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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BACKGROUND

• Outcomes for older patients with newly diagnosed AML remain poor
• TST is an oral aminopeptidase inhibitor with anti-neoplastic activity in a variety of malignancies, including AML
• 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 and hypomethylating agents

OBJECTIVES

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)

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

MAIN ELIGIBILITY CRITERIA

STUDY DESIGN & TREATMENT SCHEMA

≥60 yo untreated AML or MDS RAEB-2 + Tosedostat 120 mg QD D1-21 + Cytarabine 1 g/m² IV D1-5 + Decitabine 20 mg/m² IV D1-5

• Up to three 35-day cycles if stable/improved blast count and <grade 3 non-hematologic toxicity with cycle 1
• Could receive up to 5 cycles total if CR/CRi obtained after 3 cycles
• Failure to achieve CR/CRi after 3 cycles of therapy → Off Study

Stopping Rules:
a) 4 month survival → stop if posterior probability of >0.2 absolute increase (from 60% to 80%) is <0.05
   • Stop if <13 of first 20 alive at 4 months
b) CR → stop if posterior probability of >0.2 decrease in CR rate (from historical 50% to 30%) is >0.8
   • Stop if <4 of first 20 patients achieve CR

• Median age 69 (range, 60-83)
• 22 patients (85%) with ECOG of 1
• 19 patients (73%) with AML and 7 patients (27%) with MDS RAEB-2
• 19 patients (73%) intermediate-risk and 7 patients (27%) adverse-risk AML by European LeukemiaNet criteria
• 14 patients (54%) with 2ndary AML/MDS or antecedent hematologic disorder

• Failure to achieve CR/CRi after 3 cycles of therapy
• Could receive up to 5 cycles total if CR/CRi obtained after 3 cycles
• Up to three 35-day cycles if stable/improved blast count and <grade 3 non-hematologic toxicity with cycle 1
• Prior hypomethylating agent for MDS or hydroxyurea allowed
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RESPONSES

<table>
<thead>
<tr>
<th></th>
<th>TST + Cytarabine (N=13)</th>
<th>TST + Decitabine (N=13)</th>
<th>Total (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>6 (46%)</td>
<td>4 (31%)</td>
<td>10 (39%)</td>
</tr>
<tr>
<td>CRi</td>
<td>1 (8%)</td>
<td>3 (23%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>Treatment Failure</td>
<td>5 (39%)</td>
<td>6 (46%)</td>
<td>11 (42%)</td>
</tr>
<tr>
<td>Not Evaluable</td>
<td>1 (8%)</td>
<td>0</td>
<td>1 (4%)</td>
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<tr>
<td>Complete Response</td>
<td>7 (54%)</td>
<td>7 (54%)</td>
<td>14 (54%)</td>
</tr>
<tr>
<td>CR/CRi</td>
<td>4 (31%)</td>
<td>6 (46%)</td>
<td>10 (39%)</td>
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• Median follow-up 8.5 months (range, 0.5-17)
• Average 2 cycles required for maximal response: 5 patients required 3 cycles, 4 patients required 2 cycles, and 5 patients required 1 cycle
• CR/CRi in 3 patients with adverse risk AML and 4 patients with FLT3-ITD+ AML
• 14 CR/CRi: 10 received HCT, 3 deferred HCT, 1 died of sepsis in CRi on day 133

• 7 (54%) CR/CRi: 10 received HCT, 3 deferred HCT, 1 died of sepsis in CRi on day 133
• 14 CR/CRi: 10 received HCT, 3 deferred HCT, 1 died of sepsis in CRi on day 133

• 5 patients (19%) died within 4 months of starting therapy
• 3 died of sepsis on subsequent salvage treatments
• 1 with MDP & splenomegaly died of splenic infarction on day 15
• 1 died at age 83 during cycle 2 of unknown cause
• 8 patients (31%) treated completely outpatient without hospitalization
• 15 patients (58%) hospitalized for febrile neutropenia

GRADE 3/4 CTCAE ADVERSE EVENTS (>10%)

<table>
<thead>
<tr>
<th>CTC Category</th>
<th>TST + Cytarabine (N=13)</th>
<th>TST + Decitabine (N=13)</th>
<th>Total (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile Neutropenia</td>
<td>9 (69%)</td>
<td>4 (31%)</td>
<td>13 (50%)</td>
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<tr>
<td>Disseminated Intravascular</td>
<td>2 (15%)</td>
<td>0</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Coagulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>1 (8%)</td>
<td>2 (15%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Lung Infection</td>
<td>6 (46%)</td>
<td>2 (15%)</td>
<td>8 (31%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4 (31%)</td>
<td>1 (8%)</td>
<td>5 (19%)</td>
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</table>

CONCLUSIONS

• TST at 120 mg daily in combination with cytarabine or decitabine resulted in a 54% CR/CRi rate in 26 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

Disclosures: There are no relevant conflicts of interest to disclose