Outcomes for older patients with newly diagnosed AML remain poor. 15 patients (44%) with 2 died of sepsis; 1 during cycle 2 and 3 on subsequent salvage treatments. Determine CR rate and 4 month survival of TST in combination with either cytarabine or decitabine. TST has adequate safety and promising efficacy in Phase I/II monotherapy studies (e.g., OPAL study) for patients with relapsed AML and MDS. Pre-clinical AML blast proliferation assays demonstrated synergy between TST and both cytarabine or hypomethylating agents.

Primary Objective: • Determine CR rate and 4 month survival of TST in combination with either cytarabine or decitabine for untreated AML or high-risk MDS.

Secondary Objectives: • Assess safety and tolerability of TST with either cytarabine or decitabine; • Estimate rates of disease-free survival (DFS) and 1-year overall survival (OS).

MAIN ELIGIBILITY CRITERIA: • Adults ≥60 years of age with untreated AML and intermediate or high-risk cytogenetics or high-risk MDS (RAEB-2); • Prior hypomethylating agent for MDS or hydroxyurea allowed; • ECOG Performance Status 0-2.

STUDY DESIGN & TREATMENT SCHEMA:

- Cytarabine 1 g/m² IV D1-5
- Decitabine 20 mg/m² IV D1-5
- Tosedostat 120 mg QD D1-21 or 180 mg QD D1-35

<table>
<thead>
<tr>
<th>CTC Category</th>
<th>Total N=34 (%)</th>
<th>TST 120 mg + Decitabine N=13 (%)</th>
<th>TST 120 mg + Cytarabine N=13 (%)</th>
<th>TST 180 mg N=8 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>14 (41)</td>
<td>4 (31)</td>
<td>6 (46)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>CRi</td>
<td>4 (12)</td>
<td>3 (23)</td>
<td>1 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Complete Response (CR + CRi)</td>
<td>18 (53)</td>
<td>7 (54)</td>
<td>7 (54)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Treatment Failure</td>
<td>14 (41)</td>
<td>5 (38)</td>
<td>5 (38)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Not Evaluable</td>
<td>2 (6)</td>
<td>1 (8)</td>
<td>1 (8)</td>
<td>0</td>
</tr>
</tbody>
</table>

- Median follow-up 11.2 months (range, 0.5-22.3)
- Average 2 cycles required for maximal response: 9 patients required 3 cycles, 4 patients required 2 cycles, and 5 patients required 1 cycle.
- CR/CRi in 5 patients with adverse risk AML and 4 patients with FLT3-ITD+ AML.
- 18 CR/CRi: 11 received HCT, 6 deferred HCT, 1 died of sepsis in CRi on day 133.

- No Grade 3-4 CTC AE adverse events (10%) - Median age 70 (range, 60-83)
- 28 patients (82%) with ECOG of 1
- 29 patients (85%) with AML and 5 patients (15%) with MDS RAEB-2
- 19 patients (56%) intermediate-risk, 14 patients (41%) adverse-risk, and 1 patient (3%) favorable-risk AML by European LeukemiaNet criteria
- 15 patients (44%) with 2nd/3rd AML/MDS or antecedent hematologic disorder
- 7 patients (21%) normal cytogenetics and FLT3+

- TST 120 mg: 4 (31) CR + CRi
- TST 180 mg: 1 (8) CR + CRi

CONCLUSIONS:

- TST in combination with cytarabine or decitabine resulted in a 53% CR/CRi rate in 34 older patients with untreated AML or high-risk MDS.
- Although similar efficacy was seen with cytarabine or decitabine, Grade 3-4 febrile neutropenia and infections were more common with cytarabine.
- This approach was well tolerated as predominantly outpatient therapy and may warrant further study in a controlled trial.

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Funding: Cell Therapeutics Inc.

A Phase II Study Of Tosedostat (TST) In Combination With Either Cytarabine Or Decitabine In Newly Diagnosed Older Patients With Acute Myeloid Leukemia (AML) Or High-Risk Myelodysplastic Syndrome (MDS)

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