A Phase 2 Dose-Confirmation Study of Oral ASTX727, a Combination of Oral Decitabine with a Cytidine Deaminase Inhibitor (CDAi) Cedazuridine (E7727), in Subjects with Myelodysplastic Syndromes (MDS)

Guillermo Garcia-Manero1, Elizabeth A. Griffin2, Gail J. Roboz3, Lambert Buzauer4, Richard Wells5, Clotiduia Odier6, David P. Steenstra7, Karen W. Yen8, Stefan Faderle9, Philip Armitage9, Laura C. Michaelis10, Hagop Kantarjian11, Atom Oganesian12, James N. Lowder13, Mohammad Asab14, Michael R. Savona15


INTRODUCTION

An oral hypomethylating agent which could be administered at a dose which would emulate parenteral pharmacokinetics would be more convenient and potentially enhance adherence to treatment. Herein, rapid clearance by cytidine deaminase (CDA) during first pass has prevented good oral bioavailability for decitabine (DAC). Cedazuridine (E7727), a novel CDAi, is orally bioavailable with a large safety margin and reproducible effectiveness in preclinical models. A phase 1 dose finding study found that a fixed oral combination of 35 mg of decitabine and 100 mg of E7727 (ASTX727 with 30 mg decitabine/100 mg cedazuridine/35 mg/35 mg) should produce similar PK to decitabine administered intravenously at 20 mg/m² as a 1-hour infusion. We tested this hypothesis in a phase 2 cross-over study, and report the preliminary results here.

Figure 1. Cedazuridine Blocks First Pass Metabolism of Decitabine Permitting Oral Administration

RESULTS

Table 2: Pharmacokinetics of Decitabine

<table>
<thead>
<tr>
<th>Group</th>
<th>PK, PD</th>
<th>PK, PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>ASTX727 35/100 mg</td>
<td>ASTX727 35/100 mg</td>
</tr>
<tr>
<td>B</td>
<td>ASTX727 35/100 mg</td>
<td>ASTX727 35/100 mg</td>
</tr>
</tbody>
</table>

Table 3: Cycles Administered

- N=50
- Cycles of Therapy: 6.5 ± 1.2

Figure 3. Pharmacokinetics of Decitabine

Figure 4. Decitabine individual AUC by Day

Table 4: All Adverse Events Occurring in ≥25% of Subjects During Study

<table>
<thead>
<tr>
<th>Event</th>
<th>N=50</th>
<th>N=49</th>
<th>N=48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>22 (44%)</td>
<td>21 (43%)</td>
<td>18 (37%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20 (40%)</td>
<td>19 (39%)</td>
<td>18 (37%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (10%)</td>
<td>5 (10%)</td>
<td>4 (8.2%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
</tr>
</tbody>
</table>

Table 5: Clinical Response Data

- PB17(701)
- N=50
- RBC Transfusion Dependence at Baseline, N=48
- 92.8% CR
- 8.3% mCR
- 2.3% mPR
- 0% No Response

Figure 5. Pharmacokinetics of Cedazuridine over 5 Days of Treatment

Figure 6: LINE-1 Demethylation Similar between IV-DAC and ASTX727

CONCLUSIONS

- ASTX727 successfully emulates the AUC exposures and LINE-1 PD of 20 mg/m² IV decitabine in a 5 consecutive day regimen with a 5-day AUC ratio of 0.955.
- The 6-hour T1/2 of cedazuridine produces steady state by Day 2 and subsequent trough levels of drug which facilitates consistent decitabine oral bioavailability on Days 2 to 5 of the cycle.
- Clinical response and safety data appear similar to that reported for 20 mg/m² IV decitabine.

REFERENCES


© 2017 Astex Pharmaceuticals, Inc., Pleasanton, CA

Poster presented at: ASH Annual Meeting, Atlanta, GA Dec 9 – 12, 2017

Poster can be downloaded from www.astx.com

ASTX727-P1077(01)