SY-1425, a Potent and Selective RARα Agonist, in Combination with Azacitidine Demonstrates High Response Rates and a Rapid Onset of Clinical Responses in RARA-Positive Newly Diagnosed Unfit AML

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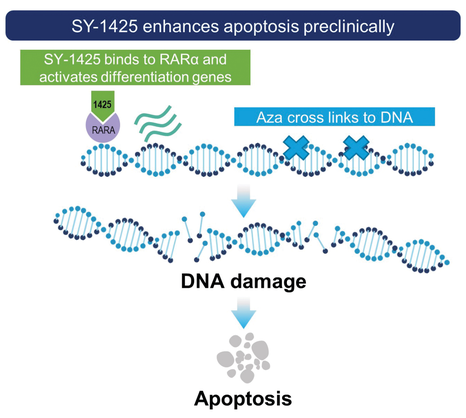
Introduction

- Despite the recent approval of new agents in AML, overall survival remains poor
- Newly diagnosed unfit patients need new treatment options that provide clinical benefit with good tolerability
- A subset of non-APL AML patients have RARA pathway activation detected by a novel blood-based biomarker test that predicts sensitivity to SY-1425 (tamibarotene), an oral selective RARα agonist
- Evidence of synergistic activity of SY-1425 with azacitidine in preclinical models supported clinical development of the combination[1]



- Early data of SY-1425 in combination with azacitidine in biomarker-positive newly diagnosed unfit AML patients showed evidence of clinical activity with a high response rate and a rapid onset of responses[2]
- Updated safety and response data of newly diagnosed unfit AML patients treated with SY-1425 plus azacitidine are presented here

Study Design

Study SY-1425-201 is a Phase 2, multi-center, open-label study currently exploring the activity of SY-1425 in combination with azacitidine in patients with newly diagnosed unfit AML (NCT02807558)

Key Entry Criteria: Treatment naïve non-APL AML unfit for intensive induction chemotherapy

Screen for RARA pathway activation in peripheral blood via clinical trial assay[a]

- Biomarker-Positive (N = 25)
- Biomarker-Negative (N = 25)

Objectives: Clinical activity, safety and tolerability

Regimen: Azacitidine 75 mg/m^2 IV or SC D1-7 followed by SY-1425 6 mg/m^2/day PO D8-28 of a 28-day cycle

Response Assessments: Bone marrow aspirates on D1 of C2, C3, C4 and every third cycle thereafter (Investigator assessment per revised IWG AML criteria)

Safety Assessments: AEs and clinical laboratory values collected at screening through 30 days after last dose of study drug.

End of Treatment: Patients treated until progressive disease or unacceptable toxicity.

a) Of 112 screened newly-diagnosed AML patients 30% were RARA positive (defined as RARA+/IRF8- or RARA+/IRF8+), and 6% were IRF8 positive (defined as RARA-/IRF8+).

Results

Patient Characteristics

Characteristic	Enrolled Population (N=40)
Median age years (range)	76 (64-91)
Male n (%)	25 (63)
Diagnosis n (%) De novo AML Secondary AML	 22 (55) 18 (45)
AML cytogenetic risk n (%) Intermediate Poor Missing	 28 (70) 11 (28) 1 (3)
Baseline bone marrow blasts n (%) ≤ 30% > 30%	 15 (38) 25 (63)

Patient Disposition

Characteristic	Enrolled Population
Safety evaluable, N[a]	40
Discontinued treatment, N (%) AE PD Lack of clinical benefit Withdrawal of consent Death Non-compliance Treatment failure Other	23 (58) 7 (18) 4 (10) 3 (8) 2 (5) 1 (3) 1 (3) 1 (3) 4 (10)

a) All patients who received at least one dose of study drug.

Responses by IWG: Biomarker-Positive Patients

Best IWG Response[3]	RARA/IRF8 Positive[a] n (%)	RARA Positive n (%)	IRF8 Positive n (%)
Response Evaluable, N[b]	17	13	4
ORR	9 (53)	8 (62)	1 (25)
CR/CRi[c]	8 (47)	8 (62)	0 (0)
CR	7 (41)	7 (54)	0 (0)
CRm	3 (18)	3 (23)	0 (0)
CRc	3 (18)	3 (23)	0 (0)
CRi	1 (6)	1 (8)	0 (0)
MLFS	1 (6)	0 (0)	1 (25)
PR	0 (0)	0 (0)	0 (0)

a) RARA positive defined as: RARA+/IRF8- (N=10) or RARA+/IRF8+ (N=3). IRF8 positive defined as RARA-/IRF8+ (N=4).
b) All patients who completed one cycle of treatment with at least one post-baseline response evaluation or discontinued earlier due to disease progression, and who have not had any major protocol violations
c) Two patients achieved CRh[4] before achieving a best response of CRi (N=1) and CR (N=1).

ORR = overall response rate; CR = complete response; CRm = molecular CR (MRD negative by flow cytometry or molecular techniques); CRc = cytogenetic CR; CRi = CR with incomplete hematologic recovery; CRh = CR with partial hematologic recovery; MLFS = morphologic leukemia-free state; PR = partial response

Most Common Adverse Events, Regardless of Causality (≥ 20%)

Preferred Term	All Grades N = 40 n (%)	≥ Grade 3 N = 40 n (%)
Patients with an AE	40 (100)	29 (73)
Hematologic		
Thrombocytopenia	11 (28)	10 (25)
Anemia	9 (23)	9 (23)
Febrile neutropenia	9 (23)	9 (23)
Non-Hematologic		
Nausea	15 (38)	0 (0)
Decreased appetite	15 (38)	3 (8)
Constipation	13 (33)	0 (0)
Fatigue	13 (33)	5 (13)
Edema peripheral	12 (30)	0 (0)
Diarrhea	11 (28)	1 (3)
Pyrexia	11 (28)	2 (5)
Hypertriglyceridemia	11 (28)	6 (15)
Dizziness	10 (25)	0 (0)
Arthralgia	9 (23)	1 (3)
Dyspnea	9 (23)	2 (5)
Dry skin	9 (23)	0 (0)
Rash[a]	9 (23)	1 (3)
Pruritus	8 (20)	0 (0)

a) Includes preferred terms rash, rash maculo-papular, rash pruritic, drug eruption and rash erythematous.

Treatment Emergent Hematologic Laboratory Abnormalities

Laboratory Abnormality	All Grades N=40 n (%)	≥ Grade 3 N = 40 n (%)
Thrombocytopenia	27 (68)	23 (58)
Leukopenia	25 (63)	21 (53)
Anemia	19 (48)	14 (35)
Neutropenia	17 (43)	14 (35)

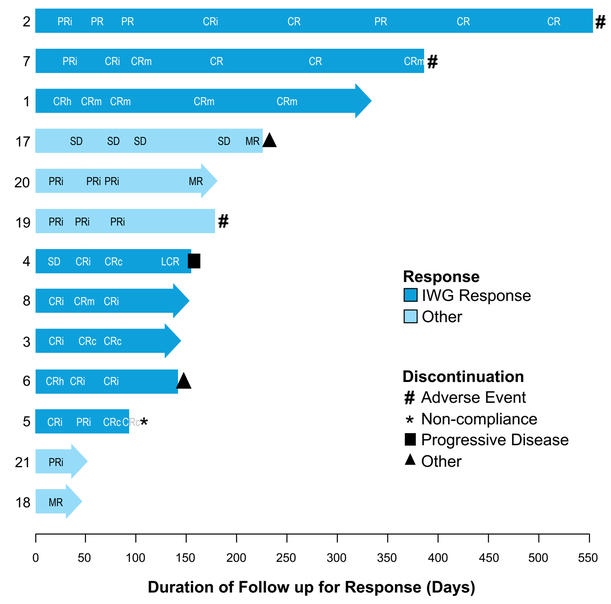
Safety Summary

- AE profile of the combination is consistent with what has been previously reported for single-agent SY-1425 or azacitidine in AML, with no evidence for increased toxicities for the combination
- Rates of myelosuppression comparable to reports of single agent azacitidine in this AML population
- The majority of non-hematologic AEs are low grade
- SAEs were reported for 23 patients; the most frequent (occurring in ≥ 3 pts) included febrile neutropenia (7 pts), pyrexia (4 pts), pneumonia (4 pts) and lung infection (3 pts)
- 7 patients discontinued due to AEs; none were reported in >1 patient

IRF8 Does Not Enrich for Response to SY-1425 Plus Azacitidine

- Prospectively defined protocol analysis to evaluate contribution of each biomarker for patient selection demonstrates:
  - 62% CR/CRi in RARA-positive vs. 0% in IRF8-positive
- Data support using only RARA-positive biomarker status for patient selection
- An analysis of response by RARA-positive vs. RARA-negative follows

RARA-Positive Patients – Time to Response and Duration of Response



Swim lane numbers correspond to patient number in the Biomarker, Mutation, Cytogenetic Risk figure below

CR = complete response; CRm = molecular CR (MRD negative by flow cytometry or molecular techniques); CRc = cytogenetic CR; CRi = CR with incomplete hematologic recovery; CRh = CR with partial hematologic recovery; MLFS = morphologic leukemia-free state; PR = partial response; PRi = PR with incomplete blood count recovery; MR = minor response; SD = stable disease; LCR = loss of CR

Higher CR/CRi Rate in RARA-Positive vs. RARA-Negative, Including Rapid Onset and MRD Negative Responses

- Median time to CR/CRi/CRh: RARA-positive 34 days vs RARA-negative 60 days
- Duration data are not mature, however:
  - Duration of CR/CRi/CRh up to 344 days in RARA-positive vs. 168 days in RARA-negative
  - Time on treatment up to 554 days in RARA-positive vs. 354 days in RARA-negative

Best IWG[3] Response	RARA Positive n (%)	RARA Negative n (%)
Response Evaluable, N[a]	13	22
ORR	8 (62)	8 (36)
CR/CRi[b]	8 (62)	6 (27)
CR	7 (54)	3 (14)
CRm	3 (23)	0 (0)
CRc	3 (23)	3 (14)
CRi	1 (8)	3 (14)
MLFS	0 (0)	1 (5)
PR	0 (0)	1 (5)

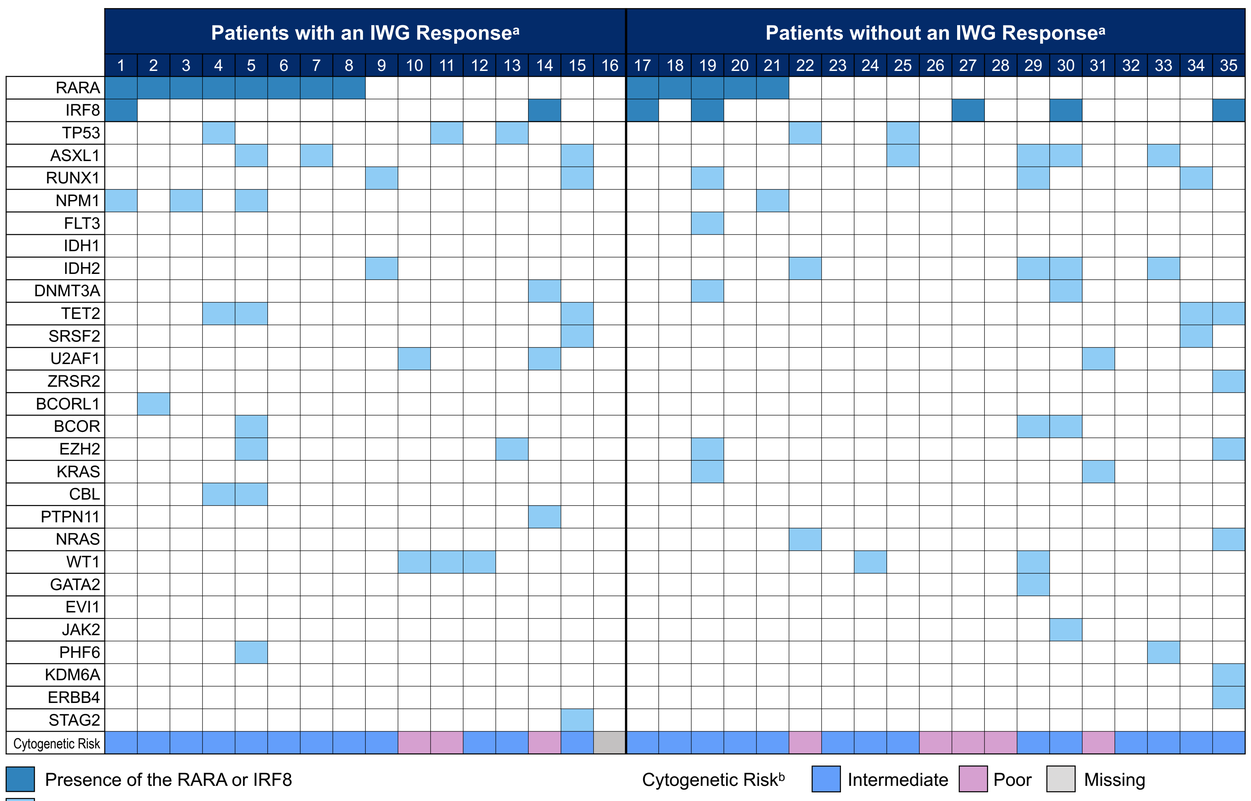
a) All patients who completed one cycle of treatment with at least one post-baseline response evaluation or discontinued earlier due to disease progression, and who have not had any major protocol violations
b) Two patients achieved CRh[4] before achieving a best response of CRi (N=1) and CR (N=1). .

ORR = overall response rate; CR = complete response; CRm = molecular CR (MRD negative by flow cytometry or molecular techniques); CRc = cytogenetic CR; CRi = CR with incomplete hematologic recovery; CRh = CR with partial hematologic recovery; MLFS = morphologic leukemia-free state; PR = partial response

Distribution of baseline characteristics RARA-positive vs. RARA-negative:

- Median age, years (range): 76 (64-91) vs. 76 (66-86);
- Male, n (%): 9 (60%) vs. 16 (64%);
- Secondary AML, n (%): 5 (33%) vs. 13 (52%);
- Baseline marrow blasts >30%, n (%): 9 (60%) vs.16 (64%).

Biomarker, Mutation, and Cytogenetic Risk Status Shows Activity in RARA-Positive Patients Across Risk Groups



a) Data shown for the 35 response evaluable patients
b) Cytogenetic risk per 2018 NCCN Guidelines

A High Proportion of RARA-Positive Patients Achieve or Maintain Transfusion Independence

Baseline Transfusion Status	N*	Transfusion Independent Post-Baseline
Dependent	7	6 (86%)
Independent	4	3 (75%)

- 9 out of 11 (82%) patients achieve or maintain transfusion independence
  - 6/7 (86%) dependent on transfusions at baseline achieve transfusion independence
  - 3/4 (75%) independent of transfusions at baseline remain transfusion independent
  - 8/8 (100%) of patients who achieve a best response of CR/CRi achieve or maintain transfusion independence

* 2 response evaluable patients on treatment <56 days not evaluable for transfusion independence. Transfusion independence defined as not requiring RBC or platelet transfusions during any 56-day post baseline period.

Conclusions

- SY-1425 in combination with azacitidine showed high response rates and rapid onset of action in RARA-positive patients with a 62% CR/CRi rate and 54% CR rate
  - Most initial responses occurred at first response assessment
  - Responses were observed across risk groups
  - Treatment duration was up to 554 days and duration of response up to 344 days
  - Transfusion independence achieved or maintained by 82% of RARA-positive patients
- CR/CRi rate was 0% in IRF8-positive patients, supporting RARA as the optimal biomarker for patient selection
  - Approximately 30% of all AML patients are RARA-positive
- The combination was generally well tolerated with no increase in toxicities beyond what is seen with either SY-1425 or azacitidine alone
  - Rates of myelosuppression, including neutropenia, were consistent with single-agent azacitidine
  - Most non-hematologic AEs were low grade
- Response rates in RARA-negative patients were comparable to the published response rates of 18-29% in newly diagnosed unfit AML patients treated with single-agent azacitidine[5-7]
- SY-1425 plus azacitidine shows promise as a novel combination for the treatment of patients with newly diagnosed unfit RARA-positive AML and warrants further evaluation, including the ongoing Phase 2 investigation in relapsed/refractory AML patients

References: 1) McKeown, *Haematologica*, 2018. **2)**Cook, *ASH*, 2018. **3)**Cheson, *JCO* 2003. **4)**Bloomfield, *Blood Rev*, 2018. **5)**Fenaux et al, *JCO* 2010. **6)**Dombret et al, *Blood* 2015. **7)**Vidaza® (azacitidine) Prescribing Information, Celgene Revision 09/2018.

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