The PI3K/Akt pathway is often aberrantly activated in breast cancers by PTEN or INPP4B tumor suppressor loss, PIK3CA or AKT mutations, and/or PIK3CA amplifications, which all contribute to chemoresistance.

Patients with DCBBR (DCBBR indicates a patient-at-risk small molecule inhibitor of Akt/kinases.

In preclinical studies, ipatasertib is efficacious in breast cancer models, including those with PIK3CA pathway alterations. Ipatasertib showed synergy with chemotherapy (including taxanes) in vitro (Figure 1a), and the combination resulted in antitumor efficacy in vivo (Figure 1b).

In Phase 1 studies, ipatasertib dose-escalated up to doses ≤1,000 mg. In preclinical studies, ipatasertib is efficacious in breast cancer models, including those with PIK3CA/AKT1 mutations or low expression of PTEN (4 of 8 patients).

CONCLUSIONS
• Ipatasertib, alone or in combination with docetaxel or paclitaxel, was safe and well-tolerated in patients with metastatic breast cancer, including triple-negative breast cancer.

METHODS
Preliminary anti-tumor activity was observed at the RP2D of ipatasertib, including in patients with tumors expressing PIK3CA/AKT1 mutations. Responses included patients with tumors PIK3CA/AKT1 mutations or low expression of PTEN (4 of 8 patients).

Pharmacokinetics (PK) and Pharmacodynamics (PD)

Patients who progressed on PI3K inhibitors can respond on subsequent therapy including Akt inhibitors.

Anti-Tumor Activity of Ipatasertib in Combination with Taxanes (Docetaxel or Paclitaxel) in Breast Cancer Patients

Table 1: Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ipatasertib 600 mg (n=10)</th>
<th>Ipatasertib 400 mg (n=6)</th>
<th>Ipatasertib 300 mg (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG 0-1</td>
<td>4 (40%)</td>
<td>3 (50%)</td>
<td>2 (50%)</td>
</tr>
<tr>
<td>No DLTs</td>
<td>9 (90%)</td>
<td>5 (83%)</td>
<td>3 (75%)</td>
</tr>
</tbody>
</table>

Figure 2: PAM4983g Study Schema

Phase Ib Dose-Escalation Study of an Akt Inhibitor, Ipatasertib, in Combination with Docetaxel or Paclitaxel in Patients with Metastatic Breast Cancer

RESULTS
Clinical Pharmacodynamics

Figure 3: Best FDG-PET Response in Organismic-Positive Breast Cancer Patients

INHIBITOR CLASS ACTIVITY/EFFICACY

Study Drug = Ipatasertib

PIK3CA/AKT1 mutations or low expression of PTEN (4 of 8 patients).

Table 2: Most Common Grade ≥2 Ipatasertib-Related Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade ≥2 Ipatasertib-Related AE</th>
<th>Grade ≥2 Ipatasertib-Related AE</th>
<th>Grade ≥2 Ipatasertib-Related AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>2 (40%)</td>
<td>1 (20%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (20%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 1. Preclinical Anti-Tumor Activity and Clinical Pharmacodynamics

- Ipatasertib, alone or in combination with docetaxel or paclitaxel, was safe and well-tolerated in patients with metastatic breast cancer, including triple-negative breast cancer.

- No DLTs up to 600 mg of ipatasertib alone, and in combination with docetaxel or paclitaxel.

- There were no evidence of PK interactions between ipatasertib and docetaxel or paclitaxel.

- The recommended Phase II dose (RP2D) of ipatasertib combined with paclitaxel in patients with metastatic breast cancer is 400 mg Q2W on days 1, 8, and 15.

- Preliminary anti-tumor activity was observed at the RP2D of ipatasertib, including in patients with tumors PIK3CA/AKT1 pathway alterations or who had progressed on prior treatment with taxanes and taxol.

- A Phase II global study (LOTUS, G022327) in patients with first-line triple-negative breast cancer leading paclitaxel + placebo (n=100) is now enrolling.

REFERENCES

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