S2-03
Preoperative window of opportunity study of the PI3K inhibitor pictilisib (GDC-0941) plus anastrozole vs anastrozole alone in patients with ER+, HER2-negative operable breast cancer

(OPPORTUNE study)

Dr. Schmid: Contract, Genentech (research support).
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Preoperative window of opportunity study of the PI3K inhibitor Pictilisib (GDC-0941) plus Anastrozole vs Anastrozole alone in patients with ER+, HER2-negative breast cancer (OPPORTUNE study)


on behalf of the OPPORTUNE study investigators

Barts Cancer Institute, St Bartholomew’s Hospital; Queen Mary University of London

Background and Rationale

– PI3K/mTOR signaling has been implicated as a resistance mechanism to endocrine therapies.4

– PIK3CA mutations are predictive of sensitivity to PI3K inhibitors in preclinical studies5, but the patient population that benefits most from PI3K/mTOR inhibition is not defined.

– Pictilisib (GDC-0941), a pan-class I PI3K inhibitor, has shown substantial preclinical activity in ER+ breast cancer models.

– Preoperative window studies are a validated strategy to evaluate novel treatments in ER+ breast cancer and can help characterise the optimal target population.7,8

– Change in Ki67 expression after 2 weeks of treatment has been shown to be closely linked with relapse free survival.9

1 Miller et al., JCO 2010; 2 Baselga et al., NEJM 2012; 3 Bachet et al., JCO 2012; 4 Krop et al., SABCS 2014; 5 O’Brien et al., CCR 2010; 6 Raymond et al., MCT 2009; 7 Dowsett et al., JCO 2005; 8 Polychronis et al., Lancet Oncol 2005; 9 Dowsett et al., CCR 2005

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OPPORTUNE Study Design

- Randomisation (2:1) favouring the combination, stratified by Centre & Grade
- Study dosing once daily for 14 days (+/- 2 days)
  - Anastrozole: 1 mg  
  - Pictilisib: initially 340 mg; changed to 260 mg in 08/2012
- Adjuvant therapy as indicated
- 1\textsuperscript{st} analysis of primary endpoint scheduled after 70 evaluable patients;  
2\textsuperscript{nd} analysis after 141 patients focusing on subset analyses and additional biomarkers

Primary Endpoint:
- Change in tumour cell proliferation (Ki67 IHC\textsuperscript{1})

Secondary Endpoints:
- Induction of tumour-cell apoptosis (Caspase-3 IHC)
- Safety and tolerability

Tertiary Endpoints: Treatment effect by
- Molecular subtype (PAM50 Nanostring)
- Baseline tumour cell proliferation (Ki67 IHC)
- PI3K pathway alterations (PIK3CA NGS, PTEN IHC)

\textsuperscript{1} Central analysis; Primary antibody: Confirm anti-Ki67 (Ventana); Target cutoff >=1000 cells; Independently scored by 2 reviewers blinded to treatment allocation

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Study Population

- 88 patients screened
- 75 randomised
- 13 screening failures

26 assigned to Anastrozole

49 assigned to Pictilisib plus anastrozole

- 2 excluded
- 1 HER2+
- 1 tumour size <1cm

47 treated with Pictilisib plus Anastrozole

- 3 excluded
- 2 had AfIs
- 1 insufficient tissue

44 evaluable

A | A + P
---|---
N | 26 | 44

<table>
<thead>
<tr>
<th>Grade</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>G1/2</td>
<td>85%</td>
<td>84%</td>
</tr>
<tr>
<td>G3</td>
<td>15%</td>
<td>16%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BL Ki67</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≤14%</td>
<td>35%</td>
<td>39%</td>
</tr>
<tr>
<td>&gt;14%</td>
<td>65%</td>
<td>61%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PAM50</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lum A</td>
<td>32%</td>
<td>41%</td>
</tr>
<tr>
<td>Lum B</td>
<td>68%</td>
<td>59%</td>
</tr>
</tbody>
</table>

---

Individual Change in Ki67

Anastrozole

- 10/26 (38.5%)

Anastrozole + Pictilisib

- 2/44 (4.5%)

- 16/26 (61.5%)
- 42/44 (95.5%)

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Individual Relative Ki67 Suppression

1 Relative Ki67 Suppression, defined as \( \ln(\text{Ki67}_{\text{Day15}}) - \ln(\text{Ki67}_{\text{baseline}}) \).

2 \( \Delta \text{Ki67} \) Response, defined as a 50% fall in Ki67 score between Day15 and Baseline.

Primary Endpoint
Geometric mean Ki67 Suppression

\[
\begin{align*}
A & \quad (n = 26) & A + P & \quad (n = 44) \\
\text{Mean Ki67 Suppression (}) & \quad -66.0\% & -83.8\% \\
\text{P = 0.004} & \\
\text{A+P/A Ratio (95%CI), 0.48 (0.29 - 0.78)} & \\
\end{align*}
\]

Geometric mean Ki67 Suppression defined as \( \ln(\text{Ki67}_{\text{Day15}}) - \ln(\text{Ki67}_{\text{baseline}}) \).

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Primary Endpoint (Secondary Analyses)
Ki67 Response Rates

End of treatment Ki67 Response, defined as $\ln(\text{Ki67}_{\text{Day15}}) \leq 2$

<table>
<thead>
<tr>
<th>Group</th>
<th>Ki67 Response Rate (%)</th>
<th>$P$</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>61.5%</td>
<td>0.003</td>
<td>1.48 (1.67-2.03)</td>
</tr>
<tr>
<td>A + P</td>
<td>90.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$\Delta$Ki67 Response Rates, defined as ≥50% fall in Ki67 score between Day15 and Baseline

<table>
<thead>
<tr>
<th>Group</th>
<th>Ki67 Response Rate (%)</th>
<th>$P$</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>53.9%</td>
<td>0.003</td>
<td>1.60 (1.10-2.33)</td>
</tr>
<tr>
<td>A + P</td>
<td>86.4%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Change in Apoptosis (Caspase-3)

% Change in Apoptosis
[Caspase-3* (%), (geometric mean, 95% CI)]

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Change in Caspase 3 (%)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>-10.4% (95%CI -43.6-42.2)</td>
<td>0.90</td>
</tr>
<tr>
<td>A + P</td>
<td>-13.9% (95%CI -45.0-34.7)</td>
<td></td>
</tr>
</tbody>
</table>

*Central analysis; Primary antibody: Cleaved Caspase-3 (Cell Signalling), target count ≥3000 cells; independently scored by 2 reviewers blinded to treatment allocation.

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Most common adverse events (≥10%)

<table>
<thead>
<tr>
<th></th>
<th>Anastrozole</th>
<th>Anastrozole + Pictilisib 340 mg</th>
<th>Anastrozole + Pictilisib 260 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fatigue</strong></td>
<td>G1 G2 G3</td>
<td>G1 G2 G3</td>
<td>G1 G2 G3</td>
</tr>
<tr>
<td></td>
<td>23% 0 4%</td>
<td>50% 38% 0</td>
<td>13% 3% 0</td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td></td>
<td>13% 13% 38%</td>
<td>8% 3% 3%</td>
</tr>
<tr>
<td><strong>Diarrhoea</strong></td>
<td>4% 0 0</td>
<td>38% 13% 0</td>
<td>44% 8% 0</td>
</tr>
<tr>
<td><strong>Dysgeusia</strong></td>
<td>4% 0 0</td>
<td>25% 0 0</td>
<td>5% 5% 0</td>
</tr>
<tr>
<td><strong>Dyspepsia</strong></td>
<td>0 0 0</td>
<td>13% 0 0</td>
<td>13% 5% 0</td>
</tr>
<tr>
<td><strong>Anorexia</strong></td>
<td>4% 0 0</td>
<td>13% 13% 0</td>
<td>13% 0 0</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>4% 8% 0</td>
<td>63% 25% 0</td>
<td>36% 5% 0</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>0 0 0</td>
<td>13% 9% 0</td>
<td>3% 10% 0</td>
</tr>
<tr>
<td><strong>Stomatitis</strong></td>
<td>0 0 0</td>
<td>0% 13% 0</td>
<td>5% 0 0</td>
</tr>
<tr>
<td><strong>Hyperglycaemia</strong></td>
<td>0 0 0</td>
<td>0% 0 0</td>
<td>5% 3% 3%</td>
</tr>
<tr>
<td><strong>Creatinine</strong></td>
<td>0 0 0</td>
<td>25% 14% 0</td>
<td>8% 0 0</td>
</tr>
<tr>
<td><strong>Arthralgia</strong></td>
<td>19% 0 0</td>
<td>13% 0 0</td>
<td>3% 0 0</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>8% 8% 0</td>
<td>0 13% 0</td>
<td>8% 0 0</td>
</tr>
<tr>
<td><strong>Hot flushes</strong></td>
<td>23% 0 0</td>
<td>0 0 0</td>
<td>3% 3% 0</td>
</tr>
</tbody>
</table>

PI3K Pathway Alterations & Response

**Geometric mean Ki67 Suppression**

<table>
<thead>
<tr>
<th></th>
<th>Favouring Anastrozole + Pictilisib</th>
<th>Favouring Anastrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA mutant(^1) (n = 25)</td>
<td>0.65 (0.33 – 1.30)</td>
<td>0.32 (0.12 – 0.89)</td>
</tr>
<tr>
<td>Helical domain (n = 9)</td>
<td>0.32 (0.12 – 0.89)</td>
<td>0.76 (0.30 – 1.94)</td>
</tr>
<tr>
<td>Kinase domain (n = 14)</td>
<td>0.76 (0.30 – 1.94)</td>
<td>0.46 (0.24 – 0.94)</td>
</tr>
<tr>
<td>PIK3CA WT (n = 38)</td>
<td>0.46 (0.24 – 0.94)</td>
<td></td>
</tr>
<tr>
<td>PTEN positive(^2) (n = 56)</td>
<td></td>
<td>0.40 (0.23 – 0.71)</td>
</tr>
<tr>
<td>PTEN negative (n = 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No PI3K alteration(^*) (n = 41)</td>
<td></td>
<td>0.32 (0.15 – 0.67)</td>
</tr>
<tr>
<td>PI3K alteration (n = 28)</td>
<td></td>
<td>0.75 (0.40 – 1.42)</td>
</tr>
<tr>
<td>All Patients</td>
<td></td>
<td>0.48 (0.29 – 0.78)</td>
</tr>
</tbody>
</table>

\(^1\) Targeted NGS (P1 chip and Ion PI Sequencing 200 v3 Kit Ampliseq Comprehensive Cancer panel)
\(^2\) Central IHC analysis, Primary antibody: PTEN (13666; Cell Signalling #6559)
\(^*\) PIK3CA mutation and/or loss of PTEN

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Geometric mean Ki67 Suppression by Subtype (PAM50)

Luminal A
(n = 20)
-76.9%
Mean Ki67 suppression (%)
P = 0.98
A+P/A Ratio (95%CI),
1.01 (0.45 – 2.26)

Luminal B
(n = 33)
-76.6%
-63.6%
-86.5%
P = 0.008
A+P/A Ratio (95%CI),
0.37 (0.18 – 0.76)

* PAM50 Nanorstring

Ki67 Suppression in Subgroups

Geometric mean Ki67 Suppression

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Favouring Anastrozole + Pictilisib</th>
<th>Favouring Anastrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A (n = 20)</td>
<td>1.01 (0.45 – 2.26)</td>
<td></td>
</tr>
<tr>
<td>Luminal B (n = 33)</td>
<td>0.37 (0.18 – 0.76)</td>
<td></td>
</tr>
<tr>
<td>Ki67 ≤14% (n = 26)</td>
<td>0.59 (0.25 – 1.36)</td>
<td></td>
</tr>
<tr>
<td>Ki67 &gt;14% (n = 44)</td>
<td>0.41 (0.22 – 0.74)</td>
<td></td>
</tr>
<tr>
<td>PgR positive (n = 55)</td>
<td>0.56 (0.32 – 0.97)</td>
<td></td>
</tr>
<tr>
<td>PgR negative/? (n = 15)</td>
<td>0.16 (0.04 – 0.59)</td>
<td></td>
</tr>
<tr>
<td>All Patients</td>
<td>0.48 (0.29 – 0.78)</td>
<td></td>
</tr>
</tbody>
</table>
Summary and Conclusions

- Addition of the PI3K inhibitor Pictilisib significantly increased the anti-proliferative response to Anastrozole in ER+ early breast cancer
- Subset analyses suggest increased benefit of Pictilisib for patients with Luminal B or highly-proliferative tumours
- PIK3CA mutations or PTEN status were not predictive of response to Pictilisib
- The addition of Pictilisib to Anastrozole was not associated with an increase in tumour cell apoptosis
- The safety profile of the combination is acceptable and consistent with other trials

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Genentech
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Queen Mary University of London