Interim Results of OPAL, a Study of Tosedostat in Elderly Relapsed/Refractory AML

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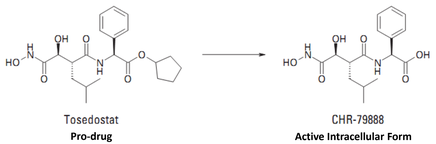
BACKGROUND

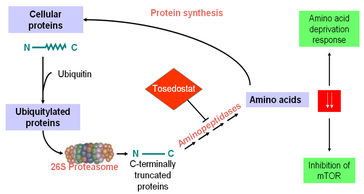
Description [1]

Tosedostat is a novel oral inducer of the **Amino Acid Deprivation Response (AADR)**.



Mechanism of Action [1]

- Tosedostat targets intracellular members of the M1/17 family of aminopeptidases. Causing **AADR**. Tumor cells undergo apoptosis >>normal cells with amino acid deprivation.



Preclinical Data [1, 2]

- Tosedostat has anti-neoplastic activity in, leukemia, myeloma and solid tumor cell lines *in vitro* [1].
- Synergy between tosedostat and both cytarabine and demethylating agents seen in AML blast proliferation assays [2].

Clinical Data [3]

- A phase 1/2 study of tosedostat in elderly and/or relapsing patients with AML or myelodysplastic syndrome showed promising anti-leukemic effects and acceptable tolerability. The ORR for patients with AML was 27% [3].
- Based on these results, the phase 2 comparing two doses of single agent tosedostat in relapsed refractory AML (OPAL) was initiated.
- The **interim** (3 month) results of the OPAL study are presented herein.

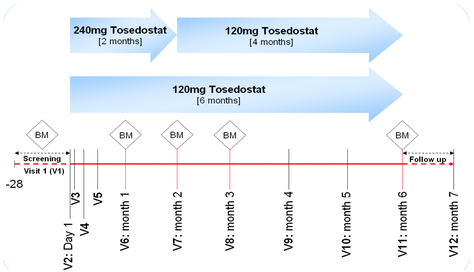
METHODS

Eligibility Criteria

- Age ≥ 60 years
- Confirmed AML: previous CR lasting <12 months or no CR after primary induction therapy
- Peripheral blast count <30,000/µl; hydroxyurea or leukapheresis may be used prior to or during the screening period
- Adequate hepatic and renal function, PS ≤ 2, and LVEF ≥ 50%
- No anti-cancer therapy within 2 weeks of trial entry except hydroxyurea.
- No significant cardiovascular disease

Study Design

- 73 patients were randomized to receive first salvage therapy with tosedostat 120 mg once daily for 6 months OR tosedostat 240 mg once daily for 2 months followed by 120 mg once daily for 4 months.



Interim Endpoint

- Primary: Proportion of patients that achieve bone marrow complete response (CR) or partial response (PR) (ORR) at any time during the first 3 months of the study,

Statistical Analysis Plan

- Interim (3 month) Analysis: Conducted after all patients have completed 3 months of study in order to select the optimal dose. With a sample size of 35 patients per arm, the 95% CI will extend 15.2% from an expected proportion of 30% of patients with a bone marrow response.
- Final (6 month) Analysis: Will take place at 6 months and use best bone marrow response and hematology data. With a sample size of 35 patients per arm, the 95% CI will extend 13.3% from an expected proportion of 20% of patients with complete response (CR) or CR with incomplete platelet recovery (CRp).

RESULTS

Patient Demographics

	Overall (N = 73)	Tosedostat 120 mg (n = 38)	Tosedostat 240 mg→120 mg (n = 35)
Median age, years	72 (64-86)	73 (64-86)	71 (65-86)
Age, n (%)			
<75 years	50 (68)	24 (63)	26 (74)
≥75 years	23 (32)	14 (37)	9 (26)
Gender, n (%)			
Male	43 (59)	26 (68)	17 (49)
Female	30 (41)	12 (32)	18 (51)

Disease Characteristics and Prior Treatment

	Overall (N = 73)	Tosedostat 120 mg (n = 38)	Tosedostat 240 mg→120 mg (n = 35)
Median days since AML diagnosis	211	226	154
AML type, n (%)			
AML NOC	37 (51)	21 (55)	16 (46)
Multi-lineage dysplasia	27 (37)	15 (39)	12 (34)
With prior MDS	18 (25)	9 (24)	9 (26)
Without prior MDS	9 (12)	6 (16)	3 (9)
Therapy-related	7 (10)	2 (5)	5 (14)
Recurrent genetic abnormalities	2 (3)	0	2 (6)
Prior AML therapy, n (%)			
Ara-C + anthracycline	26 (36)	13 (34)	13 (37)
Other Ara-C regimens	18 (25)	8 (21)	10 (30)
Hypomethylating agents	23 (33)	15 (39)	8 (24)
Other regimens	3 (4)	2 (5)	1 (3)
Remission experience, n (%)			
Refractory (no CR)	38 (52)	18 (47)	20 (57)
CR <6 months	15 (21)	7 (18)	8 (23)
CR 6-12 months	20 (27)	13 (34)	7 (20)
Mean duration, days	83	99	66

Patient Disposition

	Overall (N = 73)	Tosedostat 120 mg (n = 38)	Tosedostat 240 mg→120 mg (n = 35)
Completed treatment to week 12, n (%)	27 (37)	13 (34)	14 (40)
Not evaluable	23 (31)	10 (26)	13 (37)
Reason for withdrawal, n (%)			
Adverse event	2 (3)	1 (3)	1 (3)
Serious adverse event	8 (11)	6 (16)	2 (6)
Progressive disease (PD)	25 (34)	15 (39)	10 (29)
Consent withdrawal	4 (5)	0	4 (11)
Death	6 (8)	2 (5)	4 (11)
Other	1 (1)	1 (3)	0

Efficacy

- **The interim bone marrow response rate (ORR) was 21% and was similar between treatment arms (21% in the 120 mg arm and 20% in the 240 mg arm).**
- **In patients who had a 30 day marrow assessment (n = 50) the ORR was 30%.**
- **Most responses occurred on or after the week 8 assessment.**
- **At the interim analysis, 9 of 15 responders had received primary therapy with hypomethylating agents.**

Best Bone Marrow Response

	Overall (N = 73)	Tosedostat 120 mg (n = 38)	Tosedostat 240 mg→120 mg (n = 35)
ORR, n (%)	15 (20.5)	8 (21.1)	7 (20.0)
CR	6 (8.2)	3 (7.9)	3 (8.6)
PR	9 (12.3)	5 (13.2)	4 (11.4)
SD	21 (28.8)	13 (34.2)	8 (22.9)
PD	14 (19.2)	7 (18.4)	7 (20.0)
Not evaluable*	23 (31.5)	10 (26.3)	13 (37.1)

*If no bone marrow sample was available

Adverse Events

	Overall (N = 73)	Tosedostat 120 mg (n = 38)	Tosedostat 240 mg→120 mg (n = 35)
Treatment-emergent adverse events			
Most common grade ≥3 TEAEs n (%)			
Febrile neutropenia	21 (28.8)	11 (28.9)	10 (28.6)
Thrombocytopenia	16 (21.9)	8 (21.1)	8 (22.9)
Fatigue	15 (20.5)	7 (18.4)	8 (22.9)
Dyspnea	11 (15.1)	4 (10.5)	7 (20.0)
Serious adverse events			
Patients with ≥1 SAE, n (%)	63 (86.3)	33 (86.8)	30 (85.7)
Most common SAEs, n (%)			
Febrile neutropenia	21 (28.8)	9 (23.7)	12 (34.3)
Disease progression	8 (11.0)	5 (13.2)	3 (8.6)
Pneumonia	6 (8.2)	1 (2.6)	5 (14.3)
Atrial fibrillation	6 (8.2)	1 (2.6)	5 (14.3)

CONCLUSIONS

- **Daily oral tosedostat is reasonably well tolerated and has anti-leukemic activity in elderly patients with relapsed and refractory AML.**
- **The bone marrow ORR in this interim analysis was 21%.**
- **Nine of 23 (39%) patients with prior hypomethylating agent therapy had a response supporting the preclinical observation of synergy between these agents.**
- **The true response rates may be higher than the interim evaluation due to the long time to response observed with tosedostat.**
- **The final analysis will be available when all patients have completed the 24 week evaluation.**
- **This will be further explored in trials of tosedostat in combination with hypomethylating agents.**

References: [1] Krige et al. Cancer Res 68:6669, 2008
[2] Jenkins et al. Leuk Res 35:677, 2011
[3] Lowenberg et al. J Clin Oncol 29:4333, 2010

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