Phase II Open-Label, Safety, Pharmacokinetic and Efficacy Study of Panzem® Nanocrystal Colloidal Dispersion Administered Orally to Patients with Recurrent Glioblastoma Multiforme
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METHODS

Study Objectives

1. To assess the safety of 2ME2 administered orally at a dose of up to 1,500 mg four times daily (1500 mg, or Panzem®) in patients with recurrent GBM by evaluation of the frequency and severity of treatment emergent adverse events (AEs).

2. To determine the pharmacokinetics of 2ME2 in patients on and not on concurrent CYP3A inhibitors.

3. To determine the progression free survival (PFS) and time to progression in recurrent GBM patients overall, and between patients on and not on concurrent CYP3A inhibitors.

Eligibility Criteria

1. Histologically proven WHO grade IV malignant glioma (glioblastoma or gliosarcoma);

2. Age over 18 years;

3. No more than 2 prior episodes of progressive disease;

4. Progression during or within 90 days of completion of prior radiotherapy;

5. No more than 1 prior chemotherapy regimen (excluding bevacizumab);

6. No more than 1 prior bevacizumab regimen if prior bevacizumab dose ≤ 12 mg/kg per week;

7. No radiographic evidence of intracranial hemorrhage (except post-op grade 1);

8. No requirement for therapy with warfarin sodium;

9. Informed consent.

Study Therapy and Evaluations

Panzem® Administration

- Continuous daily dosing: 28 day cycles until PD, unacceptable toxicity or consent withdrawal

Sample Size Justification

- Primary endpoint: 6-month PFS

- Type I error: 0.051

- Sample size calculation: 11 patients per arm (total 22 patients) for 20% difference in PFS rates with α = 0.05

Statistical Design

- Fisher exact test

RESULTS

Pharmacokinetics

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cmax (ng/mL)</th>
<th>AUC0-6 (ng/mL*hr)</th>
<th>Tmax (hr)</th>
<th>Cmax (ng/mL)</th>
<th>AUC0-6 (ng/mL*hr)</th>
<th>Tmax (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 mg</td>
<td>0.07</td>
<td>0.47</td>
<td>0.4</td>
<td>0.04</td>
<td>0.26</td>
<td>0.4</td>
</tr>
<tr>
<td>1500 mg</td>
<td>0.26</td>
<td>2.0</td>
<td>0.8</td>
<td>0.28</td>
<td>1.0</td>
<td>0.8</td>
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Toxicity

<table>
<thead>
<tr>
<th>Event</th>
<th>6000 mg Cohort</th>
<th>4000 mg Cohort</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Transaminase</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Transaminase</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

CONCLUSIONS

1. Panzem® is well tolerated among multiplicity glioma patients.

2. The only grade 3 toxicity that occurred in 41% of patients was transaminase elevation.

3. Limited efficacy in terms of first 16 response disease progression or death within 3 months of enrollment.

4. Panzem® has minimal activity as a monotherapeutic for patients with recurrent GBM.