Introduction

- Prevention of telomere length is crucial to cell survival and enabling the unlimited replicative capacity of cancer cells.
- Telomerase is a promising target for novel cancer therapies.

Dose Rational

- Purposes: Multiple doses and dosing schedules of imetelstat were assessed in a Phase I study in patients with advanced solid tumors with or without known sensitization to the drug.

Table: Imetelstat Sodium (GRN163L), a Telomerase Inhibitor: Pharmacodynamics and Tumor Activity Using an Intermittent Four-Week Dosing Schedule in Patients with Advanced Solid Tumors

<table>
<thead>
<tr>
<th>Dose Regimen</th>
<th>Imetelstat Sodium (mg/kg)</th>
<th>Tumor Activity</th>
<th>Pharmacodynamics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Phase II</td>
<td>9.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Phase III</td>
<td>11.7</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Results

- Baseline Characteristics:
  - Cohort 1: 16 patients; 11.7 mg/kg imetelstat on day 1 of 28-day cycle, up to the day-of-cut-off of October 4, 2016.
  - Cohort 2: 11 patients; 9.4 mg/kg imetelstat on day 1 of 28-day cycle, up to the day-of-cut-off of October 4, 2016.
  - Cohort 3: 11 patients; 11.7 mg/kg imetelstat on day 1 of 28-day cycle, up to the day-of-cut-off of October 4, 2016.

Platelet Levels

- Platelet levels at each dose level are shown in Figure 2.

Safety

- No significant toxicity was observed at 1.75 mg/kg.
- Grade 2 telomerase-associated effects were reported at 5.25 mg/kg.
- Grade 3 telomerase-associated effects were reported at 7.0 mg/kg.
- Grade 4 telomerase-associated effects were reported at 8.5 mg/kg.

Summary

- The once every 28 day dosing schedule is well tolerated.
- The dose-limiting toxicity is neutropenia and thrombocytopenia.
- The period of cytopenia is consistent with effects on murine bone marrow and murine prolymphoproliferative growth known to express telomerase.
- Pharmacodynamic (PD) evidence of target inhibition has been observed in selected patient tissues.

Acknowledgements

- The authors gratefully acknowledge Genentech’s Sharing Memory and Change Matters for their important contributions and dedicated work throughout this study.

- The authors would like to acknowledge the patients and their families who participated in this study, and the investigators and study staff who made this study possible.

- Funding provided by Genentech Corp.

References