Cyclin CDK 4/6 inhibitors in breast cancer treatment

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Agenda

• Cell-cycle pathway

• Cyclin CDK 4/6 inhibitors:
  – Palbociclib
    • Clinical efficacy
    • Safety
    • Clinical development
  – Other inhibitors

• Conclusions
Cyclin-dependent kinase 4/6-Rb protein: a key pathway in cell cycle progression

Synergy Between ER and CDK4/6: Critical for Efficacy of Combinations in ER+ Tumours

- Cyclin D1 is a direct transcriptional target of ER.
- Inhibition of cyclin D1 inhibits oestrogen-induced S-phase entry.
- Endocrine resistance is associated with persistent cyclin D1 expression and RB phosphorylation.
- CDK4/6 inhibitors are most effective in tumours with gene amplification and overexpression of cyclin D1, which is common in ER+ breast cancer.
Palbociclib Preferentially Inhibits Proliferation of Luminal Oestrogen Receptor-Positive Human Breast Cancer Cell Lines in Vitro

Subtype
- **Luminal**
- **HER2 amplified**
- **Non-luminal/post EMT**
- **Non-luminal**
- **Immortalised**

ER+ breast cancer: related sensitivity markers to palbociclib

Sensitive cell lines:
- 76% luminal genes (0% in resistant cell lines)
- 0% non-luminal gene (59% in resistant cell lines)
  - RB - upregulated
  - cyclin D1 - upregulated
  - p16 - downregulated
Molecular Mechanisms of Palbociclib Combined With ER Antagonists in ER+ Breast Cancer

Combined inhibition of CDK4/6 and ER signalling increases senescence in ER+ breast cancer cell lines

SA**-βGal activity in T47D treated with ER antagonists and palbociclib

*P<0.001 vs. single agents

**SA= Senescence Associated

Differential response to CDK4/6 inhibition in breast cancer explants

Dean JL et al. Cell Cycle 2012; 11: 2756
CDK4/6 inhibitors in CDK4/6-dependent murine model of BC

Results of a Randomized Phase 2 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 (TRIO-18)

RS Finn,1 JP Crown,2 I Lang,3 K Boer,4 IM Bondarenko,5 SO Kulyk,6 J Ettl,7 R Patel,8 T Pinter,9 M Schmidt,10 Y Shparyk,11 AR Thummala,12 NL Voitko,13 A Breazna,14 ST Kim,15 S Randolph,15 DJ Slamon1

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Presented at SABCS 2012; December 5, 2012; San Antonio, TX, USA
Phase 2 Design

**Part 1**
- N = 66
- **RANDOMISATION**
- ER+, HER2- BC
- PD 0332991 125 mg QD\(^a\) + Letrozole 2.5 mg daily
- Letrozole 2.5 mg daily

**Part 2**
- N = 99
- **RANDOMISATION**
- ER+, HER2- BC with **CCND1 amp** and/or loss of **p16**
- PD 0332991 125 mg QD\(^a\) + Letrozole 2.5 mg QD
- Letrozole 2.5 mg QD

**Stratification Factors**
- Disease Site (Visceral vs Bone only vs Other)
- Disease-Free Interval (>12 vs ≤12 mo from end of adjuvant to recurrence or de novo advanced disease)

\(^a\) Schedule 3/1.
## Best Overall Response (ITT)

<table>
<thead>
<tr>
<th></th>
<th>PD 991 + LET (n = 84)</th>
<th>LET (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All randomised patients, n</td>
<td>84</td>
<td>81</td>
</tr>
<tr>
<td><strong>Objective Response Rate, % (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Response, n (%)</td>
<td>34 (24-46)</td>
<td>26 (17-37)</td>
</tr>
<tr>
<td>Partial Response, n (%)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td></td>
<td>29 (34)</td>
<td>20 (25)</td>
</tr>
<tr>
<td>Patients with measurable disease, n (%)</td>
<td>64 (76)</td>
<td>65 (80)</td>
</tr>
<tr>
<td><strong>Objective Response Rate, % (95% CI)</strong></td>
<td>45 (33-58)</td>
<td>31 (20-43)</td>
</tr>
<tr>
<td>Complete Response, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response, n (%)</td>
<td>29 (45)</td>
<td>20 (31)</td>
</tr>
<tr>
<td><strong>Stable Disease ≥24 weeks, n (%)</strong></td>
<td>30 (36)</td>
<td>15 (18)</td>
</tr>
<tr>
<td><strong>Clinical Benefit Rate, n (%)</strong></td>
<td>59 (70)</td>
<td>36 (44)</td>
</tr>
<tr>
<td><strong>Stable Disease &lt;24 weeks, n (%)</strong></td>
<td>14 (17)</td>
<td>22 (27)</td>
</tr>
<tr>
<td><strong>Progressive Disease, n (%)</strong></td>
<td>3 (4)</td>
<td>17 (21)</td>
</tr>
<tr>
<td><strong>Indeterminable, n (%)</strong></td>
<td>8 (10)</td>
<td>6 (7)</td>
</tr>
</tbody>
</table>

* Complete response + partial response + stable disease ≥24 weeks.
Progression-Free Survival

<table>
<thead>
<tr>
<th>PD 991 + LET (n = 84)</th>
<th>LET (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Events (%)</td>
<td>21 (25)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>26.1</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(12.7, 26.1)</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.37</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Number of patients at risk:

PD991+LET: 84 75 60 53 43 35 25 18 15 14 9 5 3 1 1
LET: 81 57 38 29 22 17 11 6 5 4 3 3 1 1
<table>
<thead>
<tr>
<th>Treatment Administration (AT)</th>
<th>(PD\ 991 + \ LET) ((n = 83))</th>
<th>(LET) ((n = 77))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Duration of Treatment, months (range)</td>
<td>8.9 (&lt;1 – 25.9)</td>
<td>5.1 (&lt;1 – 29.0)</td>
</tr>
<tr>
<td>Dose Interruptions During Cycles, n (%)</td>
<td>59 (71)</td>
<td>17 (22)</td>
</tr>
<tr>
<td>Cycle Delays, n (%)</td>
<td>62 (75)</td>
<td>NA</td>
</tr>
<tr>
<td>Dose Reductions, n (%)</td>
<td>29 (35)</td>
<td>NA</td>
</tr>
</tbody>
</table>
### Most Common Treatment-Related Adverse Events ≥10% (AT)

<table>
<thead>
<tr>
<th>Condition</th>
<th>PD 991 + LET (n = 83)</th>
<th>LET (n = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1/2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19</td>
<td>46</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>Anaemia</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Alopecia</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11</td>
<td>1</td>
</tr>
</tbody>
</table>
Palbociclib - Predictive biomarkers

Rb nuclear score

Clark AS, et al. SABCS 2013
Palbociclib predictive markers

% p16 nuclear staining

Positive

Negative

Clark AS, et al. SABCS 2013
Palbociclib: ongoing studies in endocrine-sensitive tumours

Phase III, PALOMA-2 (1008)

N:465

- Post-menopausal
- HR+, HER2– MBC
- No previous treatment for advanced disease
- AI-resistant patients excluded

Primary endpoint: PFS
Secondary endpoints:
  - ORR
  - SV
  - Safety
  - Biomarkers

Stratification factors
  - disease site
  - disease-free interval
  - previous hormonal therapy

R 2:1

Palbociclib (125 mg /daily, 3/1 schedule) + letrozole(2.5 mg daily)

Placebo (3/1 schedule) + letrozole(2.5 mg daily)
Palbociclib: ongoing studies in endocrine-resistant tumours

Phase III, PALOMA-3 (1023)

N: 417

R: 2:1

- HR+, HER2- MBC
- Pre-menopausal or post-menopausal
- Failure of previous hormonal treatment:
  - Progressed on or ≤12 months after end of adjuvant therapy (AI or tamoxifen)
  - Progressed on or ≤1 month after end of treatment with AI/other endocrine therapy for advanced disease
- 1 previous chemotherapy regimen permitted

Primary endpoint: PFS

Secondary endpoints:
- ORR
- SV
- Safety
- Biomarkers
- Quality of life

Stratification factors
- visceral metastases
- previous sensitivity to endocrine therapy
- menopausal status
- previous chemotherapy

Palbociclib (125 mg daily, 3/1 schedule) + Fulvestrant (500 mg IM q 4 wk)

Placebo (3/1 schedule) + Fulvestrant (500 mg IM q 4 wk)
Palbociclib: ongoing studies in endocrine-resistant tumours

Phase III, PEARL

N:348

- Post-menopausal
- HR+, HER2− metastatic BC
- Resistant to non-steroidal AIs:
  - Recurrence on or ≤12 months after end of adjuvant treatment with non-steroidal AI
  - Progression on or ≤1 month after end of treatment with non-steroidal AI for advanced disease

R 1:1

- Palbociclib (125 mg daily, 3/1 schedule) + Exemestane (25 mg daily)
- Capecitabine 1250 mg/m²/12 h 2/1 schedule

Primary endpoint: PFS
Secondary endpoints:
  - ORR
  - SV
  - Safety
  - Biomarkers
  - Quality of life

Stratification factors
  - visceral metastases
  - previous sensitivity to endocrine therapy
  - menopausal status
  - previous chemotherapy
  - country
Phase III Study of Palbociclib in High-risk Early BC: PENELOPE

**PENELOPE**

- Early ER+ BC “high risk” (CPS-EG ≥3)
- Premenopausal/postmenopausal
- Completed taxane-based neoadjuvant therapy, surgery; +/- radiotherapy

**RANDOMISATION**

N=800

1:1

**Primary endpoint:** iDFS

**Secondary endpoints:** OS, iDFS excluding second non-breast cancer, distant disease-free survival, local recurrence-free survival, iDFS by commercially-available multigene assay subtyping, safety, patient-reported outcomes, biomarkers

**Stratification factors:** lymph node status, age, biomarkers (Ki-67, pRB, cyclin D), and region

Non-study adjuvant endocrine therapies being taken for 5–10 years after surgery were permitted during the study:
- tamoxifen (pre- and postmenopausal women)
- goserelin agonists (premenopausal)
- aromatase inhibitors: anastrozole, letrozole (postmenopausal)

*a* In collaboration with GBG (Germany) and GEICAM (Spain)
Phase II Study of Palbociclib with Letrozole in Neoadjuvant Treatment of Early ER+, HER2− BC: PALLET study

- Localised ER+, HER− invasive early BC
- Suitable for neoadjuvant therapy with letrozole
- Post-menopausal
- N=301

Primary endpoints:
- Change in the proliferation marker Ki67 at week 14
- Clinical response at week 14

Secondary endpoints:
- Ki67 at 2 weeks
- ypCR after 14 weeks

Stratification factor:
Country

Tumour samples: biopsies taken before treatment and at 2 and 14 weeks

Palbociclib (125 mg QD, 3/1 schedule) + letrozole (2.5 mg QD) for 12 weeks

Letrozole (2.5 mg QD) for 14 weeks

Letrozole (2.5 mg daily) for 2 weeks

Palbociclib (125 mg daily) for 2 weeks

Palbociclib (125 mg daily) + letrozole (2.5 mg daily) for 2 weeks

Surgery
Other CDK 4/6 inhibitors
Other cyclin CDK 4/6 inhibitors: LEE-011

Monaleessa-1 study

Early breast cancer
Size > 1.5 cm

LEE-011 + letrozole
600 mg/d 2.5 mg/d

LEE-011 + letrozole
400 mg/d 2.5 mg/d

Letrozole
2.5 mg/d

Primary objective: Changes in Ki67
Secondary objectives: Safety
Biological response

Surgery

15 days
Other cyclin CDK 4/6 inhibitors: LEE-011

Monaleessa-2 study

Advanced disease
- RE positivity
- Postmenopausal
- 1 measurable lesion
- Non-previous treatment

LEE-011 + letrozole
600 mg/d 2.5 mg/d

Letrozole
2.5 mg/d

Primary objective: PFS
Secondary objectives: OS
Safety
ORR
CONCLUSIONS

• The cyclin D-CDK4/6-Rb pathway is an important mediator of cell cycle regulation and is downstream of multiple mitogenic cascades.

• It is an important target for anticancer therapy.

• Different CDK4/6 inhibitors are being studied in combination with endocrine therapy or other targeted therapies such as anti-HER2 agents, PI3K inhibitors or mTOR inhibitors.

• These drugs present a good opportunity to overcome endocrine resistance.
THANK YOU !!