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)

FRED HUTCHINSON CANCER RESEARCH CENTER
A LIFE OF SCIENCE

Raya Mawad,[1,2] Pamela S. Becker,[1,2] Paul Hendrie,[1,2] Bart Scott,[1,2] Brent L. Wood,[1,3] Carol Dean,[1] Vicky Sandhu,[1] H. Joachim Deeg,[1,2] Roland Walter,[1,2] Frederick R. Appelbaum,[1,2] Lixia Wang,[4] Han Myint,[4] Jack W. Singer,[2,4] Elihu Estey,[1,2] and John M. Pagel[1,2]

Division of Clinical Research[1], Fred Hutchinson Cancer Research Center; Departments of Medicine[2,] and Laboratory Medicine[3], University of Washington, Seattle, WA; Cell Therapeutics Inc., Seattle[4]

UW Medicine SCHOOL OF MEDICINE

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 or 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

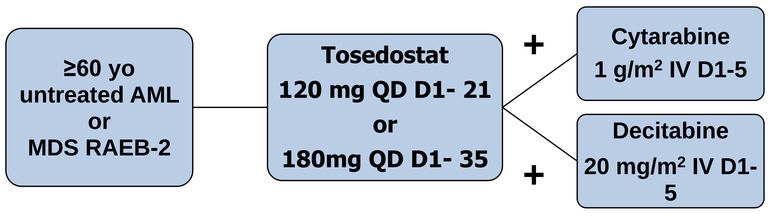
Secondary Objectives

- 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 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



- 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
- After 26 patients accrued, protocol amended to increase tosedostat dose to 180 mg/day continuously, and favorable-risk AML was eligible

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 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 2ndary AML/MDS or antecedent hematologic disorder
- 7 patients (21%) normal cytogenetics and FLT3+

RESPONSES

	Total N=34 (%)	TST 120 mg + Decitabine N=13 (%)	TST 120 mg + Cytarabine N=13 (%)	TST 180 mg N=8 (%)
CR	14 (41)	4 (31)	6 (46)	4 (50)
CRi	4 (12)	3 (23)	1 (8)	0
Complete Response (CR + CRi)	18 (53)	7 (54)	7 (54)	4 (50)
Treatment Failure	14 (41)	5 (38)	5 (38)	4 (50)
Not Evaluable	2 (6)	1 (8)	1 (8)	0

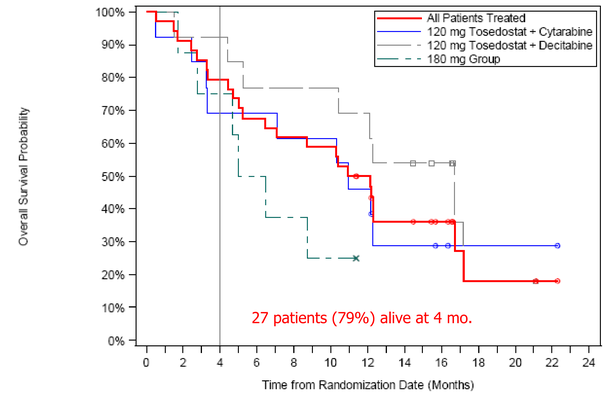
- Median follow-up 11.2 months (range, 0.5-22.3)
- Average 2 cycles required for maximal response: 9 patients required 3 cycles, 4 patients required 2 cycles, and 5 patients required 1 cycle
- CR/CRi in 5 patients with adverse risk AML and 4 patients with FLT3-ITD+ AML
- 18 CR/CRi: 11 received HCT, 6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

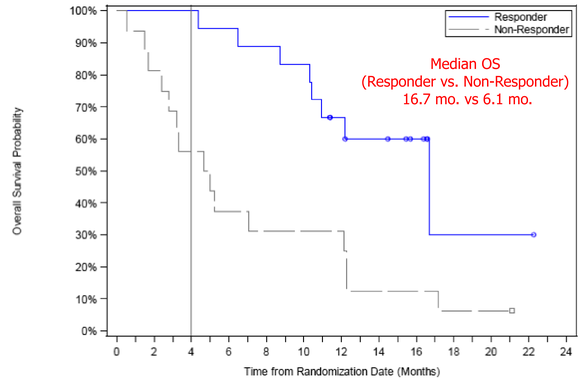
GRADE 3-4 CTCAE ADVERSE EVENTS (>10%)

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

CTC Category	Total N=34 (%)	TST 120 mg+ Decitabine N=13 (%)	TST 120 mg+ Cytarabine N=13 (%)	TST 180 mg N= 8 (%)
Febrile Neutropenia	16 (47)	4 (31)	9 (69)	3 (38)
Fever	3 (9)	2 (15)	1 (8)	0
Pneumonia	11 (32)	2 (15)	6 (46)	3 (38)
Sepsis	7 (21)	1 (8)	4 (31)	2 (25)
DIC	2 (6)	0	2 (15)	0

PATIENT OUTCOMES





- 7 patients (21%) died within 4 months of starting therapy
  - 4 died of sepsis; 1 during cycle 2 and 3 on subsequent salvage treatments
  - 1 with MDP & splenomegaly died of splenic infarction on day 15\
  - 1 died of AML after electively stopping treatment after cycle 1
  - 1 died at age 83 during cycle 2 of unknown cause
- 11 patients (32%) treated completely outpatient without hospitalization

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

Disclosures: *Lixia Wang, Han Mynt, and Jack W. Singer are employed by Cell Therapeutics Inc.; Jack W. Singer has equity ownership in Cell Therapeutics*
Funding: *Cell Therapeutics Inc.*