Introduction

- Pralatrexate is a novel targeted antifolate designed to accumulate preferentially in cancer cells.
- Pralatrexate + gemcitabine (Gem) synergize in a schedule-dependent manner in cell lines in vitro and in lymphoma xenografts (Toner et al. 2006).
- Pralatrexate is active in peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL) (O'Connor et al. 2007, Horwitz et al. 2008).

Safety

- Grade 2 Treatment-Related Adverse Events in > 1 patient that were possibly, probably, or definitely related to pralatrexate or Gem.

A: CT Baseline

A: PET Baseline

B: PET after cycle 4

Preliminary Efficacy

Patient with multiply relapsed nodular sclerosing Hodgkin lymphoma (prior ASCT x 2, previous Gem); treated in cohort A-1 (pralatrexate 10/Gem 400 [mg/m²], sequential days, 3/4 weeks)

A: Pretreatment: Right pelvic sidewall mass

B: Cycle 4 with PR by CT and resolution of PET avidity

Study Design

- The primary objective of the study is to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose of pralatrexate and Gem in combination.
- Treatment Groups:
  - A: Pralatrexate → Gem on sequential days, weekly for 3 of 4 weeks in 4-week cycle
  - B: Pralatrexate → Gem on sequential days, every (q) 2 weeks in 4-week cycle
  - C: Pralatrexate → Gem on same day (1 hour later), q 2 weeks in 4-week cycle

- The following adverse events (AEs) are considered dose-limiting toxicities (DLTs) when occurring during the first treatment cycle:
  - Grade 4 neutropenia lasting for ≥ 7 days
  - Grade 4 thrombocytopenia or any grade thrombocytopenia with neutropenia (Grade 3);
  - Grade 3 non-hematological toxicity, excluding nausea/vomiting in the absence of appropriate anti-emetic therapy
  - Dose reduction needed in cycle 1 for any treatment-related AE(s).

- The MTD is defined as the highest dose level at which ≤ 33% of patients experience a DLT.
- Response assessed using the International Workshop Criteria (IWC) every 2-3 cycles.

Patients (N = 27)

- Median age: 65 years
- Range: 19-81 years
- Median prior regimens: 3 (3 systemic)
- Range: 2-13 (1-11 systemic)

Category | n | Percentage
--- | --- | ---
Male | 17 | 63%
Female | 10 | 37%
Disease Type
  - T/NK-cell | 8 | 29%
  - DLBCL | 7 | 26%
  - Follicular lymphoma | 3 | 11%
  - Mediastinal B-cell | 1 | 4%
Composite DLBCL and T/NK | 1 | 4%

Dose-limiting Toxicities

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Number of Patients in Cohort</th>
<th>Dose Pralatrexate/Gem (mg/m²)</th>
<th>Schedule</th>
<th>Number of Patients with DLTs</th>
<th>DLT (Grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>2</td>
<td>15/400</td>
<td>Sequential days, 3/4 weeks</td>
<td>2</td>
<td>Thrombocytopenia &amp; neutropenia (Grade 4 &amp; 3)</td>
</tr>
<tr>
<td>A-1</td>
<td>2</td>
<td>10/490</td>
<td>Sequential days, 3/4 weeks</td>
<td>2</td>
<td>Thrombocytopenia (Grade 3)</td>
</tr>
<tr>
<td>A-2</td>
<td>3</td>
<td>10/380</td>
<td>Sequential days, 3/4 weeks</td>
<td>3</td>
<td>Neutropenia (Grade 3)</td>
</tr>
<tr>
<td>B1</td>
<td>3</td>
<td>10/300</td>
<td>Sequential days, q 2 weeks</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td>4</td>
<td>10/400</td>
<td>Sequential days, q 2 weeks</td>
<td>1</td>
<td>Cellulitis (Grade 3)</td>
</tr>
<tr>
<td>B3</td>
<td>3</td>
<td>15/400</td>
<td>Sequential days, q 2 weeks</td>
<td>3</td>
<td>Cellulitis (Grade 3); Pneumonia (Grade 3); Thrombocytopenia (Grade 4)</td>
</tr>
<tr>
<td>C1</td>
<td>3</td>
<td>10/300</td>
<td>Same day, q 2 weeks</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>C2</td>
<td>7</td>
<td>10/400</td>
<td>Same day, q 2 weeks</td>
<td>1</td>
<td>Hypoxia &amp; Pneumonia (Grade 3)</td>
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</tbody>
</table>

Patients Evaluable for Response (N = 22)*

<table>
<thead>
<tr>
<th>Number of Evaluable Patients</th>
<th>Histology</th>
<th>Response</th>
<th>Response Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>HL (nodular sclerosis)</td>
<td>4 PR</td>
<td>1+, 4+, 4+, 4+</td>
</tr>
<tr>
<td>7</td>
<td>DLBCL</td>
<td>2 PR</td>
<td>1.5, 2</td>
</tr>
<tr>
<td>6</td>
<td>T/NK-cell</td>
<td>2 SD</td>
<td>4 PD</td>
</tr>
<tr>
<td>1</td>
<td>Mediastinal B-cell</td>
<td>1 SD</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

- Pralatrexate + Gem on a q 2 weeks schedule is active and better tolerated than a weekly schedule in heavily pre-treated patients with refractory lymphomas.
- Responses have been observed in 6 of 22 evaluable patients
  - 4 of 6 patients with HL
  - 2 patients with DLBCL
- Responses occurred on both the sequential dosing schedule (5 patients) and the same-day dosing schedule (1 patient).
- The MTD for the q 2 weeks sequential days schedule is pralatrexate 10/Gem 300 (mg/m²).
- Enrollment is ongoing to define the MTD on q 2 weeks same day schedule.

This study was sponsored by Allos Therapeutics, Inc.


*Only includes those patients w/ case report form data in Allos clinical database and with Grade 3 or 4 AEs in > 1 patient that were possibly, probably, or definitely related to pralatrexate or Gem.