

Amonafide + ara-C in Secondary Acute Myeloid Leukemia (sAML): Consistent Efficacy in Poor Risk Populations

Abst# 7027

David A Rizzieri¹, Harry P Erba², Margaret R O'Donnell³, Bayard L Powell⁴, John M Bennett⁵, Ante S Lundberg⁶, Alfred M Ajami⁶, and Robert L Capizzi⁶

¹Duke Univ, Durham, NC, ²Univ of Michigan, Ann Arbor, MI, ³City of Hope Natl Med Ctr, Duarte CA, ⁴Wake Forest Univ, Winston-Salem NC, ⁵Univ Rochester, Rochester NY, ⁶Xanthus Pharmaceuticals, Cambridge, MA

Study Details

Secondary AML Study

AMONAFIDE

- Novel mechanism of action
 - Intercalates into DNA; disrupts chromatin resulting in apoptosis
 - Not affected by Multi-Drug Resistance (MDR) transporters
 - Neither a substrate nor inhibitor of P-glycoprotein (Pgp)
 - Retained in leukemia cells that over-express Pgp and other drug efflux proteins
- Not cross-resistant with daunorubicin, idarubicin, mitoxantrone, or etoposide in leukemia cells with MDR phenotype
- Phase 1 clinical trials showed:
 - Hematological benefit and durable CRs
 - Acceptable safety profile when combined with 7 days of ara-C

ELIGIBILITY

- AML (non M3) per WHO criteria
- Either:
 - Antecedent MDS (confirmed by central pathology review) \geq 3 months, OR
 - Prior documented exposure to leukemogenic chemo or radiation therapy
- Age \geq 18 years; ECOG PS 0-2
- No prior AML induction therapy
- LVEF \geq 50%, adequate renal, hepatic function
- No recent cytotoxic therapy, no serious concomitant illness

RESPONSE

- Complete remission (CR):
 - Bone marrow blasts $<$ 5% on 200 cell differential; no Auer rods
 - ANC \geq 1000/ μ l
 - Platelets \geq 100,000/ μ l
- Complete remission with incomplete hematopoietic recovery (CRI):
 - Satisfying all criteria for CR except:
 - ANC $<$ 1000/ μ l and/or
 - Platelets $<$ 100,000/ μ l

Study Objectives

Primary

- Rate of complete remission with or without hematopoietic recovery (CR + CRI)

Secondary

- Median duration of CR + CRI
- Proportion of subjects in CR + CRI at 6, 12 and 18 months
- Median duration of overall survival (OS)
- Safety and acceptability of amonafide and cytarabine

Treatment Plan

Remission Induction:

- ara-C 200 mg/m²/d continuous IV infusion days 1-7
- Amonafide 600 mg/m²/d IV over 4 hours daily on days 1-5
- Reinduction with the same regimen if the day 14 marrow shows persistent leukemias
- Post-remission therapy for patients achieving CR or CRI
 - Transplant for eligible patients, according to standard practice of institution
 - Ineligible for transplant:
 - Age $<$ 60, ara-C 3 gm/m² over 3 hrs every 12hrs on days 1, 3, 5 for 3 courses
 - Age \geq 60, ara-C 1 gm/m² over 3 hrs daily on days 1, 3, 5 for 3 courses

Patient Characteristics

Demographics

Male Gender (%)	41 (47)
Median Age, years (range)	63 (23-87)
ECOG PS (%)	
0	21 (23.9)
1	51 (58.0)
2	14 (15.9)
3	2 (2.3)

Characteristics of sAML

Prior MDS Only	40 (45.5%)
Prior treatment for MDS	20
No prior treatment for MDS	19
Treatment unknown	1
Prior Leukemogenic Therapy with prior MDS	48 (54.5%)
Prior treatment for MDS	8
No prior	2
No prior	6
Exposure to Prior Leukemogenic Agents	48
Radiation therapy	20
Anti-cancer drug	46
Prior anti-cancer drugs per patient, median (range)	4 (1-29)
Prior treatment regimens per patient, median (range)	2 (1-6)

Cytogenetic Risk Group

Cytogenetic Risk Group*	n(%)
Favorable	11(11)
t(8;21)	1(1.1)
37 (42.0)	29 (40.0)
Diploid	3 (3.4)
+5	5 (5.7)
Other	4 (4.5)
Intermediate	37 (42.0)
-5 or -5q	7 (9.1)
-7 or -7q	9 (10.2)
11q23 abnormality	7 (8.0)
Complex**	19 (21.6)
Other***	2 (2.3)
Unfavorable	41 (46.6)
-5 or -5q	4 (4.5)
-7 or -7q	9 (10.2)
11q23 abnormality	7 (8.0)
Complex**	19 (21.6)
Other***	2 (2.3)
Unknown	9 (10.2)

*SWOG-ECOG Criteria (Slovak et al 2000) with karyotype of unknown prognostic significance included in the "intermediate" category
 **Includes 1 patient with -5/5q, 4 with -7/7q, and 7 with both -5/5q and -7/7q, and
 ***Abnormal 3q; abnormal 3q and abnormal 20q

Efficacy – Primary Endpoint

CR + CRI ¹	n=88
Reported by Site ²	45% (40/88)
Assessed per Protocol ³	42% (37/88)
CR	34
CRI	3*

- Complete remission with (CR) or without (CRI) complete hematopoietic recovery
- Investigator assessment of CR
- Protocol requirement of $<$ 5% blasts not met for:
 - 2 patients with exactly 5% blasts;
 - 1 patient transferred care to non-participating institution prior to day 37 bone marrow assessment; CR confirmed by investigator review and central pathology review of bone marrow.
- Incomplete hematopoietic recovery:
 - 3 patients with incomplete platelet recovery

Central Pathology Review

Criteria	Confirmed	Not Confirmed
Prior MDS	38	5 [†]
AML Diagnosis	86	2 [‡]
Complete Remission	35 [§]	4 [¶]

- Not confirmed: 3 patients with BM blasts $>$ 20% (2 with antecedent MDS per FAB criteria); 1 patient each with missing or poor quality sample
- Not confirmed: 1 patient each with BM blasts 18% and 14%
- Confirmed: Includes 2 CR patients per central review reported as blasts $>$ 5% per site; not included above is a third patient reported as CR per central pathology review who transferred care to non-participating institution prior to day 37 bone marrow assessment
- Not confirmed: 2 patients with blasts $>$ 5% and evidence of MDS; 1 patient with blasts $>$ 5% at remission and $<$ 5% after PRT, with evidence of MDS; and 1 patient with inadequate sample.

CR Maintained in Poor-Risk Subsets

Category	CR+CRI Rate
Age	
$<$ 60	39.4% (13/33)
\geq 60	43.6% (24/55)
Cytogenetics	
Favorable	100% (1/1)
Intermediate	62.1% (23/37)
Unfavorable	22.0% (9/41)
Unknown	44.4% (4/9)
Type of Secondary AML	
Prior leukemogenic therapy	40.0% (18/45)
Prior MDS only	44.2% (19/43)
Treatment for Prior MDS [†]	
Yes	36.0% (9/25)
No	43.5% (10/23)

[†]Includes patients with both prior MDS and IAML

Cytogenetic Complete Remissions

- Ten CR patients with abnormal baseline cytogenetics and informative post-treatment cytogenetics, 6 of whom achieved Cytogenetic CR

Cytogenetics	Pre-treatment	Post-treatment	Clinical Response
t(11;19) (q23;p13.1)	Normal	Normal	CR
t(11;19) (q23, p13.3)	Normal	Normal	CR
+4,+13,+14,+18,+20	Normal	Normal	CR
-7	Normal	Normal	CR
del(20) (q11.2, q13.3), +mar	Normal	Normal	CR
+11q	Normal	Normal	CR

Clinical Results - Safety

Time to Hematopoietic Recovery

- Median Time to platelets 20,000/ μ l and 100,000/ μ l of 17 and 35 days, respectively
- Median Time to ANC 500/ μ l and 1000/ μ l of 28 and 34 days, respectively

Deaths on Study

All deaths on study	51 (58%)
Early death ($<$ 14d)	6 (6.8%)
Complications from aplasia	9 (10.2%)
Resistant AML	16 (18.2%)
Relapsed AML	8 (9.1%)
Other	12 (13.6%)
Death \leq 28 days	18 (20.5%)
Early death ($<$ 14d)	6 (6.8%)
Complications from aplasia	5 (5.7%)
Resistant AML	3 (3.4%)
Other	4 (4.5%)

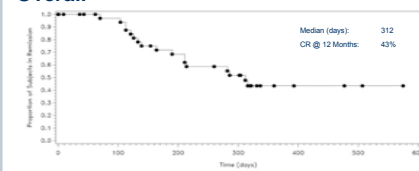
Grade 3, 4, 5 AEs

Preferred Term	Grade 3 n (%)		Grade 4 n (%)		Grade 5 n (%)	
Diarrrhea	All	Related	All	Related	All	Related
	6 (6.8)	6 (6.8)	0 (0)	0 (0)	0 (0)	0 (0)
Fatigue	7 (8.0)	4 (4.5)	1 (1.1)	1 (1.1)	0 (0)	0 (0)
Pyrexia	8 (9.1)	4 (4.5)	1 (1.1)	1 (1.1)	0 (0)	0 (0)
Bacteremia	12 (13.6)	6 (6.8)	0 (0)	0 (0)	1 (1.1)	1 (1.1)
Pneumonia	8 (9.1)	3 (3.4)	3 (3.4)	3 (3.4)	2 (2.3)	1 (1.1)
Resp. failure	2 (2.3)	1 (1.1)	3 (3.4)	2 (2.3)	3 (3.4)	2 (2.3)
Rash	6 (6.8)	6 (6.8)	0 (0)	0 (0)	0 (0)	0 (0)
Hypotension	9 (10.2)	3 (3.4)	2 (2.3)	2 (2.3)	3 (3.4)	2 (2.3)

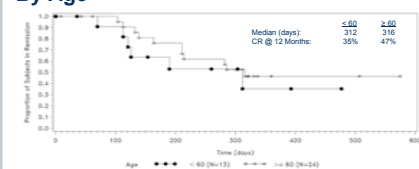
Clinical Results - Efficacy

Duration of Remission

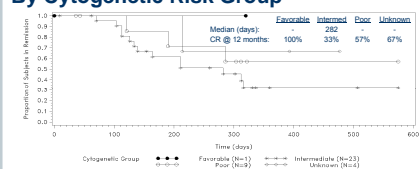
Overall



By Age

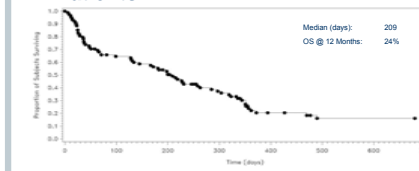


By Cytogenetic Risk Group

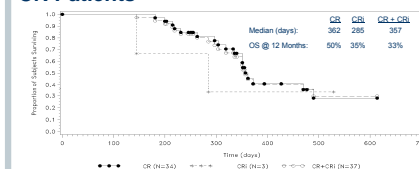


Overall Survival

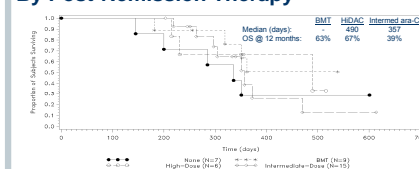
All Patients



CR Patients



By Post-Remission Therapy



CONCLUSIONS

- Novel DNA intercalating agent, not affected by Multi-drug resistance/Pgp and other efflux pump-mediated resistance mechanisms
- Clinical efficacy
 - CR rate overall (42%) maintained in poor risk subsets of
 - Age \geq 60 (43.6%),
 - Treatment-related AML (40%)
 - Prior treatment for MDS (36.0%)
 - Durable CR in overall and elderly populations, both median ($>$ 10 months) and rate at 1 yr (43% and 47%)
 - Similar in younger and older patients
 - Median $>$ 10 months
 - CR @ 12 months: 43% overall; 47% in older patients
- Safety predictable and manageable in this poor-risk population
- Randomized Phase 3 trial of amonafide + ara-C in sAML underway