Early Results from a Biomarker-Directed Phase 2 Trial of SY-1425 in Combination with Azacitidine or Daratumumab in Non-APL Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS)

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Introduction

- SY-1425 (tamibarotene) is an oral, potent and selective RARα agonist
- In AML preclinical models, RARA pathway activation (increased RARA and/or IRF8 expression) was associated with activity of SY-1425 *in vitro* and *in vivo,* including induction of differentiation, inhibition of proliferation, and anti-tumor activity[1]
- In patients with R/R AML and higher-risk MDS who were biomarker-positive for RARA pathway activation, single-agent SY-1425 was generally well tolerated and demonstrated evidence of biological and clinical activity; 43% showed evidence of hematologic improvement and/or marrow blast reductions; myeloid differentiation was observed including CD38 upregulation[2]

Rationale for Combination with Azacitidine

- SY-1425 was evaluated in combination with a hypomethylating agent, azacitidine, in RARA-high and RARA-low cell lines. Evidence of DNA damage and apoptosis was observed in RARA-high cell lines, but not RARA-low cell lines, and to a far greater extent with the combination than either agent alone. The combination also induced deeper and more durable *in vivo* responses than either agent by itself in a preclinical PDX model[3]

Rationale for Combination with Daratumumab

- SY-1425 activates genes associated with myeloid differentiation in models of RARA pathway activated AML, and is associated with upregulation of CD38 expression preclinically and in patients
- Cancer cells that express CD38 can be selectively targeted for elimination by the immune system using a therapeutic CD38-targeted antibody such as daratumumab
- In *in vitro* co-culture systems evaluating a RARA-high AML cell line model, the combination of SY-1425 with daratumumab induces immune-mediated cell death

Study Design

- Study SY-1425-201 is a Phase 2, multi-center, open-label study exploring the activity of SY-1425 in patients with newly diagnosed unfit AML, or R/R AML or higher-risk MDS (NCT02807558)
- Herein we report on the results from patients who received SY-1425 in combination with either azacitidine (n = 19) or daratumumab (n = 9) as of 29 October 2018

Screen for RARA pathway activation in peripheral blood via clinical trial assay
36% of patients screened were biomarker-positive, consistent with previously reported data[4]

Biomarker-Positive (N = 25)	Biomarker-Negative (N = 25)	Biomarker-Positive (N = 12)
SY-1425 + Azacitidine Newly Diagnosed Unfit AML	SY-1425 + Azacitidine Newly Diagnosed Unfit AML	SY-1425 + Daratumumab R/R AML and Higher-Risk MDS

Objectives
Clinical activity, safety and tolerability

Key Entry Criteria
Treatment-naïve non-APL AML
Unfit for standard intensive chemotherapy

Azacitidine 75 mg/m^2 IV or SC on D1-7 followed by SY-1425 6 mg/m^2/day PO divided into two doses on D8-D28 of each 28-day cycle

Objectives
Clinical activity, safety, tolerability, and characterization of CD38 induction

Key Entry Criteria
R/R non-APL AML or R/R HR MDS
No prior exposure to anti-CD38 therapy

SY-1425 6 mg/m^2/day PO divided into two doses as single-agent for a 7-day lead-in from D-7 to D-1, followed by combination treatment with daratumumab starting C1D1 with continuous SY-1425 daily dosing. Daratumumab 16 mg/kg IV weekly for 8 doses, then every 2 weeks for 8 doses, then every 4 weeks thereafter (per label)

Assessments
Response: Bone marrow aspirates on D1 of C2, C3, C4, and every 3rd cycle thereafter (Investigator assessment per revised IWG AML criteria[5] and MDS criteria[6])
CD38 Expression: Central immunophenotyping of peripheral blood blasts at D-7, D-4, C1 (D1, D8, D15) and then D1 of every cycle thereafter in patients treated with SY-1425 + daratumumab
Safety: AEs and clinical laboratory values collected from screening through 30 days after last dose of study drug
End of Treatment: Patients treated until progressive disease or unacceptable toxicity

Author disclosures are available on the ASH program website: https://ash.confex.com/ash/2018/webprogram/Paper117903.html

Results: Newly Diagnosed Unfit AML (SY-1425 + Azacitidine)

Patient Characteristics

Characteristic	Biomarker-Positive[a] N = 11	Biomarker-Negative N = 8
Median age, years (range)	76 (64-85)	78 (66-86)
Male, n (%)	9 (79)	6 (75)
Diagnosis, n (%)		
De novo AML	7 (64)	4 (50)
Secondary AML[b]	4 (36)	4 (50)
AML cytogenetic risk status, n (%)[c]		
Favorable	2 (18)	0
Intermediate	3 (27)	1 (13)
Poor	6 (55)	5 (63)
Missing	0	2 (25)
Baseline bone marrow blasts, n (%)		
≤ 30%	4 (36)	4 (50)
31-50%	4 (36)	1 (13)
> 50%	3 (27)	3 (38)

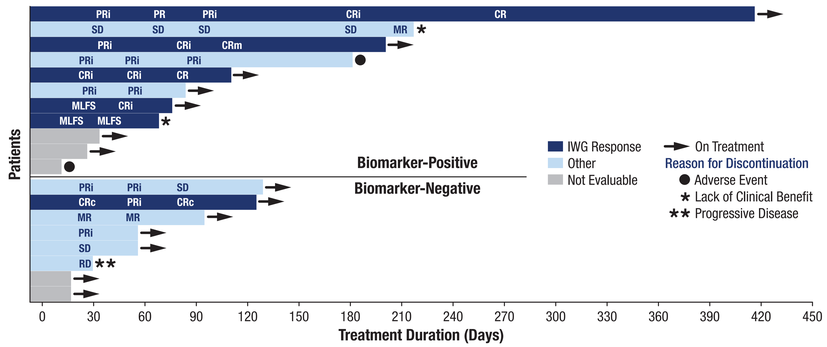
[a] Includes 9 RARA-positive patients and 2 IRF8-positive patients
[b] AML evolved from antecedent hematologic malignancy
[c] European Leukemia Net (ELN) AML recommendations[7]

Patient Disposition

Characteristic	Biomarker-Positive N = 11	Biomarker-Negative N = 8
Enrolled, n	11	8
Safety Evaluable, n[a]	10	7
Response Evaluable, n[b]	8	6
Discontinued Treatment, n	4	1
AE	2	0
Lack of Clinical Benefit	2	0
PD	0	1

[a] All patients who have received at least 1 dose of SY-1425
[b] All patients who completed 1 cycle of treatment with at least 1 post-baseline response evaluation or discontinued earlier due to disease progression, and who have not had any major protocol violations

Duration of Treatment and Responses



Biomarker-Positive Patients

- 8/8 evaluable biomarker-positive patients had a response, including 5 patients with an IWG response
- 7/8 of the responses were first reported at C2D1, including 3/5 IWG responses
- Duration of IWG responses ranged from 29 to 337 days
- 7/11 patients remain on treatment, including 4/5 with IWG responses, 1 with a PRi, and 2 who are not yet response-evaluable
- 1 patient with AML (swim lane 2) developed from prior CMML with 2 distinct blast populations by immunophenotyping had SD (AML blasts unchanged), but achieved a CR of CMML marrow blasts by flow at C3D1. The patient was taken off study due to lack of clinical benefit but was confirmed to have a minor response at that time.

Biomarker-Negative Patients

- 4/6 evaluable biomarker-negative patients had a response, including 1 patient with an IWG response
- 7/8 patients remain on treatment, including the patient with an IWG response, 3 with other responses including 2 PRi and 1 MR, 1 with SD, and 2 who are not yet response-evaluable

Responses per IWG

Best Response	Biomarker-Positive n (%)	Biomarker-Negative n (%)
Response Evaluable, N	8	6
ORR[a]	**5 (63)**	**1 (17)**
CR/CRi	4 (50)	1 (17)
CR	3 (37)	1 (17)
CRm	1 (13)	0
CRc	0	1 (17)
CRi	1 (13)	0
MLFS	1 (13)	0
PR	0	0
Other		
PRi	2 (25)[b]	2 (33)[c]
MR	1 (13)	1 (17)
SD	0	1 (17)
RD	0	1 (17)

[a] ORR includes CR + CRi + MLFS + PR per IWG[5]
[b] Biomarker-positive patients with PRi achieved reduction in marrow blasts from 42% and 80% at Baseline to 12% and 8%, respectively.
[c] Biomarker-negative patients with PRi achieved reduction in marrow blasts from 80% and 59% at Baseline to 18% and 13%, respectively.

ORR = overall response rate; CR = complete response; CRi = CR with incomplete hematologic recovery; CRm = molecular CR; CRc = cytogenetic CR; MLFS = morphologic leukemia-free state; PR = partial response; PRi = PR with incomplete blood count recovery; MR = minor response; SD = stable disease; RD = resistant disease

Most Common AEs, Regardless of Causality (≥ 3 Patients)

Preferred Term	All Grades N = 17 n (%)	Grade 3+ N = 17 n (%)
Patients with an AE	15 (88)	12 (70)
Hematologic		
Febrile neutropenia	4 (24)	4 (24)
Thrombocytopenia	4 (24)	4 (24)
Neutropenia	3 (18)	2 (12)
Non-Hematologic		
Decreased appetite	7 (41)	1 (6)
Fatigue	6 (35)	2 (12)
Hypertriglyceridemia	6 (35)	1 (6)
Edema peripheral	5 (29)	0
Diarrhea	4 (24)	1 (6)
Constipation	4 (24)	0
Pruritus	4 (24)	0
Nausea	3 (18)	0
Fall	3 (18)	0
Weight decreased	3 (18)	0
Dehydration	3 (18)	1 (6)

- AE profile of the combination was consistent with what has been previously reported for single-agent SY-1425 or azacitidine in AML
- 8 patients had an AE resulting in dose delay; none were reported in > 1 patient
- 9 patients had an SAE; febrile neutropenia (4 patients) and pneumonia and dehydration (2 patients each) were the only SAEs reported in ≥ 2 patients
- 2 patients discontinued treatment due to unrelated SAEs (gait apraxia and acute myocardial infarction)

Results: R/R AML and HR MDS (SY-1425 + Daratumumab)

Patient Characteristics

Characteristic	Biomarker-Positive[a] N = 9
Median age, years (range)	68 (35-79)
Male, n (%)	3 (33)
Diagnosis, n (%)	
R/R AML	8 (89)
Higher-Risk MDS	1 (11)
Prior Therapies, %	
1 / 2 / 3 / missing	34 / 22 / 22 / 22
AML cytogenetic risk status n (%)[b]	
Favorable	0
Intermediate	3 (33)
Poor	5 (56)

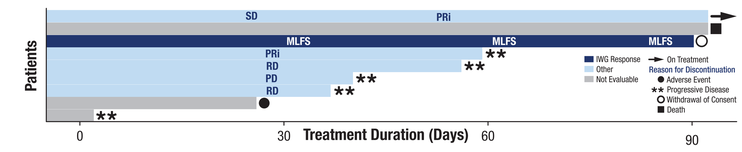
[a] Includes 7 RARA-positive patients and 2 IRF8-positive patients
[b] European Leukemia Net (ELN) AML recommendations[7]; 1 HR MDS patient had good cytogenetic risk per IPSS-R[8]

Patient Disposition

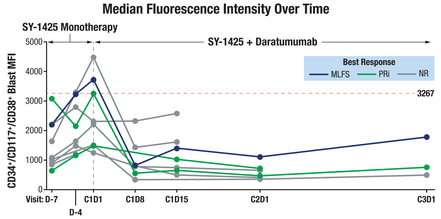
Characteristic	Biomarker-Positive N = 9
Enrolled, n	9
Safety Evaluable, n[a]	9
Response Evaluable, n[b]	6
Discontinued Treatment, n	8
AE	1
Death	1
Progressive Disease	5
Withdrawal of Consent	1

[a] All patients who have received at least 1 dose of SY-1425
[b] All patients who completed 1 cycle of treatment with at least 1 post-baseline response evaluation or discontinued earlier due to disease progression, and who have not had any major protocol violations

Duration of Treatment and Responses



Expression Level of CD38 in Myeloid Blast Population



Assay utilizes an orthogonal anti-CD38 antibody which is not affected by daratumumab. MLFS = morphologic leukemia-free state; PRi = partial response with incomplete blood count recovery; NR = non-responders

- 8/9 patients had a moderate increase in CD38 MFI in CD34$^+$/CD117$^+$ blasts after 7 days (median 1.57-fold induction)
- 2/9 patients induced CD38 MFI in blasts, exceeding the MM cell line (RPMI-8226) level of 3267
  - 1 patient with MLFS response
  - 1 patient progressed without responding
- CD38 levels declined after initial dose of daratumumab, consistent with the known effects on CD38 expression in relapsed MM

Treatment Summary

- MLFS in 1 patient with R/R AML who had 8% blasts in marrow and pancytopenia at study entry; marrow blasts reduced to 2% (C2D1) and maintained through C4D1 (59 days)
- 2 patients had a PRi, with 1 patient remaining on treatment

Responses per IWG

Best Response	All Patients n (%)
Response Evaluable, N	6
ORR[a]	**1 (17)**
MLFS	1 (17)
Other	
PRi	2 (33)[b]
RD/PD	3 (50)

[a] ORR includes CR + CRi + MLFS + PR per IWG[5,6]
[b] Patients with PRi achieved reduction in marrow blasts from 32% and 55% at Baseline to 15% and 6%, respectively.

ORR = overall response rate; MLFS = morphologic leukemia-free state; PRi = partial response with incomplete blood count recovery; RD = resistant disease; PD = progressive disease

Most Common AEs, Regardless of Causality (≥ 3 Patients)

Preferred Term	All Grades N = 9 n (%)	Grade 3+ N = 9 n (%)
Patients with an AE	9 (100)	9 (100)
Hematologic		
Febrile neutropenia	6 (67)	6 (67)
Anemia	4 (44)	4 (44)
Thrombocytopenia	3 (33)	3 (33)
Leukopenia	3 (33)	3 (33)
Non-Hematologic		
Nausea	4 (44)	0
Vomiting	4 (44)	0
Infusion-related reaction	4 (44)	0
Diarrhea	3 (33)	0
Hypertriglyceridemia	3 (33)	0
Hyponatremia	3 (33)	0
Cough	3 (33)	0

- AE profile of the combination was consistent with previously reported for single-agent SY-1425 in AML/MDS or single-agent daratumumab in MM populations
- 4 patients with an AE that led to dose delay; none were reported in > 1 patient
- 1 patient discontinued treatment due to an AE (non-related bronchopulmonary aspergillosis)
- 7 patients had an SAE; febrile neutropenia (5 patients) was the only SAE reported in ≥ 2 patients, and 1 SAE (sepsis) led to death

Conclusions

SY-1425, in combination with azacitidine, in biomarker-positive newly diagnosed unfit AML patients shows evidence of clinical activity with a high response rate and a rapid onset of responses

- ORR was 63% (5/8) and the CR/CRi rate was 50% (4/8) with the majority of initial responses at C2D1. This compares favorably to single-agent azacitidine in unfit AML patients, which shows a response rate of 18-29%[9-11] and with initial response generally occurring after 4 treatment cycles in the majority of patients with responses[12]
- In biomarker-negative patients the ORR was 17% (1/6), with 1 CR observed; while these data are less mature, they support the importance of the RARA pathway activation biomarker for patient selection
- SY-1425 + azacitidine was generally well tolerated with no evidence for increased toxicities of the combination
- The study continues to enroll and follow patients to further characterize the clinical activity

SY-1425 treatment in biomarker-positive patients with R/R AML and HR-MDS increased CD38 expression in blasts in the majority (8/9) of patients

- However, only 2 induced to the level of a myeloma cell line control. One of these 2 had an IWG response to SY-1425 + daratumumab
- The combination was generally well tolerated, and the study continues to enroll patients to complete the pilot

References: **1)** McKeown et al, *Cancer Discovery* 2017. **2)** Jurcic et al, ASH 2017. **3)** McKeown et al, *Hematologica* 2018. **4)** Vigil et al, ESH 2017. **5)** Cheson et al, *JCO* 2003. **6)** Cheson et al, *Blood* 2006. **7)** Döhner et al, *Blood* 2017. **8)** Greenberg et al, *Blood* 2012. **9)** Fenaux et al, *JCO* 2010. **10)** Dombret et al, *Blood* 2015. **11)** Vidaza® (azacitidine) Prescribing Information, Celgene Revision 09/2018. **12)** Thepot et al, *AJH* 2014.

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