
  - None
  - Concurrent

Randomize

SURGERY

IBCSG
International Breast Cancer Study Group
SABCS 2008
Breast Cancer Events
Tam→Let vs. Let

Overall

By Nodal Status*

*42% of the population is node positive; 58% node negative
UPFRONT AI TRIALS: COMBINED ANALYSIS

**Upfront adjuvant AIs decrease the recurrence and improve the DFS. Impact on OS uncertain.**

*As first event, heterogeneity, p = 0.08

Dowsett M et al JCO 2009
Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)∗

Lancet 2015; 386: 1341-52
Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)*

Recurrence

Breast cancer mortality

11,798 women, 1,616 events
RR=0.82 (95% CI 0.75-0.91)

10-year gain 2.0% (95% CI 0.2 to 3.8)
Log-rank 2p=0.0001

11,798 women, 789 deaths
RR=0.84 (95% CI 0.72-0.96)

10-year gain 1.5% (95% CI 0.1 to 2.9)
Log-rank 2p=0.01

Recurrence rate/year (%), events/woman-years and log-rank statistics

Death rates (%/year: total rate minus rate in women without recurrence) and log-rank statistics
Women already on adjuvant ET : Tam for 2-3 yrs : The Switching Trials

Recurrence rate/year (%)

Time (years)

Node +ve

Node -ve

Randomisation

Tamoxifen

Anastrozole

Intergroup Exemestane Study (IES)
Italian Tamoxifen Anastrozole (ITA); Austrian Breast & Colorectal Cancer Study Group (ABCSG) 8 / Arimidex-Nolvadex (ARNO) 95

Adapted from EBCTCG. Lancet 1998;352:930-942
SWITCHING TRIALS: COMBINED ANALYSIS

Switching to AIs decreases the recurrence rate and improves the DFS. Impact on OS uncertain.

*As first event, heterogeneity, p = 0.4

Trials
- IES
- ABCSG VIII
- ARNO
- ITA

Dowsett M et al JCO 2009
Women who have completed 5 years of Tam

The Extended Adjuvant Trials

Extended adjuvant

Randomisation

0
2
4
6
8
10

Time (years)

Recurrence rate/year (%)

0
4
8
12
16

Node +ve

Node -ve

Tamoxifen

Placebo

Letrozole

MA 17
ABCSG 6a
NSABP 33

Adapted from EBCTCG. Lancet 1998;352:930-942
MA 17 Trial

• Unblinded at the first planned interim analysis ~2.4 years, due to a significant difference in events that favored the letrozole arm (↓ recurrence by 43% vs placebo (HR 0.57, P = 0.00008)).

• At a median follow-up of 5.3 years, the DFS (HR 0.37; P < 0.0001) and distant DFS (HR 0.39; P = 0.004) were significantly superior in the letrozole arm.

• Node-positive patients on letrozole also showed a significant OS benefit (letrozole decreased mortality by 39% compared with placebo p = 0.04).

• Letrozole therapy was generally well tolerated and most adverse events were mild (grade 1 or 2). More self-reported new diagnoses of osteoporosis and significantly more clinical fractures occurred in the women who took letrozole (P = 0.02).

• Overall, letrozole did not show a substantial adverse effect on QOL relative to placebo.

Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer: ASCO Clinical Practice Guideline Focused Update

Harold J. Burstein, MD, PhD; Christina Lacchetti, MHS; Holly Anderson, RN; Thomas A. Buchholz, MD; Nancy E. Davidson, MD

Focused Update Recommendations

Recommendation 1. Many women with node-negative breast cancer are potential candidates for and may be offered extended AI therapy for up to a total of 10 years of adjuvant endocrine treatment based on considerations of recurrence risk using established prognostic factors. However, as the recurrence risk is lower, the benefits are likely narrower for such patients. Women with low-risk node-negative tumors should not routinely be offered extended therapy.

Recommendation 2. Women with node-positive breast cancer should be offered extended AI therapy for up to a total of 10 years of adjuvant endocrine treatment.

Recommendation 3. Women who receive extended adjuvant endocrine therapy should receive no more than 10 years of total treatment.

Recommendation 4. As prevention of secondary or contralateral breast cancers is a major benefit of extended AI therapy, the risk of second breast cancers (or not) based on prior therapy should inform the decision to pursue extended treatment.

Recommendation 5. Extended therapy carries ongoing risks and side effects, which should be weighed against the potential absolute benefits of longer treatment in a shared decision-making process between the clinical team and the patient.

Qualifying Statement. To date, none of the studies have shown improvement in overall survival with longer-duration AI therapy. As such, the recommendations on extended adjuvant AI therapy are based on benefits that include prevention of distant recurrence and prevention of second breast cancers.
BONE HEALTH WITH AIS IN BREAST CANCER: ROLE OF BISPHOSPHONATES
• 18,766 women with mFU of 5.6 woman-years.

• **Adjuvant bisphosphonates** (Zoledronate, Ibandronate, Alendronate, Pamidronate, Clodronate):
  – Reduced the rates of breast cancer recurrence in the bone. (RR 0.84)
  – Definite benefit only in women who were postmenopausal when treatment began.
  – Reductions in recurrence (RR 0.86), distant recurrence (0.82), bone recurrence (0.72) and breast cancer mortality (0.82, 0.73–0.93) in postmenopausal women.
Bisphosphonates should be considered as adjuvant therapy for all postmenopausal patients with breast cancer.

Zoledronic acid (4mg IV over 15 mins q 6 months for 3 – 5 years) and Clodronate (1600 mg/day for 2-3 years) are the recommended bisphosphonates.

While results for adjuvant Denosumab look promising, data are insufficient at this time to make a recommendation.

The optimal timing to start bisphosphonates is unclear; however, most of the clinical trials started it soon after surgery or CT.

A dental assessment is recommended, where feasible, prior to commencement of bisphosphonates, and any pending dental or oral health problems should be dealt with prior to starting treatment, if possible to prevent BRONJ.
ENDOCRINE THERAPY IN ADVANCED BREAST CANCER
Evolution of Breast Cancer Treatment

Early-stage breast cancer

Neoadjuvant therapy: Reduce tumour size prior to surgery + reduce risk of recurrence

Goal: curative treatment

Advanced breast cancer

Adjuvant therapy: Reduce risk of recurrence after surgery

30% will progress to advanced disease, many ≥2 years following adjuvant therapy

Palliative therapy: Prolong survival and control disease symptoms

Goal: survival and quality of life

30% will progress to advanced disease, many ≥2 years following adjuvant therapy

International Treatment Guidelines Emphasise Endocrine Therapy for HR+/HER2− ABC

Major treatment guidelines (ABC 4, ASCO, ESMO, NCCN, EUSOMA recommend Endocrine therapy over Chemotherapy for Advanced Breast Cancer with HR+ Her2neu- disease).

- Less toxic
- Better QoL

Treatment of “Rapidly Progressive Disease”

**VISCERAL CRISIS**¹ is defined as *severe organ dysfunction* as assessed by signs and symptoms, laboratory studies, and *rapid progression of disease*. Visceral crisis is *not the mere presence of visceral metastases* but implies important visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible. *(LoE: Expert opinion)*.

ET is the preferred option for HR-positive disease, *even in the presence of visceral disease, unless there is visceral crisis* or concern/proof of endocrine resistance. *(LoE I/A).*

For pre-menopausal women, for whom ET was decided, **OFS/OFA combined with additional ET** is the preferred choice. *(LoE I/A).*

When to Switch from ET to CT

“Chemotherapy should be reserved for cases of rapidly progressive disease or proven endocrine-resistance.” – ESMO/ABC2 guidelines

“Endocrine therapy, rather than chemotherapy... except for immediately life threatening disease or if there is concern regarding endocrine resistance.” – ASCO guidelines

LTD, life threatening disease; PD, progressive disease.

Als better than Tam in Postmenopausal

<table>
<thead>
<tr>
<th>Drug</th>
<th>TTP (months)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letrozole</td>
<td>9.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Anastrozole</td>
<td>10.7</td>
<td>0.022</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>Exemestane</td>
<td>10.5</td>
<td>0.028</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>5.5</td>
<td></td>
</tr>
</tbody>
</table>


Al, aromatase inhibitor; TAM, tamoxifen.
Primary Endocrine Resistance is defined as:¹
• Relapse while on the first 2 years of adjuvant ET, or
• PD within first 6 mos of initiating 1st-line ET for MBC, while on ET

Secondary (Acquired) Endocrine Resistance is defined as:
• Relapse while on adjuvant ET but after the first 2 years, or
• Relapse within 12 months of completing adjuvant ET, or
• PD ≥6 months after initiating ET for MBC, while on ET

ET resistance is a “progressive, step-wise process, and the underlying mechanism remains unclear.”²

Aromatase inhibitors are first-line endocrine therapy for postmenopausal patients

Approximately 50% of ER+ patients do NOT respond to initial treatment

Even those who do respond to initial treatment will eventually progress

“Optimal post-aromatase inhibitor treatment is uncertain”

ER+, estrogen receptor positive
Targets and pathways for Endocrine Therapy in Breast Cancer

OPTIONS FOR ENDOCRINE THERAPY IN ADVANCED BREAST CANCER
Options for 1\textsuperscript{st} line / progression beyond 1\textsuperscript{st} line in Advanced Breast Cancer

• Progestins
  – Megestrol acetate
  – Medroxyprogesterone acetate

• CDK4 / 6 inhibitors
  – Palbociclib
  – Ribociclib
  – Abemaciclib

• PI3K inhibitors
  – Buparlisib
  – Alpelisib
  – Taselisib
Fulvestrant

- Is an injectable selective estrogen receptor downregulator that binds, blocks & ↑ degradation / apoptosis of the ER.

- First studies in advanced disease showed similar efficacy to anastrozole, exemestane and tamoxifen, but doses and schedules were sub-optimal (250 and no loading doses).

- Greater antitumor activity CONFIRMed with the high dose schedule (500 mg with loading dose).

- Toxicities: GI disturbances, hot flashes, asthenia, injection site reactions.
CONFIRM
Fulvestrant HD 500 mg vs AD 250 mg

PFS, OS, TTP, ORR, CBR and DoCB improved with Fulvestrant HD, toxicities similar.

DiLeo et al. J Clin Oncol 2013
Median Duration of Response in pts with or without visceral metastases

<table>
<thead>
<tr>
<th>Group</th>
<th>Median Duration of Objective Response (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population (n=152)</td>
<td>[18, 15, 12, 9, 6, 0, 3]</td>
</tr>
<tr>
<td>No visceral metastases (n=97)</td>
<td>[18, 15, 12, 9, 6, 0, 3]</td>
</tr>
<tr>
<td>All patients with visceral metastases (n=55)</td>
<td>[18, 15, 12, 9, 6, 0, 3]</td>
</tr>
<tr>
<td>Visceral metastases only (n=25)</td>
<td>[18, 15, 12, 9, 6, 0, 3]</td>
</tr>
</tbody>
</table>

Fulvestrant HD vs AI : Phase II FIRST Study

Postmenopausal patients with Stage III B or IV, ER/PR+HER2-
Primary Objective: CB (no differences)

PFS
- Fulvestrant 500 mg (n=102) 23.4 mo
- Anastrozole 1 mg (n=103) 13.1 mo

HR = 0.66
95% CI 0.47, 0.92
p = 0.01

OS
- Fulvestrant 500 mg (n=102) 54.1 mo
- Anastrozole 1 mg (n=103) 48.4 mo

HR = 0.70
95% CI 0.50, 0.98
p = 0.041

CB, clinical benefit; HD, high dose.

Everolimus

- Is an oral mTOR inhibitor used for 2\textsuperscript{nd} line ABC, mRCC and aPNET.

- Compared to Exemestane alone after progression on NSAI in 2\textsuperscript{nd} line setting.

- Starting dose of 10 mg / day, can be titrated in 2.5 mg steps.

- Toxicities: Stomatitis, diarrhoea, rash, fatigue.

  Hyperglycaemia, dyslipidaemia, pneumonitis.
BOLERO 2 Everolimus + Exe in 2\textsuperscript{nd} line ABC

\begin{itemize}
\item N = 724
\item PMW with HR+, HER2- ABC refractory to LET or ANA, defined as
  \begin{itemize}
  \item Recurrence during or within 12 months after end of adjuvant treatment, or
  \item Progression during or within 1 month after end of treatment for advanced disease
  \end{itemize}
\item Everolimus 10 mg/day + Exemestane 25 mg/day (n = 485)
\item Placebo + Exemestane 25 mg/day (n = 239)
\item Stratification
  \begin{enumerate}
  \item Sensitivity to prior endocrine therapy
  \item Presence of visceral disease
  \end{enumerate}
\item No crossover
\end{itemize}

Primary endpoint
\begin{itemize}
\item PFS
\end{itemize}

Secondary endpoints
\begin{itemize}
\item OS, ORR, CBR, safety, QOL, bone markers
\end{itemize}

ANA, anastrozole; LET, letrozole.
BOLERO 2 – Results in ITT post NSAI resistance

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No.</th>
<th>Hazard Ratio (95% CI)</th>
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<tbody>
<tr>
<td>All patients</td>
<td>724</td>
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</tr>
<tr>
<td>Age</td>
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<tr>
<td>&lt;65 yr</td>
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<td>Sensitivity to previous hormonal therapy</td>
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<td>Neoadjuvant or adjuvant therapy only</td>
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EVE, everolimus; EXE, exemestane.

Palbociclib

- Is an oral CDK 4 / 6 inhibitor that targets the G1/S cell cycle checkpoint dependent on Cyclin & CDK 4 / 6.

- Starting dose of 125 mg / day, 3/1 schedule.

- Toxicities: Predominantly hematological, nausea, fatigue.
  - Grade 3 and 4 leucopenia, neutropenia, thrombocytopenia, anemia.
  - Febrile neutropenia low.
  - Treatment compliance not majorly affected.
PALOMA 2
Palbociclib and Letrozole in Advanced Breast Cancer
Richard S. Finn, M.D., Miguel Martin, M.D., Hope S. Rugo, M.D., Stephen Jones, M.D., Seock-Ah Im, M.D., Ph.D.,

- HR+, HER2– ABC
- Postmenopausal
  - Metastatic or locally recurrent disease with no prior systemic therapy in this setting
  - If neoadjuvant or adjuvant ET administered, a disease free interval of >12 months since completion of ET
  - ECOG PS ≤1

**RANDOMIZATION**

2:1

- **Palbociclib 125 mg (3 weeks on 1 week off)**
  - plus
  - letrozole: 2.5 mg QD until PD

- **Placebo (3 weeks on 1 week off)**
  - plus
  - letrozole: 2.5 mg QD until PD

**Primary endpoint:**
Investigator-assessed PFS

**Secondary endpoint:**
OS, Response rates, Safety

**Stratification factors:**
- Metastatic site (visceral, bone only, or other)
- Prior ET (AI, no ET, or other)
A Investigator Assessment

Probability of Progression-free Survival (%)

Hazard ratio, 0.58
(95% CI, 0.46–0.72)
Two-sided P<0.001

Months

No. at Risk
Palbociclib–Letrozole 444 395 360 328 295 263 238 154 69 29 10 2
Placebo–Letrozole 222 171 148 131 116 98 81 54 22 12 4 2

Palbociclib and Letrozole in Advanced Breast Cancer

Richard S. Finn, M.D., Miguel Martin, M.D., Hope S. Rugo, M.D., Stephen Jones, M.D., Seock-Ah Im, M.D., Ph.D.
PALOMA-3: 2nd line FUL ± PAL in Pre/Postmeno

Objectives

- To determine efficacy and safety of palbociclib (PAL) plus fulvestrant (FUL) in pts with HR+/HER2− mBC progressing on prior ET

Methodology

N = 521

- HR+/HER2− ABC progressing on prior ET in advanced setting
- Pre/peri or postmenopausal

PAL + FUL (n = 347)

PBO + FUL (n = 174)

Evaluation

- Primary: PFS
- Secondary: OS, ORR, DOR, CBR, safety, HRQoL, biomarkers

ABC, advanced breast cancer; CBR, clinical benefit rate; DOR, duration of response; ET, endocrine therapy; FUL, fulvestrant; HRQoL, health related quality of life; MBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PAL, palbociclib; PFS, progression free survival.

PALOMA 3 Results in ITT post ET progression

A Assessment by Investigators
Hazard ratio, 0.42 (95% CI, 0.32–0.56)
P<0.001

Palbociclib–fulvestrant (N=347)
Median progression-free survival, 9.2 mo (95% CI, 7.5–NE)

Placebo–fulvestrant (N=174)
Median progression-free survival, 3.8 mo (95% CI, 3.5–5.5)

B Central Assessment
Hazard ratio, 0.27 (95% CI, 0.16–0.46)
P<0.001

Palbociclib–fulvestrant (N=147)
Median progression-free survival, NE

Placebo–fulvestrant (N=64)
Median progression-free survival, 3.7 mo (95% CI, 3.4–7.2)

No. at Risk
Palbociclib–fulvestrant 347 279 132 59 16 6
Placebo–fulvestrant 174 109 42 16 6 1

No. at Risk
Palbociclib–fulvestrant 147 118 53 24 7 2
Placebo–fulvestrant 64 37 12 4 1 1

Ribociclib

- Is an oral CDK 4 / 6 inhibitor that targets the G1/S cell cycle checkpoint dependent on Cyclin & CDK 4 / 6.

- Starting dose of 600 mg (200 mg x 3)/ day, 3/1 schedule.

- Toxicities: Predominantly nausea, fatigue.
  - Grade 3 and 4 leucopenia, neutropenia, less common.
  - QTc prolongation, especially > 480 ms reported.
  - Liver enzyme elevation reported.
MONALEESA-2: A Phase III, Double-blind, Placebo-Controlled Study of Ribociclib + Letrozole

- Postmenopausal women with HR+/HER2– advanced breast cancer
- No prior therapy for advanced disease
- N=668

Randomization (1:1)
Stratified by the presence/absence of liver and/or metastases

Ribociclib (600 mg/day) 3-weeks-on/1-week-off + Letrozole (2.5 mg/day) n=334

Placebo + Letrozole (2.5 mg/day) n=334

Primary endpoint
- PFS (locally assessed per RECIST v1.1)

Secondary endpoints
- Overall survival (key)
- Overall response rate
- Clinical benefit rate
- Safety

- Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter
- Final analysis planned after 302 PFS events
  - 93.5% power to detect a 33% risk reduction (hazard ratio, 0.67) with one-sided α=2.5%
- Interim analysis planned after ~70% PFS events
  - Two-look Haybittle–Peto stopping criteria: hazard ratio, ≤0.56 and P<0.0000129

PFS, progression-free survival.
MONALEESA-2 is registered at ClinicalTrials.gov (NCT01958021).

Hortobagyi et al; NEJM 2016
MONALEESA-2: A Phase III, Double-blind, Placebo-Controlled Study of Ribociclib + Letrozole

Main AEs: QTc prolongation, ALT, AST rise, neutropenia.

Hortobagyi et al; NEJM 2016
MONALEESA-7: Phase III placebo-controlled study of ribociclib and tamoxifen/NSAI + goserelin

Tripathi et al. SABCS 2017

- Pre/perimenopausal women with HR+, HER2– ABC
- No prior endocrine therapy for advanced disease
- ≤1 line of chemotherapy for advanced disease
- N=672

Randomization (1:1)

Stratified by:
- Presence/absence of liver/lung metastases
- Prior chemotherapy for advanced disease
- Endocrine therapy partner (tamoxifen vs NSAI)

Ribociclib (600 mg/day; 3-weeks-on/1-week-off) + tamoxifen/NSAI + goserelin*

n=335

Placebo + tamoxifen/NSAI + goserelin*

n=337

Primary endpoint
- PFS (locally assessed per RECIST v1.1)‡

Secondary endpoints
- Overall survival (key)
- Overall response rate
- Clinical benefit rate
- Safety
- Patient-reported outcomes

- Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter
- Primary analysis planned after ~329 PFS events
  - 95% power to detect a 33% risk reduction (hazard ratio 0.67) with one-sided α=2.5%, corresponding to an increase in median PFS to 13.4 months (median PFS of 9 months for the placebo arm¹,²), and a sample size of 660 patients

NSAI, non-steroidal aromatase inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors.
* Tamoxifen = 20 mg/day; NSAI: anastrozole = 1 mg/day or letrozole = 2.5 mg/day; goserelin = 3.6 mg every 28 days;
† PFS by Blinded Independent Review Committee conducted to support the primary endpoint.
MONALEESA-7: Primary endpoint: PFS (investigator-assessed)

Tripathi et al. SABCS 2017

- PFS (investigator assessment)
  - Ribociclib + tamoxifen/NSAI n=335
  - Placebo + tamoxifen/NSAI n=337

- Number of events, n (%)
  - Ribociclib: 131 (39.1)
  - Placebo: 187 (55.5)

- Median PFS, months (95% CI)
  - Ribociclib: 23.8 (19.2–NR)
  - Placebo: 13.0 (11.0–16.4)

- Hazard ratio (95% CI)
  - 0.553 (0.441–0.694)

- One-sided p value
  - 0.0000000983

---

Goserelin included in all combinations.

CI, confidence interval; NR, not reached.
### PFS by endocrine therapy partner (investigator-assessed)

Tripathi et al. SABCS 2017

<table>
<thead>
<tr>
<th>PFS (investigator assessment)</th>
<th>Tamoxifen</th>
<th>NSAI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ribociclib arm n=87</td>
<td>Placebo arm n=90</td>
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<tr>
<td>Number of events, n</td>
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<td>55</td>
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<tr>
<td>Median PFS, months (95% CI)</td>
<td>22.1 (16.6–24.7)</td>
<td>11.0 (9.1–16.4)</td>
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<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.585 (0.387–0.884)</td>
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</table>
**MONARCH3: Study Design**

**Statistics:** Study powered to 80% at one-sided alpha of 0.025 assuming a hazard ratio of 0.67 with analyses at 189 and 240 PFS events. Positive study at the interim required a hazard ratio <0.56 and two-sided p<0.0005

**Enrollment:** From November 2014 to November 2015 patients enrolled in 158 centers from 22 countries

**Median follow-up:** 17.8 months (interim analysis)

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**RANDOMIZATION**

- **HR+, HER2- ABC**
- **Postmenopausal**
- Metastatic or locally recurrent disease with no prior systemic therapy in this setting
- If neoadjuvant or adjuvant ET administered, a disease free interval of >12 months since completion of ET
- **ECOG PS ≤1**

**N=493**

**Abemaciclib:** 150 mg BID (continuous schedule) plus anastrozole: 1 mg or a letrozole: 2.5 mg QD until PD

**Placebo:** BID (continuous schedule) plus anastrozole: 1 mg or a letrozole: 2.5 mg QD until PD

**Primary endpoint:**
Investigator-assessed PFS

**Secondary endpoint:**
OS, Response rates, Safety

**Stratification factors:**
- Metastatic site (visceral, bone only, or other)
- Prior ET (AI, no ET, or other)

---

* Per physician’s choice: 79.1% received letrozole, 19.9% received anastrozole.
MONARCH3: Updated results

AEs: neutropenia (21.1% v 1.2%), diarrhea – most common AE (9.5% v 1.2%), and leukopenia (7.6% v 0.6%).

Johnston et al; Nature Breast Cancer 2019
MONARCH 2 Study Design

- HR+, HER2- ABC
- Pre/peri-\textsuperscript{a} or postmenopausal
- ET resistant:
  - Relapsed on neoadjuvant or on/within 1 yr of adjuvant ET
  - Progressed on first-line ET
- No chemo for MBC
- No more than 1 ET for MBC
- ECOG PS ≤ 1

**Randomization**

- 2:1
- abemaciclib: 150 mg\textsuperscript{b} BID (continuous schedule)
- fulvestrant: 500 mg\textsuperscript{c}
- placebo: BID (continuous schedule)
- fulvestrant: 500 mg\textsuperscript{c}

**Primary endpoint:**
Investigator-assessed PFS

**Secondary endpoint:**
Overall Survival, Response, Clinical Benefit Rate, Safety

**Stratification factors:**
- Metastatic site (visceral, bone only, or other)
- ET resistance (primary vs secondary)\textsuperscript{1,2}

- Patients were enrolled in 142 centers in 19 countries
- Statistics: 378 events for 90% power at one-sided \(\alpha\) of .025 assuming a true HR of .703
- \textbf{114 pre/peri-menopausal patients were randomized in the study}

\textsuperscript{a}aged <60 years and have natural menstrual bleeding. Patients were required to receive gonadotropin releasing hormone (GnRH) agonist

\textsuperscript{b}dose post-amendment

\textsuperscript{c}fulvestrant administered per label

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Abbreviations: ABC, advanced breast cancer; BID, twice daily dose; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2-; HR, hazard ratio; HR+, hormone receptor+; MBC, metastatic breast cancer; PFS, progression-free survival

PFS in Pre/Peri-menopausal Population

Median PFS
- abemaciclib + fulvestrant: not reached
- placebo + fulvestrant: 10.5 months

HR (95% CI): .446 (.264, .754); p = .002

Patients at risk:
- abemaciclib: 72
- placebo: 42

PFS benefit confirmed by blinded independent central review
- HR: .432; 95% CI: .236, .793; p < .005
Thank You

drabhishekbasu@yahoo.com