Evaluation of Tolerability and Anti-Tumor Activity of GDC-0032, a PI3K Inhibitor with Enhanced Activity Against PIK3CA Mutant Tumors, Administered to Patients with Advanced Solid Tumors

Dejan Juric1, Jeffrey R. Infante2, Ian E. Krop1, Carla Kurkjian4, Manish R. Patel1, Richard A. Graham3, Timothy R. Wilson4, Jerry Y. Hsu5, Jose Baselga6, Daniel D. Von Hoff6
1Massachusetts General Hospital Cancer Center, Boston, MA; 2Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; 3Dana Farber Cancer Institute, Boston, MA; 4University of Oklahoma, Oklahoma City, OK; 5Sarah Cannon Research Institute/Florida Cancer Care Specialists, Sarasota, FL; 4Genentech, Inc., South San Francisco, CA; 6Memorial Sloan-Kettering Cancer Center, New York, NY; 7Virginia G. Piper Cancer Center/TGen, Scottsdale, AZ

BACKGROUND

- Aberrant PI3K/Akt pathway activation, including PIK3CA mutations, is frequent and may be important for cancer growth and survival.
- GDC-0032 is an orally bioavailable, potent, and selective inhibitor of Class I PI3K alpha, delta, and gamma isoforms, with 30-fold less inhibition of the PI3K beta isoform relative to the PI3K alpha isoform.
- Preclinical data show that GDC-0032 has enhanced activity against PIK3CA alpha isoform mutant cancer cell lines.
- In an ongoing Phase I study, GDC-0032 has been well-tolerated with maximum administered dose of 16 mg daily during dose escalation.
- Updated clinical data on the dose escalation phase and on expansion cohorts in solid tumors and HER2+ breast cancer are presented here.

OBJECTIVES

- Primary Objectives
  - Evaluate safety and tolerability and estimate the maximum tolerated dose (MTD) of increasing oral doses of GDC-0032 given daily.
  - Evaluate safety and tolerability of GDC-0032 at the RP2D (9 mg) in patients with all solid tumors and HER2-positive breast cancer.
- Additional Objectives
  - Preliminary assessment of anti-tumor activity of GDC-0032 via RECIST.
  - Evaluate pharmacokinetics of GDC-0032.
  - Evaluate PI3K pathway inhibition via FDG-PET and paired tumor biopsies.

METHODS

Study Design

- Phase I dose escalation study with modified 3+3 design to evaluate daily doses of GDC-0032 with a starting dose of 3 mg.
- Dose expansion in patients with solid tumors or HER2+ breast cancer.

RESULTS

- Data were updated and presented as of 1 March 2013.
- Primary analysis is limited to patients with 3+3 dose expansion at the RP2D of 9 mg.

Safety

- No dose-limiting toxicities (DLTs).
- DLTs: 12 mg - Grade 3 acute renal failure (1); 16 mg - Grade 4 hyperglycemia (1), Grade 3 fatigue (1).
- Grade 4 related adverse events (AEs): hyperglycemia in a single patient (16 mg).
- Rapid absorption Tmax = 3 hrs, single dose half-life ~40 hrs.
- Dose-linear and time-independent PK with moderate PK variability.

Clinical Activity/Efficacy

- All patients were evaluable for response.
- Metabolic partial response rates of 18-33% for patients with PIK3CA mutant tumors.

Pharmacodynamics and Biomarkers

- Reverse phase protein array (RPPA) from pre- vs. on-treatment paired tumor biopsies from 2 NSCLC patients showed downregulation of the PI3K pathway at the lowest (3 mg) and highest (16 mg) dose tested.
- Dose escalation to RP2D of 9 mg QD based on safety, tolerability, and preliminary efficacy.
- RP2D of GDC-0032 was 9 mg QD based on safety, tolerability, and preliminary efficacy.

CONCLUSIONS

- GDC-0032 clinical PK data support daily dosing.
- GDC-0032 safety profile consistent with toxicities observed with PI3K inhibitors.
- Pharmacodynamic knockdown of the PI3K pathway observed at lowest dose level tested (3 mg) via FDG-PET and paired tumor biopsies.
- Promising preliminary clinical activity in PIK3CA mutant cancers, especially PIK3CA mutant and HER2-positive breast cancer.
- GDC-0032 is being explored further in solid tumors both as a single agent and in combination with endocrine therapies and other anticancer therapies.

ACKNOWLEDGMENTS

- We thank the patients who participated in the study, and their families.
- Genentech provided support for this poster.

Table 1. Patient Baseline Characteristics. Data Cutoff 1 Mar 2013

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Dose Escalation N=34</th>
<th>Dose Expansion N=23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>56 (24–82)</td>
<td>56 (26–74)</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>11 (32)</td>
<td>7 (30)</td>
</tr>
<tr>
<td>ECOG status, n (%)</td>
<td>20 (60)</td>
<td>11 (48)</td>
</tr>
<tr>
<td>0</td>
<td>14 (41)</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Prior systemic regimens, median (range)</td>
<td>4 (0–13)</td>
<td>5 (0–16)</td>
</tr>
</tbody>
</table>

Figure 1. Study Schema

- Dose-escalation with modified 3+3 design.
- Eligibility: Patients with study-advanced or metastatic solid tumors.
- QD dosing at GDC-0032.
- Tumor assessments every 2 cycles.
- Endpoints: PK, safety, MTD, exploratory PD.
- PD markers: FDG-PET tumor biopsy.

Figure 2. GDC-0032 Pharmacokinetics

- Concentration (nM)
- Time (hr)
- LLOQ = 0.87 nM
- 3 mg: n=6
- 5 mg: n=3
- 8 mg: n=4
- 12 mg: n=10
- 16 mg: n=11
- *Rash includes: rash, rash erythematous, exfoliative rash, rash maculo-papular, skin exfoliation.

Figure 4. Pharmacodynamic Effects Observed via FDG-PET after GDC-0032 Treatment

- Metabolic partial responses of 18–33% for patients with PIK3CA mutant tumors.

Figure 6. Patient #1: Confirmed Partial Response to GDC-0032 in Patient with PIK3CA Mutant Breast Cancer

Figure 7. Patient #2: Confirmed Partial Response to GDC-0032 in Patient with PIK3CA Mutant Breast Cancer

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