Endocrine Therapy for Metastatic Breast Cancer

Ian E Smith
Royal Marsden Hospital and Institute of Cancer Research, London
ESMO Madrid September 2014
ON THE TREATMENT OF INOPERABLE CASES OF CARCINOMA OF THE MAMMA: SUGGESTIONS FOR A NEW METHOD OF TREATMENT, WITH ILLUSTRATIVE CASES.

BY GEORGE THOMAS BEATSON, M.D. EDIN.
SURGEON TO THE GLASGOW CANCER HOSPITAL; ASSISTANT SURGEON TO THE 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
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?
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 15 - 24 months

When Should Endocrine Therapy Be Used in Metastatic Breast Cancer?

• ASCO Clinical Practice Guidelines for Treatment of Metastatic Breast Cancer
• Co –Chairs Partridge A and Smith IE

• Recommendation 1
  Endocrine therapy, rather than chemotherapy, should be offered as the standard first-line treatment for advanced/metastatic breast cancer patients with ER+ve disease, except for immediately life threatening disease
  - The main benefit is less toxicity and better quality of life for the patient associated with endocrine therapy compared with chemotherapy (potential benefit: high).
  - The quality of the evidence is intermediate, and is based on the NCCC systematic review
  - The strength of this recommendation is strong and is supported by the evidence and expert consensus

Partridge et al JCO 2014
What Is the Optimal Endocrine Therapy for Metastatic Breast Cancer?

- **SERMs**
  - Tamoxifen
  - Toremifene

- **SERDs**
  - Fulvestrant

- **Aromatase inhibitors**
  - Anastrozole
  - Letrozole
  - Exemestane

- **Progestins**
  - Megestrol acetate
  - Medroxyprogesterone acetate

- **Estrogens**
  - Estradiol
  - DES (diethylstilbestrol)

- **Androgens**
  - Fluoxymesterone

- **LHRH analogs**
  - Goserelmin
  - Leuprolide
  - Buserelin

SERM = selective endocrine receptor modulator; SERD = selective estrogen receptor down-regulator;

<table>
<thead>
<tr>
<th>Type</th>
<th>Count</th>
<th>n=17</th>
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<tbody>
<tr>
<td>Progestagens</td>
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<tr>
<td>Estrogens</td>
<td>1</td>
<td></td>
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<tr>
<td>Androgens</td>
<td>1</td>
<td></td>
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<tr>
<td>Anti-Estrogens</td>
<td>2</td>
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<tr>
<td>AG</td>
<td>3</td>
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<tr>
<td>Formestane</td>
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<tr>
<td>Fadrozole</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Fulvestrant</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Tamoxifen always better or at least as good

Inhibiting the Effects of Estrogen

Androgens → E

Aromatase inhibitors
- Anastrozole
- Letrozole
- Exemestane

E + ER → Antiestrogens

Tumor cell

Inhibition of cell proliferation
First Line Trials of AI v Tamoxifen in Metastatic Breast Cancer

- Randomize
- Tamoxifen 20 mg
  - Anastrozole 1 mg (2 Trials)
    - or
  - Letrozole 2.5 mg
    - or
  - Exemestane 25 mg

- 4 Trials 3320 patients
- 2 (letrozole and exemestane) better for Overall Response
- 3 better for Time To Progression
- None better for Overall Survival

Mouridsen H, JCO 2001 and JCO 2003
Nabholtz JM et al JCO 2000
Bonneterre J et al JCO 2000
Bonneterre al Cancer 2001
Paridaens R et al. JCO 2008
What Is the Optimal Endocrine Therapy in Metastatic Breast Cancer After an Adjuvant AI?

- These endocrine trials in metastatic breast cancer were done BEFORE the era of adjuvant AIs (ATAC; BIG 1-98; TEAM)

- What is the best endocrine therapy for a patient with mbc who has relapsed during or after an adjuvant AI?

- Options: Exemestane, Tamoxifen, Fulvestrant, Progestogens, Estrogens
How Good Is Exemestane After a Non-Steroidal AI?
Data from Trials vs Fulvestrant 591 pts

<table>
<thead>
<tr>
<th></th>
<th>Response</th>
<th>Clinical Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFFECT</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exemestane (342 pts)</td>
<td>6.7%</td>
<td>31.5%</td>
</tr>
</tbody>
</table>

|                  |          |                  |
| **SOFEA**<sup>2</sup> |          |                  |
| Exemestane (249 pts) | 2.8%     | 39.8%            |

<sup>1</sup>Chia S, et al. JCO 2008

<sup>2</sup>Johnston et al, LBA2 - EBCC Vienna 2012
How About Tamoxifen after AI Failure?

Not a lot of data

Anastrozole v. Tamoxifen¹:
Retrospective crossover data for tamoxifen

TAMRAD²:
Tamoxifen + Everolimus v Tamoxifen alone in patients with previous AI exposure

²Bachelot T, et al. SABCS 2010. Abstract S1-6
Anastrozole v Tamoxifen Trials in MBC
Tamoxifen Cross-Over after Anastrozole

- 2 trials. 511 patients randomised to anastrozole
- Questionnaire data were available for 119 patients crossed-over to tamoxifen after anastrozole
- 58 (49%) gained clinical benefit
- 12 (10%) had an objective response

TAMRAD: Tam v Tam + Everolimus
Primary Endpoint: Clinical Benefit Rate

\[ P = 0.045 \text{ (exploratory analysis)} \]

**Tamoxifen**

- 42% (29.1-55.9)

**Tam+ Ev**

- 61% (46.9-74.1)

Fulvestrant: Mechanism of Action.

Osborne et al British Journal of Cancer (2004) 90, S2–S6

ERE Estrogen response element; ER estrogen receptor; F fulvestrant
Fulvestrant versus Tamoxifen in Postmenopausal Patients with Advanced Breast Cancer

<table>
<thead>
<tr>
<th>Objective tumor response to treatment in patients with ER-and/or PR-positive tumors</th>
<th>Fulvestrant (n=247)</th>
<th>Tamoxifen (n=212)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>8.90%</td>
<td>5.70%</td>
<td>NR</td>
</tr>
<tr>
<td>Partial response</td>
<td>24.3%</td>
<td>25.5%</td>
<td>NR</td>
</tr>
<tr>
<td>Stable disease ≥ 24 wk</td>
<td>23.9%</td>
<td>31.6%</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Objective response rate</strong></td>
<td>33.2%</td>
<td>31.1%</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>Clinical benefit rate</strong></td>
<td>57.1%</td>
<td>62.7%</td>
<td>0.22</td>
</tr>
<tr>
<td>Time to progression</td>
<td>8.2 mo</td>
<td>8.3 mo</td>
<td>0.39</td>
</tr>
</tbody>
</table>

NR = not reported

Kaplan-Meier plot for time to progression (patients with estrogen receptor-positive and/or progesterone receptor-positive tumors)

Howell A et al. J Clin Oncol 2004
Does Fulvestrant Enhance the Efficacy of AIs?
Experimental Rationale Using Xenografts

Brodie A et al, Cancer Res 65:5439-44, 2005

Macedo et al, Cancer Res 68, 3516-22, 2008
ER &/or PgR +ve postmenopausal patients with locally advanced (LABC) / metastatic breast cancer (MBC) following progression on NSAI as adjuvant treatment for at least 12 months

Or as 1st line therapy for LABC or MBC for at least 6 months 2nd-line non-steroidal AI failures

- Fulvestrant LD* + placebo (n=250)
- Fulvestrant LD + anastrozole 1 mg orally daily (n=250)
- Exemestane 25 mg orally daily (n=250)

Patients continue treatment until disease progression

Follow-up for survival

*500 mg Day 1, 250 mg Days 14 & 28, and monthly
SOFEA: Fulvestrant (F) + Anastrozole versus F

Progression-Free Survival

Median PFS:
- F+A: 4.4 months
- F: 4.8 months

Hazard ratio = 1.00, 95% CI (0.83, 1.21)
Log rank p = 0.98

F=221/231
F+A=235/243

Number of events/at risk:
- F+A: 0/243, 98/148, 56/89, 22/67, 16/51, 16/34, 9/23, 6/17, 4+8*/13
- F: 0/231, 83/149, 59/90, 34/55, 11/44, 15/29, 8/18, 5/12, 1+5*/11

Overall Response:
- F+A: 7.0%
- F: 6.9%

Women surviving progression-free (%)

Time from randomisation (months)

Johnston SRD et al, LBA2 - EBCC Vienna 2012
### Fulvestrant Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Arms</th>
<th>n</th>
<th>Median TTP (mo)</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT (1&lt;sup&gt;st&lt;/sup&gt; line) ¹</td>
<td>FULV LD + Ana Ana</td>
<td>258</td>
<td>15 (P&lt;.007)*</td>
<td>37.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>256</td>
<td>13.5</td>
<td>38.2</td>
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<tr>
<td>SWOG S0226 (1&lt;sup&gt;st&lt;/sup&gt; line) ²</td>
<td>FULV LD + Ana Ana</td>
<td>355</td>
<td>15 (P&lt;.007)*</td>
<td>47.7 (P=.049)*</td>
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<td></td>
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<td>352</td>
<td>13.5</td>
<td>41.3</td>
</tr>
<tr>
<td>FIRST (1&lt;sup&gt;st&lt;/sup&gt; line) ³</td>
<td>FULV HD Ana</td>
<td>102</td>
<td>23.4 (P=.01)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>103</td>
<td>13.1</td>
<td>-</td>
</tr>
<tr>
<td>EFECT (3&lt;sup&gt;rd&lt;/sup&gt; line or more) ⁴</td>
<td>FULV LD Exe</td>
<td>351</td>
<td>-</td>
<td>nr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>342</td>
<td>-</td>
<td>nr</td>
</tr>
<tr>
<td>SOFEA (acquired AI resistance) ⁵</td>
<td>FULV LD + Ana FULV LD Exe</td>
<td>243</td>
<td>-</td>
<td>-</td>
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<tr>
<td></td>
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<td>231</td>
<td>-</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>249</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CONFIRM (2nd line) ⁶</td>
<td>Fulv HD 500mg Fulv AD 250mg</td>
<td>362</td>
<td>6.5 (P=.006)</td>
<td>25.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>374</td>
<td>5.5</td>
<td>22.8</td>
</tr>
</tbody>
</table>

*benefits restricted to tamoxifen-naive patients (n=414, 60%, unplanned subgroup analysis)

HD (high dose) = 500mg i.m. at day 0 + 500mg i.m. at days 14 and 28, thereafter 500mg i.m. monthly until PD
AD (approved dose) = 250mg i.m. monthly
LD (loading dose regimen) =500mg i.m. at day 0, 250mg at days 14, 28, and 250mg monthly thereafter

CONFIRM Overall survival
(final analysis at 75% maturity – full analysis set)

Proportion of patients alive

- Fulvestrant 500 mg
- Fulvestrant 250 mg

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>0.81 (0.69, 0.96)</td>
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</table>

p-value

0.016

Median time to death (months)

- Fulvestrant 500 mg: 26.4 months
- Fulvestrant 250 mg: 22.3 months

Time (months)

Patients at risk:

<table>
<thead>
<tr>
<th>500 mg</th>
<th>250 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>362 333 288 254 227 202 178 163 141 123 114 98 81 64 47 30 26 15 8 1 0</td>
<td>374 338 299 261 223 191 164 137 112 96 87 74 64 48 37 22 14 8 3 2 0</td>
</tr>
</tbody>
</table>

Di Leo et al JCO 2010 Update
Fulvestrant: Conclusions

- Equivalent to tamoxifen as first-line treatment (study 0025)
- Equivalent to anastrozole first line (FIRST), maybe better (FACT;SO226)
- Equivalent to exemestane post NSAI (EFECT;SOFEA)
- Superior PFS comparing 500mg vs 250mg as second-line therapy (CONFIRM)
Estrogen deprivation therapy with AIs has been hypothesized to sensitize ER+ve breast cancer tumor cells to low-dose estradiol

**Clinical benefit rate:**
- 30mg 28% (9/32 pts)
- 6mg 29% (10/34 pts)

**Adverse event rate (≥grade 3):**
- 30mg 34% (11/32 pts)
- 6mg 18% (4/34 pts) \(P=.03\)

*The efficacy of the lower dose should be further examined in phase III clinical trials*

Ellis et al, SABCS 2008 Abstract 16; Ellis M et al, JAMA 2009
Case Study 59yr old

- **Mar 2011** 5cm L breast carcinoma. Core biopsy - Grade II invasive ductal carcinoma. ER8/8, PgR 8/8, HER-2 negative, axillary node cytology C5. CT scan and bone scan metastatic bone disease including collapse T5.
- Letrozole and zoledronate radiotherapy to T4. Stable Disease

- **Feb 2013** Progressive bone disease on MRI scan CA15-3 up. Exemestane and Everolimus Clinical improvement CA 15-3 down.
- **May 2014** Progression bone disease, pain and CA15-3 up

- Next Treatment?
Case Study 59yr old (cont)

- **June 2014**  Tamoxifen

- **July 2014**  CA 15-3 rapidly up then down

- **Sept 2014**  Symptom-free. CA15-3 continues to fall

- **Moral** – don’t forget tamoxifen!
Sequential Endocrine Treatment

The optimal sequence has not been defined

1st Line
2nd Line
3rd Line
4th Line
Both premenopausal and postmenopausal women with metastatic breast cancer who have responded to endocrine therapy will benefit from additional endocrine therapy at the time of disease progression.

**Postmenopausal** The optimal sequence has yet to be determined.

Second-line in postmenopausal women: one option is **fulvestrant = anastrozole** after disease progression on tamoxifen\(^1\)

Second- or third-line following a NSAI: **fulvestrant = exemestane** in terms of TTP and response\(^2\)

Optimal dosing of fulvestrant remains unclear, with the suggestion of increased benefit with 500-mg intramuscularly monthly dosing\(^3\)

**Premenopausal** Previous anti-estrogen therapy within the previous year: ovarian suppression with LHRH agonist.

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1. Osborne 2002; Howell 2002
2. Chia 2008
3. DiLeo 2010; Bergh 2009
Endocrine Therapy in Metastatic Breast Cancer: My Suggested Guidelines

• No Previous AI
  - Use an AI (or tamoxifen if side effects)
• Previous AI
  - Tamoxifen and Fulvestrant of some benefit
  - Exemestane – some clinical benefit but OR rare
    - Optimal order not known
  - Progestogens and Estrogens may be of benefit
• Premenopausal (After tamoxifen)
  - AI with ovarian suppression
Why Do ER+ve Breast Cancers Not Always Respond to Endocrine Therapy?

What Is the Basis for De Novo and Acquired Resistance?
ER-positive Cancers Are Heterogeneous at Diagnosis and at Recurrence

Sorlie et al. PNAS 2003
Can We Improve on Endocrine Therapy? Cross-Talk Signalling

[Diagram showing cellular pathways involving growth factors, Estrogen receptors (ER), protein kinases (PI3-K, AKT, mTOR, MEK), transcription factors (p160, CBP, ERE), and signaling cascades involving EGFR/HER2 and EGFR]

©2010 by American Association for Cancer Research
Crosstalk between ER and mTOR Signalling

- mTORC1 activates ER in a ligand-independent fashion
- Hyperactivation of the PI3K/mTOR pathway is observed in endocrine resistant breast cancer cells
- mTOR is a rational target to enhance the efficacy of hormonal therapy
- Everolimus is one of a group of mTOR inhibitors

Yamnik, RL. J Biol Chem 2009; 284(10):6361-636
Miller, TW. J Clin Invest 2010; 120(7):2406-2413
BOLERO-2: A Phase 3 Trial (724 patients*) of Exemestane + Everolimus
Primary Endpoint, PFS

Hazard ratio, 0.43 (95% CI, 0.35–0.54)
P<0.001 by log-rank test

* Refractory to anastrozole or letrozole

BOLERO-2: Exemestane+/-Everolimus
Update: Overall Survival

Piccart et al  Ann Oncol Sept 2014

HR 0.09 (0.73-1.10)
Log-rank p0.14
K-M medians
Ev + E  31  months
Pl + E  26.6 months
HORIZON: Letrozole + Temsirolimus

Phase 3 Placebo controlled study
N = 1112
Postmenopausal women with ER+ advanced breast cancer
AI naïve

Letrozole 2.5mg/day + Temsirolimus 30 mg/d 5 days q2 weeks

Letrozole 2.5 mg/day + Placebo

TAMRAD: Phase II trial in Metastatic Postmenopausal women with ABC with previous exposure to AIs

Phase 2 study
N = 111
Postmenopausal women with ER+ HER2- advanced breast cancer
March 2008-May 2009

Everolimus 10 mg/d + Tamoxifen 20 mg/d (n = 485)

Tamoxifen 20 mg/d (n = 239)

Primary endpoint: Clinical benefit Rate

Stratification: Primary or Secondary Resistance

Primary: Relapse during adjuvant AI; progression within 6 months of starting AI treatment in metastatic setting

Secondary: Late relapse (≥ 6 months) or prior response and subsequent progression to metastatic AI treatment

TAMRAD: Tam v Tam + Everolimus
Phase 2 (Prior AI): Time to Progression

Hazard Ratio (HR) = 0.53; 95% CI (0.35-0.81)
Exploratory log-rank: $P = 0.0026$

TAM: 4.5 mo.
TAM + RAD: 8.6 mo.

TAMRAD: TTP as a Function of Intrinsic Hormone Resistance

**Primary hormone resistance**

HR = 0.70 (95% CI = 0.40, 1.21)

\( P = \text{NS} \)

- Tamoxifen: 3.8 mo
- Tamoxifen + Everolimus: 5.4 mo

**Secondary hormone resistance**

HR = 0.46 (95% CI = 0.26, 0.83)

\( P = .0087 \)

- Tamoxifen: 5.5 mo
- Tamoxifen + Everolimus: 14.8 mo

Primary Resistance
Relapse during adjuvant AI; progression within 6 months of starting AI treatment in the metastatic setting

Secondary Resistance
Late relapse (≥ 6 months) or prior response and subsequent progression to metastatic AI treatment

Targeting the Cell Cycle: Cyclin D1/CDK 4-6

- In AI resistance models, ER drives a CDK 4/E2F-dependent transcriptional program.
- CDK 4-6 inhibition reduces cell proliferation in both ER-dependent and ER-independent, AI resistance breast cancer models.
- PD 0332991 (palbociclib), a selective inhibitor of CDK-4/6, prevents DNA synthesis by blocking cell cycle progression.

Palbociclib: CDK 4/6 Inhibitor

**Preferential activity on ER+ luminal breast cancer cell lines with or without HER2 amplification**

- Resistance to Palbociclib in many of the nonluminal breast cancer cell lines may be explained by the absence of pRb.
- Lack of pRb in basal-like breast cancer tissue can result in the characteristic epithelial-to-mesenchymal transition changes

PD 0332991 (Palbociclib): CDK 4/6 Inhibitor
First Line Phase 2 Trial: Palbociclib + Letrozole v Letrozole

**Progression-Free Survival (ITT)**

<table>
<thead>
<tr>
<th></th>
<th>PAL + LET (N=84)</th>
<th>LET (N=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Events (%)</td>
<td>41 (49)</td>
<td>59 (73)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>20.2 (13.8, 27.5)</td>
<td>10.2 (5.7, 12.8)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.488 (0.319, 0.748)</td>
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</tr>
<tr>
<td>p-value</td>
<td>0.0004</td>
<td></td>
</tr>
</tbody>
</table>

Finn RS et al. AACR 2014 abstr CT101
PD 0332991 (Palbociclib): CDK 4/6 Inhibitor
Phase 2 Trial: Palbociclib + Letrozole v Letrozole

- Response rate 27%* v 23%
- Clinical Benefit 59%* v 44%
- Commonest side effects* neutropenia, leukopenia, fatigue

* Combination arm
Palbociclib(P): Next Steps

• PALOMA 2  Phase 3  P + Letrozole  v  letrozole

• PALOMA 3  Phase 3  P + Fulvestrant v Fulvestrant

• PALLET      Phase 2  Neoadjuvant  P + letrozole
  Which patients are most likely to benefit?
PALLET Trial Design: Ph2 Study of Palbociclib with Letrozole in the Neoadjuvant Treatment of ER+ BC

Ph2 Study (ICR-CTSU & NSABP): To Support Patient Selection for Ph 3

- Patients Characteristics
  - Postmenopausal women with localized ER+HER2-negative early breast cancer suitable for neoadjuvant therapy with letrozole

- Letrozole (given for 14 weeks)
  - Letrozole (given 2 wks)
  - Palbociclib (given 2 wks)
  - Letrozole + Palbociclib (given 2 wks)

- Surgery
  - Letrozole + Palbociclib (given 12 weeks)

- To perform gene expression profile analysis by a commercially available assay such as PAM 50, Oncotype Dx etc. and identify with tumor subsets (such as luminal B, or RS >=18) that benefit from palbociclib treatment

- N=301 Open label, Multicenter (UK & USA), Active controlled, Ph2
- Primary Endpoints: Decrease in Ki67 at wk 14; Clinical response at 3 mo
- Secondary Endpoints: Ki67 at 2 weeks, pCR after 14 weeks
- Stratification Factors: by country

- PIs - Johnston, Dowsett, Osborne, Wolmark
Conclusions: Endocrine Therapy for ER+ve Metastatic Breast Cancer

• When it works endocrine therapy is still the best treatment in terms of duration of benefit and low toxicity
• First line treatment except for immediately life-threatening visceral disease
• AIs best for postmenopausal women if no previous treatment
Conclusions: Endocrine Therapy for ER+ve Metastatic Breast Cancer

• After AIs, no single best second line, but don’t forget tamoxifen
• If previous responses, keep trying sequential therapies
• Edge of a new era in which targeted therapies will help overcome resistant disease
PD 0332991 (Palbociclib): CDK 4/6 Inhibitor
P + Let vs Let. Progression-Free Survival


Hazard ratio = 0.35
95% CI, 0.17-0.72
P = 0.006

Progression-Free Survival Probability

Number of subjects at risk
PD 0332991 + LET 34 30 27 25 24 21 17 13 10 6 2
LET 32 22 15 11 9 8 8 7 5 3 3 1 1

26 mo
7.5 mo
BOLERO-2: Overall Response Rate and Clinical Benefit Rate by Local Assessment

Central assessment:
- Response rate: 7.0% vs 0.4%
- Clinical benefit rate: 30.9% vs 15.1%

Presented by J. Baselga at the 2011 European Multidisciplinary Cancer Congress (ECCO/ESMO), September 26, 2011. Abstract: 9LBA.
TAMRAD: Tam v Tam + Everolimus
Primary Endpoint: Clinical Benefit Rate

$P = 0.045$ (exploratory analysis)

42% (29.1-55.9)

61% (46.9-74.1)
PALLET

A phase II randomised study evaluating the biological and clinical effects of the combination of palbociclib with letrozole as neoadjuvant therapy in post-menopausal women with ER+ primary breast cancer

RECRUITMENT
TARGET
306 patients (global), 100-200 patients (UK)
ASCO 2013

• A phase II trial of an oral CDK 4/6 inhibitor, PD0332991, in advanced breast cancer.

• 2013 ASCO Annual Meeting abstr 519

• Author(s):
  • Angela DeMichele, Amy Sanders Clark, Daniel Heitjan, Sophia Randolph, Maryann Gallagher, Priti Lal, Michael D Feldman, Paul J. Zhang, Allison Schnader, Kelly Zafman, Susan M. Domchek, Keerthi Gogineni, Stephen Michael Keefe, Kevin R. Fox, Peter J. O'Dwyer; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; Hospital of the University of Pennsylvania, Philadelphia, PA; University of Pennsylvania, Philadelphia, PA; Pfizer Oncology, San Diego, CA; University of Pennsylvania Health System, Philadelphia, PA

• Abstract:

  • Background: The G1/S checkpoint of the cell cycle is frequently dysregulated in breast cancer (BC). Initial efficacy of PD0332991, a potent oral inhibitor of cyclin-dependent kinases (CDKs) 4/6 was shown in a variety of solid tumors and in combination with letrozole in a randomized phase II trial. Methods: We performed a phase II, single arm trial of PD0332991 in women with advanced BC. The primary objectives were safety and efficacy. Eligible patients had histologically-confirmed, stage IV BC with primary or metastatic tumor positive for retinoblastoma (Rb) protein expression, measurable disease by RECIST and adequate organ function/performance status. PD0332991 was given at 125 mg orally, days 1 – 21 of a 28-day cycle. Tumor was assessed every 2 cycles. A two-stage statistical design was employed. Secondary objectives included predictive biomarker assessment. Results: 36 patients were enrolled; 28 who completed cycle 1 are reported: 18 (64%) HR+/Her2-, 2 (7%) HR+/Her2+ and 8 (29%) HR-/Her2-. 90% had prior chemotherapy for metastatic disease (median 3 lines); 78% had prior hormonal therapy (median 2 lines). Grade 3/4 toxicities were limited to transient neutropenia (50%) and thrombocytopenia (21%). One episode of neutropenic sepsis occurred in cycle 1 in patient with 6 prior chemo regimens. All other toxicities were grade 1/2. Treatment was interrupted in 7 (25%) and dose reduced in 13 (46%) pts for cytopenias. For response data see table. Responses occurred at dose levels as low as 50 mg. Median PFS (months, 95% CI) was 4.1 (2.3,7.7) for ER+/Her2-, 18.8 (5.1,∞) for ER+/Her2+ and 1.8 (0.9,∞) for ER-/Her2-. 27/28 patients discontinued study for progressive disease (PD); 1 due to patient preference. Conclusions: Therapy with PD0332991 alone is well-tolerated and demonstrates response or prolonged stable disease (SD) in patients with BC despite prior hormonal and chemotherapy. Expansion within subtypes and molecular predictors of response are being investigated. Clinical trial information: NCT01037790.

<table>
<thead>
<tr>
<th>Response</th>
<th>HR+/Her2- (&lt;n=18&gt;)</th>
<th>HR+/Her2+ (&lt;n=2&gt;)</th>
<th>HR-/Her2- (&lt;n=8&gt;)</th>
<th>Total (&lt;n=28&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response (PR)</td>
<td>1 (6%)</td>
<td>1 (50%)</td>
<td>0</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>SD &gt; 6 months</td>
<td>3 (17%)</td>
<td>0</td>
<td>1 (13%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>SD &lt; 6 months</td>
<td>9 (50%)</td>
<td>1 (50%)</td>
<td>0</td>
<td>10 (36%)</td>
</tr>
<tr>
<td>PD</td>
<td>5 (27%)</td>
<td>0</td>
<td>7 (87%)</td>
<td>12 (43%)</td>
</tr>
<tr>
<td>Clinical benefit (PR + SD&gt;6 months)</td>
<td>4 (23%)</td>
<td>1 (50%)</td>
<td>1 (13%)</td>
<td>6 (21%)</td>
</tr>
</tbody>
</table>
Abstract

Abstract Number: CT101

Presentation Title: Final results of a randomized Phase II study of PD 0332991, a cyclin-dependent kinase (CDK)-4/6 inhibitor, in combination with letrozole vs letrozole alone for first-line treatment of ER+/HER2- advanced breast cancer (PALOMA-1; TRIO-18)

Presentation Time: Sunday, Apr 06, 2014, 10:15 AM -10:35 AM

Author Block: Richard S. Finn, et al.

Abstract Body: Background: PD 0332991 (palbociclib), a selective inhibitor of CDK-4/6, prevents DNA synthesis by blocking cell cycle progression. Preclinical studies identified luminal ER+ breast cancer cell lines with elevated expression of cyclin-D1, Rb and reduced p16 expression as being associated with palbociclib sensitivity (Finn et al. 2009). In addition, synergistic activity was seen in vitro when combined with tamoxifen. As a result of these data Phase Ib safety testing was performed, and led to this randomized Phase II study using a recommended Phase II dose of palbociclib (P) 125 mg QD for 3 weeks followed by 1 week off plus letrozole (L) 2.5 mg QD continuously.

Methods: This Phase II trial was designed as a two-part study evaluating P+L in front-line ER+/HER2- metastatic breast cancer (MBC). Part 1 enrolled post-menopausal patients (pts) with this subtype using ER+/HER2- biomarkers while Part 2 enrolled pts with the same MBC subtype additionally screened for CCND1 amplification and/or loss of p16. The primary endpoint was investigator assessed progression-free survival (PFS) defined as time from randomization to objective progression or death. Secondary endpoints included objective response rate, overall survival, safety, and correlative biomarker studies. In both parts, post-menopausal women with ER+/HER2- MBC were randomized 1:1 to receive either P+L or L alone. Pts continued until disease progression, unacceptable toxicity, or consent withdrawal and were followed for tumor assessments every 2 months. The trial had 80% power to detect a 50% improvement in median PFS (hazard ratio 0.67 [P+L vs. L] with a 1-sided alpha=0.10).

Results: A total of 165 pts were randomized in this Phase II study; 66 pts in Part 1 and 99 pts in Part 2. Baseline characteristics were balanced between treatment arms. The final analysis of primary endpoint showed a statistically significant improvement in PFS for the P+L arm (20.2 months) vs. L arm (10.2 months) with hazard ratio (HR)=0.488 (95% CI: 0.319, 0.748) and 1-sided p=0.0004. The treatment effects were also demonstrated when Part 1 and Part 2 were analyzed separately (HR=0.299 [95% CI: 0.156, 0.572]; 1-sided p=0.0001 for Part 1 and HR=0.508 [95% CI: 0.303, 0.853]; 1-sided p=0.0046 for Part 2). The OS analysis with 61 events demonstrated a trend in favor of P+L vs. L (37.5 months vs. 33.3 months, respectively; HR=0.813; p=0.2105). The most common adverse events in the P+L arm were neutropenia, leukopenia, fatigue, and anemia.

Conclusions: P+L demonstrated a statistically significant improvement in PFS and showed significant clinical benefit as first-line treatment of ER+/HER2- advanced BC. A Phase III study of P+L in this same MBC population is ongoing.
The G1/S checkpoint of the cell cycle is frequently dysregulated in breast cancer (BC). Initial efficacy of PD0332991, a potent oral inhibitor of cyclin-dependent kinases (CDKs) 4/6 was shown in a variety of solid tumors and in combination with letrozole in a randomized phase II trial. **Methods:** We performed a phase II, single arm trial of PD0332991 in women with advanced BC. The primary objectives were safety and efficacy. Eligible patients had histologically-confirmed, stage IV BC with primary or metastatic tumor positive for retinoblastoma (Rb) protein expression, measurable disease by RECIST and adequate organ function/performance status. PD0332991 was given at 125 mg orally, days 1 – 21 of a 28-day cycle. Tumor was assessed every 2 cycles. A two-stage statistical design was employed. Secondary objectives included predictive biomarker assessment. **Results:** 36 patients were enrolled; 28 who completed cycle 1 are reported: 18 (64%) HR+/Her2-, 2 (7%) HR+/Her2+ and 8 (29%) HR-/Her2-. 90% had prior chemotherapy for metastatic disease (median 3 lines); 78% had prior hormonal therapy (median 2 lines). Grade 3/4 toxicities were limited to transient neutropenia (50%) and thrombocytopenia (21%). One episode of neutropenic sepsis occurred in cycle 1 in patient with 6 prior chemo regimens. All other toxicities were grade 1/2. Treatment was interrupted in 7 (25%) and dose reduced in 13 (46%) pts for cytopenias. For response data see table. Responses occurred at dose levels as low as 50 mg. Median PFS (months, 95% CI) was 4.1 (2.3,7.7) for ER+/Her2-, 18.8 (5.1,∞) for ER+/Her+ and 1.8 (0.9,∞) for ER-/Her2-. 27/28 patients discontinued study for progressive disease (PD); 1 due to patient preference. **Conclusions:** Therapy with PD0332991 alone is well-tolerated and demonstrates response or prolonged stable disease (SD) in patients with BC despite prior hormonal and chemotherapy. Expansion within subtypes and molecular predictors of response are being investigated. Clinical trial information: [NCT01037790](https://clinicaltrials.gov/ct2/show/NCT01037790).
PD 0332991 (palbociclib)

- PD 0332991 (palbociclib), a selective inhibitor of CDK-4/6, prevents DNA synthesis by blocking cell cycle progression.
- Preclinical studies identified luminal ER+ breast cancer cell lines with elevated expression of cyclin-D1, Rb and reduced p16 expression as being associated with palbociclib sensitivity (Finn et al. 2009).
- In addition, synergistic activity was seen in vitro when combined with tamoxifen.

Randomized Phase II study palbociclib (P) 125 mg QD for 3 weeks followed by 1 week off plus letrozole (L) 2.5 mg QD continuously.
- In front-line ER+/HER2- metastatic breast cancer (MBC).
- Part 1 enrolled post-menopausal patients (pts) with this subtype using ER+/HER2- biomarkers.
- Part 2 enrolled pts with the same MBC subtype additionally screened for CCND1 amplification and/or loss of p16.
- Results: A total of 165 pts were randomized in this Phase II study; 66 pts in Part 1 and 99 pts in Part 2.
- statistically significant improvement in PFS for the P+L arm (20.2 months) vs. L arm (10.2 months) with hazard ratio (HR)=0.488 (95% CI: 0.319, 0.748) and 1-sided p=0.0004.
- The treatment effects were also demonstrated when Part 1 and Part 2 were analyzed separately (HR=0.299 [95% CI: 0.156, 0.572]; 1-sided p=0.0001 for Part 1 and HR=0.508 [95% CI: 0.303, 0.853]; 1-sided p=0.0046 for Part 2).
- The OS analysis with 61 events demonstrated a trend in favor of P+L vs. L (37.5 months vs. 33.3 months, respectively; HR=0.813; p=0.2105).
- The most common adverse events in the P+L arm were neutropenia, leukopenia, fatigue, and anemia.
- Conclusions: P+L demonstrated a statistically significant improvement in PFS and showed significant clinical benefit as first-line treatment of ER+/HER2- advanced BC. A Phase III study of P+L in this same MBC population is ongoing.
BOLERO-2: Exemestane+/-Everolimus
Phase 3 Trial  724 post menopausal patients recurrence after letrozole or anastrozole

HR = 0.44 (95% CI: 0.36-0.53)
Log rank P value: <1 x 10^-16
EVE + EXE: 7.4 months
PBO + EXE: 3.2 months

Fulvestrant (Faslodex) is an oestrogen receptor antagonist without known agonistic properties that downregulates cellular levels of ER in a dose-dependent manner.

Final analysis of overall survival for the Phase III CONFIRM trial: fulvestrant 500 mg versus 250 mg

Angelo Di Leo, Guy Jerusalem, Lubos Petruzela, Igor N. Bondarenko, Rustem Khasanov, Didier Verhoeven, José L. Pedrini, Iva Smirnova, Mikhail R. Lichinitser, Kelly Pendergrass, Sally Garnett, Yuri Rukazenkov, Miguel Martin, on behalf of the CONFIRM investigators
Trial design and main eligibility criteria

- Post-menopausal
- Advanced disease
- ER+

Fulvestrant 250 mg (1 injection i.m.) + placebo (1 injection i.m.) days 0, 14 (2 placebo injections), 28, and every 28 days thereafter

Fulvestrant 500 mg (2 injections 250 mg i.m.) days 0, 14, 28, and every 28 days thereafter

Allowed prior hormonotherapy (HT)

Relapsing pts.

start adjuvant HT 5 yrs. 12 mos. gap 1st line HT

“de novo” advanced pts.

1st line HT
Primary endpoint: progression-free survival

Proportion of patients progression-free

Time (months)

HR = 0.80; 95% CI: 0.68, 0.94; p=0.006

Median PFS (months)
- Fulvestrant 500 mg: 6.5 months
- Fulvestrant 250 mg: 5.5 months

Patients at risk:
- 500 mg: 362, 216, 163, 113, 90, 54, 37, 19, 12, 7, 3, 2, 0
- 250 mg: 374, 199, 144, 85, 60, 35, 25, 12, 4, 3, 1, 1, 0

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

Secondary endpoint: overall survival (first analysis at 50% maturity – full analysis set)

Proportion of patients alive

Median time to death (months)
- Fulvestrant 500 mg: 25.1 months
- Fulvestrant 250 mg: 22.8 months

HR = 0.84; 95% CI: 0.69, 1.03; p=0.091

Patients at risk:
- 500 mg: 362, 330, 285, 251, 223, 165, 116, 74, 46, 29, 16, 6, 0
- 250 mg: 374, 338, 299, 260, 222, 157, 107, 61, 34, 18, 10, 6, 0

Overall survival: first (50% events) and final (75% events) analyses

50% events

HR = 0.84; 95% CI: 0.69, 1.03; p = 0.091

Median time to death (months)
- Fulvestrant 500 mg: 25.1
- Fulvestrant 250 mg: 22.8

Proportion of patients alive

75% events

HR (97% CI): 0.31 (0.69, 0.96)
p-value: 0.016

Median time to death (months)
- Fulvestrant 500 mg: 26.4
- Fulvestrant 250 mg: 22.3

*Nominal value, cannot be claimed as statistically significant

Patients at risk:
- Fulvestrant 500 mg:
  - 500 mg: 362
  - 250 mg: 374
- Fulvestrant 250 mg:
  - 500 mg: 333
  - 250 mg: 338

## First subsequent therapies

<table>
<thead>
<tr>
<th></th>
<th>Fulvestrant 500</th>
<th>Fulvestrant 250</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% pts. with available information</strong></td>
<td>63 (N=230)</td>
<td>64 (N=239)</td>
</tr>
<tr>
<td><strong>Type of 1st subsequent therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- % chemotherapy / anti-HER-2</td>
<td>59 / -</td>
<td>59 / 0.4</td>
</tr>
<tr>
<td>- % endocrine therapy other than fulvestrant*</td>
<td>35</td>
<td>31</td>
</tr>
<tr>
<td><strong>% objective response / clinical benefit</strong></td>
<td>8 / 33</td>
<td>8 / 41</td>
</tr>
</tbody>
</table>

* 8 out of 374 patients (2.1%) shifted from fulvestrant 250 mg to fulvestrant 500 mg.
### SAEs with outcome of death during the whole treatment period

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Number (% of patients)</th>
<th>Fulvestrant 500 mg</th>
<th>Fulvestrant 250 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N=361</td>
<td>N=374</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td></td>
<td>0</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td></td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Aspiration</td>
<td></td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Cardiopulmonary failure</td>
<td></td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Suicide</td>
<td></td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Death (death cause unknown)</td>
<td></td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
<td>2 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Intestinal adenocarcinoma</td>
<td></td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Meningitis</td>
<td></td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

All events occurring after first dose are summarized
Patient numbers are not mutually exclusive
Conclusions

- Final OS analysis at 75% maturity shows that fulvestrant 500 mg is associated with 4.1-month increase in median OS and a 19% reduction in the risk of death compared with fulvestrant 250 mg.

- These results are consistent with the previously reported PFS and OS data (J Clin Oncol. 28: 4594-00, 2010).

- Analysis of 1st subsequent therapies does not support any imbalance between the two study arms.

- Only 2% of patients crossed-over from 250 to 500 mg. However, activity for 500 mg after pre-treatment with 250 mg is unknown.

- The safety results do not support any clinically relevant difference between fulvestrant 250 and 500 mg and they are consistent with the previously reported safety profile of fulvestrant 500 mg.