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A first-in-human trial of GDC-0068: A novel, oral, ATP-competitive Akt inhibitor, demonstrates robust suppression of the Akt pathway in surrogate and Akt-targeted tumors

BACKGROUND
Akt is the final effector in the PI3K-Akt-mTOR pathway
- Activation of the Akt pathway is a marker of poor prognosis and resistance to chemotherapeutic agents
- GDC-0068 inhibits AKT at micromolar concentrations but is >100-fold selective over a closely related Protein Kinase A (PKA)
- GDC-0068 shows an excellent safety profile and is being tested in Phase Ib clinical trial

OBJECTIVES
Primary Objectives
- Evaluate safety and tolerability and estimate the maximum tolerated dose (MTD) of increasing oral dose of GDC-0068
- Evaluate changes in tumor expression of downstream markers in paired biopsies by reverse phase protein array (RPPA)
- Evaluate changes in pGSK3α/β levels in paired biopsy specimens

METHODS
- Open-label, single-center, Phase 1 dose-escalation study using a standard 3+3 design
- GDC-0068 was administered on Day 1, followed by 1 week of washout to evaluate single dose and PK markers. GDC-0068 was then dosed orally on Days 1-21 of each 28-day cycle
- Tumors were selected for study if they had a minimum diameter of 1 cm
- GDC-0068 was continued until disease progression, unacceptable toxicity, or 30 mg orally daily for 28 days

RESULTS
Patient Status
- The tumor of the 30 patients enrolled (closed between 25-430 mg daily) in the PANNAK4T study, as of 30 September 2011, is summarized in Figure 3.

Table 1: Molecular Characteristics of Patients with Prolonged (>15 weeks Stable Disease) by Tumor Type

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Number of Patients</th>
<th>Number of Patients with Stable Disease &gt;15 Weeks</th>
<th>pAKT Normalized to Total</th>
<th>pGSK3α/β Normalized to Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>10</td>
<td>7</td>
<td>0.93</td>
<td>0.77</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>4</td>
<td>3</td>
<td>0.82</td>
<td>0.65</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>1</td>
<td>1</td>
<td>0.86</td>
<td>0.92</td>
</tr>
<tr>
<td>Colorectal</td>
<td>12</td>
<td>9</td>
<td>0.94</td>
<td>0.83</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>3</td>
<td>2</td>
<td>0.41</td>
<td>0.6</td>
</tr>
<tr>
<td>NSCLC</td>
<td>5</td>
<td>3</td>
<td>0.85</td>
<td>0.79</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
<td>0.84</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Pharmacokinetics
- There was a dose-proportional increase in Cmax and AUC for GDC-0068 as doses increased from 25 mg to 400 mg (Table 4)

Pharmacodynamics
- A dose-dependent and time-dependent pharmacodynamic response was demonstrated, with a decrease in pGSK3α/β level of 75% at doses of 150 mg GDC-0068 (Figure 6) The maximum decrease at 400 mg was achieved in less than 24 hours (Figure 7). The combination of GDC-0068 + docetaxel and GDC-0068 + FOLFOX is being tested in Phase II clinical trial

CONCLUSIONS
- GDC-0068 is growing well tolerated when administered daily, at doses of 25 mg to 400 mg on a 3-week-on/1-week-off treatment schedule
- The MTD for GDC-0068 was 400 mg daily on a 3-week-on/1-week-off treatment schedule
- Pharmacokinetics (PK) data demonstrated dose-appropriate increases in Cmax and AUC with a mean half-life of 25.5 hours over the dose range 25-400 mg
- Pharmacodynamics (PD) data showed dose-appropriate inhibition of pGSK3α/β and pS6 at the MTD of 400 mg GDC-0068
- GDC-0068 is select for AKT and demonstrates significant decrease in AKT pathway in paired pre- and post-treatment biopsies
- A patient with colorectal cancer (with low expression of PI3K, mutation of PTEN (1034G), and loss of PTEN) showed intratumoral AKT phosphorylation knockdown by multiple markers

ACKNOWLEDGEMENTS
We thank the patients who participated in the study, and their families. Generalizability of GDC-0068 finds the, and role of Jose Baselga for their contributions. Genentech Inc. sponsored these studies and provided support for the preparation of this poster.