Rigosertib sodium

**Molecular formula:** C21H24NO8SNa

**Molecular weight:** 437.47

**Structural formula:**

- Rigosertib is a small molecular entity that interferes with Ras binding domains containing proteins. Rigosertib induces G2/M arrest leading to suppression of cell cancer and myeloblasts while causing minimal damage to normal cells.
- Rigosertib interferes with the Ras binding domains of RAF kinases and inhibits the RAF-MEK and PI3K pathways.
- A Phase I study in the U.S. showed the safety and good tolerability of oral-rigosertib in patients with low, intermediate-1, intermediate-2, or high risk myelodysplastic syndromes (MDS).

**Objectives**

- Examine tolerability, investigate DLT and determined recommended dose (RD) for Phase II
- Explore pharmacokinetics and antitumor effect when rigosertib was orally administered to Japanese patients with recurrent/refractory MDS

**[Primary endpoints]**
- Number of patients experienced with dose-limiting toxicity (DLT) in the 1st cycle

**[Secondary endpoints]**
- 1) Safety: Adverse events and changes in laboratory test values
- 2) Efficacy:
  - Hematologic remission rate of the overall response per IWG 2006
  - Hematologic improvement rate of the overall response per IWG 2006
  - Cytophenic response rate per IWG2006
- 3) Pharmacokinetics: Pharmacokinetic parameters

**Key Inclusion Criteria**

1. Diagnosed with MDS and classified as one of the following (WHO) or FAB: RA, RAEB, RAEB-T, RA or CMML
2. Reduction in at least one hematologic parameter of the following:
   - Neutrophil count: <1,500/mm3
   - Platelet count: <100,000/mm3
   - Hemoglobin level: <10 g/dL
3. Patients with previous MDS treatment who meet one of the following:
   - Failed to achieve complete remission, partial remission, or hematologic improvement
   - Recurrence/relapse after achievement of complete remission, partial remission, or hematologic improvement
   - Intolerance and discontinuation due to liver or renal disorder
4. Age: ≥20 years
5. ECOG PS: 0 to 2
6. Adequate major organ functions:
   - AST/ALT ≤2.5-fold ULN
   - Total bilirubin: ≤1.5-fold ULN
   - Serum creatinine: ≤1.5-fold ULN

**Treatment Scheme**

- 1 cycle = 21 days
- Up to 6 cycles were allowed
- 280 or 560 mg/day of oral rigosertib administered twice daily for 14 days every 21 days
- Dose escalation performed by use of a modified 3+3 design

<table>
<thead>
<tr>
<th>Patient Demographics and Disease Characteristics (1=9)</th>
<th>Grade 3 or Higher Adverse Events (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>Class (0)</td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>(×10³/mm³)</td>
</tr>
<tr>
<td>Platelet count</td>
<td>(×10³/mm³)</td>
</tr>
<tr>
<td>Hemoglobin level</td>
<td>(g/dL)</td>
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</tbody>
</table>

**Pharmacokinetics**

- C21H24NO8SNa

**Summary**

- DLTs were observed in 1/3 pts in the 280 mg BD group (type 2 diabetes mellitus and gastrointestinal bleeding in 1/2 pts in 560 mg BD group (urinary tract infection and prolonged QT interval)
- A total of 57 events of adverse reactions were developed in the 5 pts:
  - The adverse events that developed in ≥2 pts included anemia, vomiting, diarrhea, dysgeusia, increased aspartate aminotransferase, decreased lymphocyte count, and neutrophil count decreased
  - One pt in the 560 mg BD group died of septic shock that had been caused by urinary tract infection during the study period
- The hematological remission rate in 19 pts (11.1%: 1/2, 9/9 pts) and the hematological improvement rate was 11.1% (1/2, 9/9 pts)
- No cytogenetic response was seen
- Plasma concentrations of rigosertib increased rapidly after oral administration and there was no sign of accumulation of rigosertib after repeated administration

**Conclusion**

The present regimen of oral rigosertib was well tolerated. Our study indicates that the recommended dose for a Phase II clinical study is 560 mg BD in Japanese patients with recurrent/refractory MDS.