Table 1. Patient Demographic and Baseline Clinical Characteristics

Abbreviations: CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; MM, multiple myeloma; HCL, hairy cell leukemia

Table 2. Grade 2 and above treatment-related adverse events during Cycles 1 and 2 (n=16)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MCL</td>
<td>CLL</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>MCL</td>
<td>CLL</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>MCL</td>
<td>CLL</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>MCL</td>
<td>CLL</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>MCL</td>
<td>CLL</td>
<td>-</td>
</tr>
</tbody>
</table>

Materials and Methods

Phase I study of ON 01910.Na (rigosertib), a multikinase PI3K inhibitor in relapsed/refractory B-cell malignancies

Mark Roschewski, Mohammed Farooqui, Georg Aue, Clifton Mo, Janet Valdez, Susan Soto, Patricia Perez-Galan, Francois Wilhelm, and Adrian Wiestner

1Metabolism Branch, NCI, NIH; 2Hematology Branch, NHLBI, NIH; 3Hematology-Oncology, Walter Reed National Military Medical Center; 4Department of Hemato-Oncology, Institut d’Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; 5Onconova Therapeutics Inc, Newton, PA

Background

- B-cell malignancies such as CLL and MCL universally relapse after initial therapy and effective salvage therapies are needed
- Myelosuppression is a common barrier to salvage therapy in these relapsed B-cell malignancies
- Rigosertib is a multikinase inhibitor that inhibits PI3 kinase and PLK-1 kinase pathways and induces apoptosis in CLL and MCL cells, in vitro
- Pre-clinical testing of rigosertib demonstrated selectivity for CLL and MCL cell lines with minimal effect on normal B and T cells
- Minimal myelosuppression with rigosertib which is undergoing phase III testing in refractory myelodysplastic syndrome at a 1800 mg/day for 3 days every other week dosing

Materials and Methods

- Phase 1, dose-escalation study in patients with relapsed/refractory CLL, MCL, and related B-cell malignancies
- Primary endpoint was toxicity after 2 cycles
- Baseline cytopenias permitted if ANC ≥ 500 and PLT ≥ 10K
- Infusion cycles every 14 days; responding patients allowed to continue until disease progression or unacceptable toxicity
- Dosing via ambulatory infusion pump at following schedules:
  - Cohort 1: 1200mg/m² IV over 48 hours
  - Cohort 2: 1500mg/m² IV over 48 hours
  - Cohort 3: 1800mg/m² IV over 48 hours
  - Cohort 4: 1800mg FLAT dose over 72 hours
  - Cohort 5: 2100mg over 72 hours

  *Dosing schedule changed to 72 hours based on efficacy observed in MDS

Results - Toxicity

- 2 events of G4 neutropenia observed in cohort 5 in patient with pre-existing G3 neutropenia
- 4 events of G3 neutropenia observed in cohort 5 in patient with pre-existing G2 neutropenia

All events felt possibly due to drug and possibly due to disease

Results - Response

- Rigosertib is well-tolerated in patients with relapsed/refractory B-cell lymphoid malignancies – no MTD identified
- Hematologic toxicity is limited and rigosertib can be safely administered to patients with pre-existing cytopenias
- As a single agent, rigosertib did not induce objective responses even at doses higher than currently being investigated in MDS
- Rigosertib’s relative lack of myelosuppressive activity may allow for combination strategies in B-cell lymphoid malignancies

Conclusions

Disclaimer/Disclosure

This work was supported by the Intramural Research Program of the NHLBI of the NIH. None of the authors have significant disclosures of conflict of interest.

Correspondence: roschewski@mail.nih.gov