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

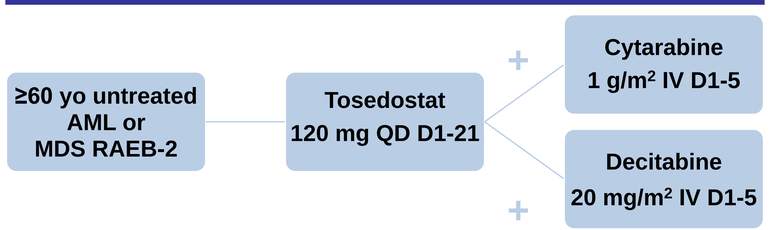
Secondary Objectives

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

MAIN ELIGIBILITY CRITERIA

- 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

STUDY DESIGN & TREATMENT SCHEMA



- 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

PATIENT CHARACTERISTICS

- 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 2^{ndary} AML/MDS or antecedent hematologic disorder

RESPONSES

	TST + Cytarabine (N=13)	TST + Decitabine (N=13)	Total (N=26)
CR	6 (46%)	4 (31%)	10 (39%)
CRi	1 (8%)	3 (23%)	4 (15%)
Treatment Failure	5 (39%)	6 (46%)	11 (42%)
Not Evaluable	1 (8%)	0	1 (4%)
Complete Response (CR + CRi)	7 (54%)	7 (54%)	14 (54%)
Received Transplant	4 (31%)	6 (46%)	10 (39%)

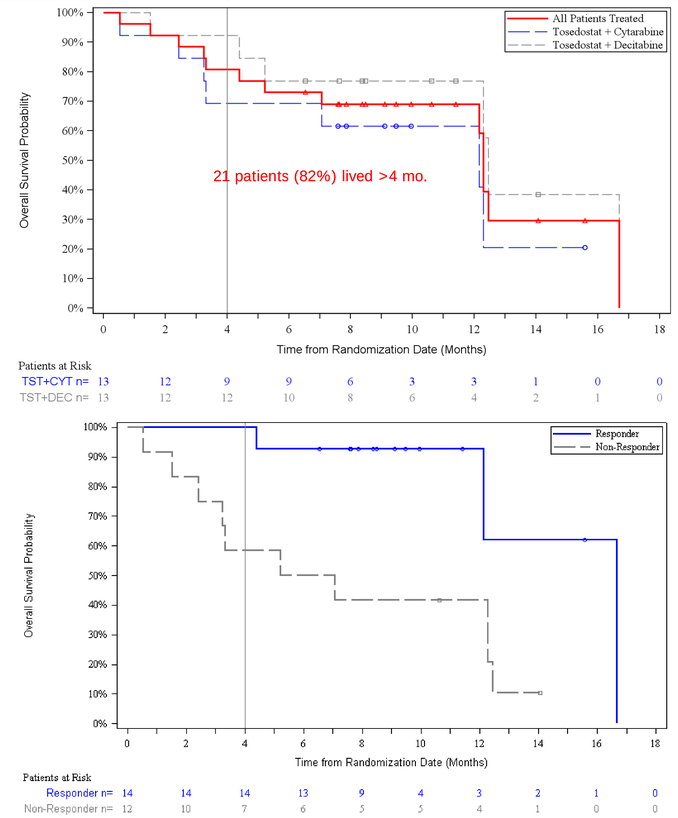
- Median follow-up 8.5 months (range, 0.5-17)
- Average 2 cycles required for maximal response: 5 patients required 3 cycles, 4 patients required 2 cycles, and 5 patients required 1 cycle
- CR/CRi in 3 patients with adverse risk AML and 4 patients with FLT3-ITD^{+} AML
- 14 CR/CRi: 10 received HCT, 3 deferred HCT, 1 died of sepsis in CRi on day 133

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

- No Grade 3-4 CTCAE 4.3 non-hematologic toxicities observed

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

PATIENT OUTCOMES



- 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

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*