My Journey in Endocrine Therapy for Breast Cancer

Ian E Smith
Royal Marsden Hospital and Institute of Cancer Research, London
April 2019, Korea
On the Treatment of Inoperable Cases of Carcinoma of the Mamma: Suggestions of a New Method of Treatment, with Illustrative Cases.

George Thomas Beatson  Lancet, 2 (1896) 104
ON THE TREATMENT OF INOPERABLE CASES OF CARCINOMA OF THE MAMMA: SUGGESTIONS FOR A NEW METHOD OF TREATMENT, WITH ILLUSTRATIVE CASES.\footnote{1}

BY GEORGE THOMAS BEATSON, M.D. EDIN.,
SURGEON TO THE GLASGOW CANCER HOSPITAL; ASSISTANT SURGEON, GLASGOW WESTERN INFIRMARY; AND EXAMINER IN SURGERY TO THE UNIVERSITY OF EDINBURGH.

I have no doubt it has fallen to the lot of nearly every medical man to have been consulted from time to time by patients suffering from carcinoma so widely spread or so situated that it has been quite apparent that nothing in the way of operative measures could be recommended. Such
Early Types of Endocrine Therapy for Breast Cancer

- Oophorectomy
- Adrenalectomy
- Hypophysectomy
- Oestrogens
- Androgens
Oestrogen Receptor (ER)  
Jensen and Jacobsen (1962)

$^3$H-estrogen bound by target tissues in rats  
- uterus, vagina, pituitary

Could the binding of estrogen by breast cancer determine endocrine response?

Would the absence of estrogen binding (ER-negative) indicate poor likelihood of response?
Estrogen Receptor

80% of Breast Cancers ER+ve
HER2 Immunohistochemical Staining

- **0**: 15,000 - 25,000 Receptors, 1.0 - 1.2 Gene Ratio
- **1+**: 80,000 - 110,000 Receptors, 1.2 - 1.4 Gene Ratio
- **2+**: 370,000 - 630,000 Receptors, 2.4 Gene Ratio
- **3+**: 2,000,000 - 10,000,000 Receptors, 3.4 - 5.6 Gene Ratio
Some Breast Cancers Are Very Sensitive to Estrogen Withdrawal

Letrozole

6 mo
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.

Tamoxifen Efficacy

• In ER+ve metastatic breast cancer:
  • 86 clinical studies involving 5353 patients
  • 30% response rate; 20% stable disease
  • Median Response Durations up to 24 months
  • But resistance occurs sooner or later

Adjuvant Tamoxifen Oxford Analysis 2006

≈ 5 years tamoxifen vs. No adjuvant
RECURRENT
ER+ / ER unknown

Recurrence rates (% / year) and logrank analyses

<table>
<thead>
<tr>
<th></th>
<th>Years 0 – 4</th>
<th>Years 5 – 9</th>
<th>Years 10 – 14</th>
<th>Year 15+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>3.18 (508 / 15967)</td>
<td>2.46 (313 / 12735)</td>
<td>2.51 (231 / 9187)</td>
<td>3.56 (167 / 4693)</td>
</tr>
<tr>
<td>Control</td>
<td>6.18 (907 / 14678)</td>
<td>3.46 (371 / 10712)</td>
<td>2.52 (193 / 7657)</td>
<td>3.28 (126 / 3846)</td>
</tr>
<tr>
<td>Rate ratio, from (O-E) / V</td>
<td>0.49 SE 0.04</td>
<td>0.65 SE 0.07</td>
<td>0.96 SE 0.10</td>
<td>1.07 SE 0.13</td>
</tr>
<tr>
<td></td>
<td>-228.6 / 534.1</td>
<td>-66.6 / 157.0</td>
<td>-3.7 / 98.3</td>
<td>-4.4 / 69.9</td>
</tr>
</tbody>
</table>

Logrank 2p < 0.000001

15–y gain 13.3% (SE 1.3)

≈ 5 y Tam alone

Breast cancer mortality

Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

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<tr>
<td>Tamoxifen</td>
<td>1.60 (268 / 16719)</td>
<td>2.06 (290 / 13937)</td>
<td>1.95 (206 / 10562)</td>
<td>2.25 (161 / 7143)</td>
</tr>
<tr>
<td>Control</td>
<td>2.31 (379 / 16428)</td>
<td>3.02 (401 / 13286)</td>
<td>2.57 (249 / 9703)</td>
<td>2.39 (152 / 6363)</td>
</tr>
<tr>
<td>Rate ratio, from (O-E) / V</td>
<td>0.68 SE 0.07</td>
<td>0.66 SE 0.06</td>
<td>0.77 SE 0.09</td>
<td>1.00 SE 0.12</td>
</tr>
<tr>
<td></td>
<td>-57.0 / 148.2</td>
<td>-65.6 / 159.6</td>
<td>-26.5 / 103.9</td>
<td>-0.3 / 70.6</td>
</tr>
</tbody>
</table>

Logrank 2p < 0.000001

15–y gain 8.4% (SE 1.2)

≈ 5 y Tam alone

Nil

45.7%

32.4%

3.82

23.4

14.1

Nil

32.8%

24.4%

11.1

7.7

16.5

23.7
Led to:

- Low dose AG as an AI
- Letrozole - first in man
- Letrozole –phase 1
- BIG 1-98
Inhibiting the Effects of Estrogen

Androgens → X → E → E×ER

Aromatase

- Sub cut tissues
- Muscle
- Liver
- Breast

Aromatase inhibitors
- Anastrozole
- Letrozole
- Exemestane

Antiestrogens
- Tamoxifen

Nucleus

Inhibition of cell proliferation

Tumor cell
Adjuvant Letrozole v Tamoxifen: BIG 1-98 Median 8 Years FU

DFS

HR 0.82 (95% CI 0.74-0.92)
p = 0.0002

5-year DFS
Letrozole 85.5%
Tamoxifen 82.0%

8-year DFS
Letrozole 76.4%
Tamoxifen 72.0%

OS

HR 0.79 (95% CI 0.69-0.90)
p = 0.0006

5-year OS
Letrozole 91.8%
Tamoxifen 90.3%

8-year OS
Letrozole 85.4%
Tamoxifen 81.4%

Regan et al Lancet Oncology 12:1101 2011
Aromatase Inhibitors v Tamoxifen in Early Breast Cancer: Meta-analysis

Recurrence

9885 women, 1791 events
RR=0.80 (95% CI 0.73–0.88)
10-year gain 3.6% (95% CI 1.7 to 5.4)
Log-rank 2p<0.00001

Deaths

9885 women, 1936 deaths
RR=0.89 (95% CI 0.8–0.97)
10-year gain 2.7% (95% CI 0.1 to 4.7)
Log-rank 2p=0.01

EBCTCG Lancet 2015
Endocrine Therapy in Breast Cancer

• Only effective in women with ER+ve cancer (75-80%)

• **Tamoxifen** Oestrogen antagonist. Doesn’t affect circulating E2 levels. Effective in pre- and postmenopausal women

• **Aromatase Inhibitors***. Inhibit oestrogen synthesis. Dramatically reduce circulating E2 levels. Only effective in postmenopausal women. Slightly more effective than tamoxifen

* Letrozole; anastrozole; exemestane
Tamoxifen and Aromatase Inhibitors
Side Effects/Morbidity

• Both usually well tolerated compared with chemotherapy

• **Tamoxifen**
  - Venous thrombo-embolism
  - Uterine cancer

• **Aromatase Inhibitors**
  - Joint stiffness
  - Bone loss
  - Vaginal dryness
Only 30% of patients with ER+ve metastatic breast respond to endocrine therapy and a further 20% achieve stable disease

Likewise not all patients benefit from adjuvant endocrine therapy

Why?
Cross-talk Between Signal Transduction and Endocrine Pathways

CDK4/6 in Breast Cancer

- Resistance to endocrine therapy presents a major clinical challenge.
- The growth of HR+ breast cancer is dependent on Cyclin D1, a direct transcriptional target of ER.
- Cyclin D1 activates CDK 4/6 resulting in G1–S phase transition and entry into the cell cycle.\(^1\)

\(\text{ER}\alpha\)  
Mitogenic signalling  
\(\text{CDK1/2} \rightarrow \text{CDK1} \rightarrow \text{Cyclin A} \rightarrow \text{S phase transcription program} \)  
\(\text{G1/S transition} \)  
\(\text{E2F} \)  
\(\text{CDK4/6} \rightarrow \text{Cyclin D} \rightarrow \text{pRB} \)  
\(\text{G1} \rightarrow \text{G2} \rightarrow \text{M} \)  
\(\text{CDK1} \rightarrow \text{Cyclin B} \rightarrow \text{pRB} \)  
\(\text{S phase transcription program} \)

\(\text{Figure adapted from Asghar, et al. Nat Rev Drug Dis. 2015;14:130-146}\)
Selective CDK 4/6 inhibitors

Abemaciclib

Palbociclib

Ribociclib

<table>
<thead>
<tr>
<th>IC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>Abemaciclib (LY-2835219)</th>
<th>Palbociclib (PD-0332991)</th>
<th>Ribociclib (LEE011)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDK1</td>
<td>&gt;1 μM</td>
<td>&gt;10 μM</td>
<td>&gt;100 μM</td>
</tr>
<tr>
<td>CDK2</td>
<td>&gt;500 nM</td>
<td>&gt;10 μM</td>
<td>&gt;50 μM</td>
</tr>
<tr>
<td>CDK4</td>
<td>2 nM</td>
<td>9–11 nM</td>
<td>10 nM</td>
</tr>
<tr>
<td>CDK5: ND</td>
<td></td>
<td>&gt;10 μM</td>
<td>ND</td>
</tr>
<tr>
<td>CDK6: 5 nM</td>
<td></td>
<td>15 nM</td>
<td>39 nM</td>
</tr>
<tr>
<td>CDK7: 300 nM</td>
<td></td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>CDK9: 57 nM</td>
<td></td>
<td>ND</td>
<td>ND</td>
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PALOMA-2 & MOLALEESA-2: Design of Phase III Studies

**PALOMA-2**

- **Randomised**
- **N=666**
- **Primary endpoint:** PFS
- **Secondary endpoints:**
  - Response, OS, safety, biomarkers, PROs

Randomisation:

- Postmenopausal ER+ HER2– advanced breast cancer with no prior treatment for advanced disease, AI-resistant patients excluded

- **Palbociclib** (125 mg QD, 3/1 schedule) + letrozole (2.5 mg QD)
- **Placebo + letrozole** (2.5 mg QD)

**MOLALEESA-2**

- **Randomised**
- **N=668**
- **Primary endpoint:** PFS
- **Secondary endpoints:**
  - OS (key), ORR, CBR, safety

Randomisation:

- Postmenopausal women with HR+/HER2– advanced breast cancer with no prior therapy for advanced disease

- **Ribociclib** (600 mg QD, 3/1 schedule) + letrozole (2.5 mg QD)
- **Placebo + letrozole** (2.5 mg QD)

Stratified by the presence/absence of liver and/or lung metastases
PALOMA-2 & MONALEESA-2: PFS

**PALOMA-2**

- **palbociclib**

  - mPFS (months)
    - Palbociclib–letrozole: 24.8
    - Placebo–letrozole: 14.5
  - Hazard ratio, 0.58 (95% CI, 0.46–0.72)
  - Two-sided P<0.001

**MONALEESA-2**

- **ribociclib**

  - mPFS (months)
    - Ribociclib–letrozole: NR
    - Placebo–letrozole: 14.7
  - Hazard ratio, 0.56 (95% CI, 0.43–0.72)
  - P=3.29×10⁻⁶ for superiority

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The Role of Adjuvant Chemotherapy in ER+ve Early Breast Cancer
Polychemo. + tamoxifen vs. Tam. alone

RECURRENT

ER+, entry age < 50

Recurrence rates (% / year) and logrank analyses

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<td>Polychemo.</td>
<td>2.62 (129 / 4931)</td>
<td>2.20 (84 / 314)</td>
<td>1.81 (39 / 2149)</td>
</tr>
<tr>
<td>Control</td>
<td>4.35 (203 / 4671)</td>
<td>2.74 (94 / 3427)</td>
<td>2.49 (46 / 1850)</td>
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Rate ratio, from (O–E) / V

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<td>0–4</td>
<td>–43.3 / 74.5</td>
<td>–10.1 / 41.5</td>
<td>–5.5 / 20.3</td>
<td>–2.2 / 2.0</td>
</tr>
</tbody>
</table>

15–y gain 9.8% (SE 2.4)
Logrank 2p < 0.00001

Tam alone 37.0%

Chemo. + Tam 27.2%
The Big Current Question in the Adjuvant Treatment of Early Breast Cancer

Adjuvant chemotherapy is also an effective treatment for some patients with ER+ve breast cancer.

So how can we select which patients only need endocrine therapy alone, and which need additional treatment (eg chemotherapy or a CD4/6 inhibitor)?
Genomic Health Multi-Gene Assay: Oncotype DX

- 21 gene assay
- Includes PgR
- Formalin-fixed PE
- Based on B14 and B20 Trials
- N-ve ER+ve

Likelihood of distant recurrence according to recurrence score

Rate distant recurrence as continuous function of recurrence score

Paik et al NEJM 2004; 351;2817
Genomic Platforms to Identify Prognosis in ER+ Early Breast Cancer

- Oncotype DX
- Prosigna
- Endopredict
- MammaPrint
An Important Thing About Breast Cancer

• Anatomically, the primary offers a unique opportunity to assess systemic therapies

• We should take advantage of this as much as possible
Neoadjuvant Therapy for Breast Cancer:
Opportunity for Serial Molecular Markers (eg Proliferation) in the Individual Patient

![Graph showing Ki67 (%)](image)
IMPACT: 2 Week Effect of Anastrozole on Ki67 in Individual Patients

Innate biology – Prognostic

Reflects treatment sensitivity in the individual patient-Predict outcome better?
RFS by Ki67 in IMPACT: Pre vs 2 Week

Relapse Free Survival by baseline LnKi67

Relapse Free Survival by 2 week LnKi67

Not significant ← Multivariate analysis → HR 2.01 p 0.002

Dowsett, Smith et al JNCI 2007
Postmenopausal ER-positive early breast cancer

Randomize 2:1 ratio

**Perioperative Therapy**
- AI* treatment for 2 weeks
- Surgery
- AI for 2 weeks post-op

**No Perioperative Therapy**
- Surgery
- 2 weeks

Further treatment in accordance with local practice

Baseline core biopsy
- 2 week core excision biopsy

4486pts. 130 UK centres. >16,000 bloods. >10,000 tumour samples

Smith I, Robertson J, Bliss J, Dowsett M and many others

* Aromatase Inhibitor
TTR* by baseline Ki67 – peri-op AI patients

<table>
<thead>
<tr>
<th>Ki67&lt;sub&gt;B&lt;/sub&gt;</th>
<th>% Total</th>
<th>5yr Absolute risk</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>31%</td>
<td>4.9%</td>
<td>3.5, 7.0</td>
</tr>
<tr>
<td>H</td>
<td>69%</td>
<td>12.1%</td>
<td>10.1, 14.1</td>
</tr>
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</table>

Unadjusted HR: 2.60 (95% CI 1.82 – 3.73)
Log-rank test p<0.0001

*Time to recurrence
In patients with Ki67_B ≥10%
HR for Ki67_{2w} ≥10% is 2.22 (95%CI: 1.68, 2.94; p<0.001)

*Time to recurrence
Conclusions (1)

- Endocrine therapy is an enormously important treatment for women with ER+ve breast cancer (75-80% of total)

- It acts either by blocking E2 stimulation of the cancer (tamoxifen) or by switching off synthesis (aromatase inhibitors, ovarian suppression)

- It is not always effective – primary or secondary resistance
Conclusions (2)

• Targeted therapies are emerging to block endocrine resistance pathways eg CD4/6 inhibitors

• A major current challenge is to identify which patients with ER+ early breast cancer require additional adjuvant therapies (chemotherapy, CD4/6 inhibitors) to standard endocrine therapy

• Short term preoperative endocrine therapy to measure the effect of endocrine therapy on Ki67 offers a simple potential new approach to this.
Cell free DNA (cfDNA) is released into the blood of patients with a wide range of malignancies.

Only a low fraction of cfDNA consists of tumour-derived DNA or circulating tumour DNA (ctDNA) the remainder being derived from non-cancerous somatic cells.

ctDNA is detected in >90% patients with metastatic breast cancer.

The frequency of tumor specific alterations in the blood is as low as 0.01%.

Half life short 1.5hrs

Diehl et al Nat Med 2008
Perkins G et al PLoS ONE 2011
Forshew et al STM 2012
Dawson et al NEJM 2013
Crowley et al Nat Rev Clin Oncol 2013
Bettegowda et al STM 2014
Genomic Mutations in ER+ Advanced Breast Cancer. ESR 1

ESR1 mutations occur in ~20% of endocrine resistant ER positive breast cancer

**ESR1** mutations in ctDNA Confer Resistance to Subsequent Aromatase Inhibitor

Retrospective single centre series
PFS on subsequent AI therapy

Schiavon *et al* AACR 2015, STM 2015
Plasma ESR1 Mutations and the Treatment of Estrogen Receptor–Positive Advanced Breast Cancer


**ESR1 mutated**

- Exemestane: Median PFS, 2.6 months (95% CI, 2.4 to 6.2)
- Fulvestrant-containing regimen: Median PFS, 5.7 months (95% CI, 3.0 to 8.5)

**ESR1 wild type**

- Exemestane: Median PFS, 8.0 months (95% CI, 3.0 to 11.5)
- Fulvestrant-containing regimen: Median PFS, 5.4 months (95% CI, 3.7 to 8.1)

HR, 0.52 (95% CI, 0.30 to 0.92); P = .02

HR, 1.07 (95% CI, 0.68 to 1.67); P = .77

PALOMA3 (Fulvestrant + Palbociclib) by ESR1 mutation status

ESR1 Mutant (25%)

Fulvestrant-Palbociclib
Fulvestrant-Placebo

ESR1 Wild type

Fulvestrant-Palbociclib
Fulvestrant-Placebo

HR = 0.43 95% CI 0.25 – 0.74, p = 0.002

HR = 0.49 95% CI 0.35 – 0.70, p < 0.001

Hypothesis

• ESR-1 mutations are induced by AI exposure
• Fulvestrant overrides the mutation by degrading the receptor
• Palbociclib overrides the mutation by blocking a constitutively active ‘escape’ pathway
• Late relapses are likely to have a high incidence of ESR1 mutations
• They are therefore more likely to be controlled by fulvestrant or a CD4/6 combination therapy than by an AI alone