Phase Ib Dose Escalation Study of the Akt Inhibitor GDC-0068 with Docetaxel or mFOLFOX6 in Patients with Advanced Solid Tumors

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BACKGROUND
- Aberrant activation of the PI3K/Akt pathway, via loss of PTEN tumor suppressor and/or mutations of the PIK3CA gene, is frequent in cancers and may lead to enhanced survival and chemoresistance.
- GDC-0068 is a potent ATP-competitive small molecule inhibitor of all Akt isoforms.
- In preclinical models, GDC-0068 synergistically combined with taxanes and 5-FU/platinum (Figure 1a).
- In an ongoing Phase Ia study, GDC-0068 has been well tolerated with maximum tolerated dose (MTD) of 600 mg daily (21 days on/7 days off); pharmacodynamic (PD) down-regulation of Akt signaling in tumors has been observed at doses ≥ 100 mg (Figure 1b).

OBJECTIVES
- Primary Objectives
  - To evaluate the safety and tolerability and estimate the MTD of increasing oral doses of GDC-0068 in combination with docetaxel or mFOLFOX6.
- Additional Objectives
  - To evaluate the anti-tumor activity (overall response and duration of treatment) of GDC-0068 in combination with chemotherapy.
  - To evaluate the PK of GDC-0068 given in combination with chemotherapy.

METHODS
- Study Design
  - Open-label, multi-center, two-stage, Phase Ib dose-escalation combination study using a standard 3+3 design.

RESULTS
- Table 1. Baseline Characteristics, Data Cutoff 27 Aug 2012

<table>
<thead>
<tr>
<th>Event Term</th>
<th>100 mg (n=5)</th>
<th>200 mg (n=6)</th>
<th>400 mg (n=2)</th>
<th>600 mg (n=2)</th>
<th>All Subjects (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year), median (range)</td>
<td>62 (28–75)</td>
<td>59 (33–77)</td>
<td>67 (67–84)</td>
<td>67 (67–84)</td>
<td>67 (67–84)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>74</td>
<td>56</td>
<td>44</td>
<td>38</td>
<td>44</td>
</tr>
<tr>
<td>ICOR Score 0</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Prior systemic therapies, median (range)</td>
<td>4 (0–12)</td>
<td>5 (0–11)</td>
<td>1 (3)</td>
<td>2 (1)</td>
<td>5 (0–11)</td>
</tr>
<tr>
<td>Prior taxanes</td>
<td>14 (46)</td>
<td>15 (48)</td>
<td>11 (37)</td>
<td>7 (23)</td>
<td>15 (48)</td>
</tr>
<tr>
<td>Prior platinum agents</td>
<td>20 (74)</td>
<td>28 (17)</td>
<td>14 (47)</td>
<td>3 (11)</td>
<td>28 (17)</td>
</tr>
<tr>
<td>Prior S-FU</td>
<td>12 (44)</td>
<td>21 (82)</td>
<td>15 (50)</td>
<td>8 (27)</td>
<td>21 (82)</td>
</tr>
</tbody>
</table>

- Table 2a. Grade ≥ 2 AEs Related to GDC-0068: Arm A (GDC-0068 + Docetaxel)

<table>
<thead>
<tr>
<th>Event Term</th>
<th>100 mg (n=5)</th>
<th>200 mg (n=6)</th>
<th>400 mg (n=2)</th>
<th>600 mg (n=2)</th>
<th>All Subjects (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 GDC-0068-related AEs:</td>
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<tr>
<td>Arm A: Diarrhea (n=2), hypophosphatemia (n=2), rash, leukopenia, hypocalcemia, and hypomagnesemia (each n=1)</td>
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<tr>
<td>Arm B: Nausea (n=2), neutropenia, thrombocytopenia, fatigue, hypophosphatemia, hypocalcemia, and hypomagnesemia (each n=1)</td>
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- CONCLUSIONS
  - GDC-0068, when combined with docetaxel or mFOLFOX6, was safe and well tolerated up to the single agent MTD dose (600 mg).
  - No DLTs were observed up to the maximum administered dose, 2/16 patients discontinued due to GDC-0068-related AEs.
  - There were no PK interactions between GDC-0068 and docetaxel or mFOLFOX6.
  - Both combinations showed evidence of anti-tumor activity, including in patients with PIK3CA pathway alterations and prior treatment with taxanes (Arm A) and platinum and/or 5-FU agents (Arm B).
  - A Phase II trial in first line metastatic gastric/GEJ cancer testing FOLFOX6 + GDC-0068 will soon commence.

ACKNOWLEDGMENTS
- We thank the patients who participated in the study, and their families.
- We thank the Genentech/Array GDC-0068 team.
- Genentech provided support for the poster.

REFERENCES