Early Results from a Biomarker-Directed Phase 2 Trial of SY-1425 in Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS) Demonstrate DHRS3 Induction and Myeloid Differentiation Following SY-1425 Treatment

Abstract 2633

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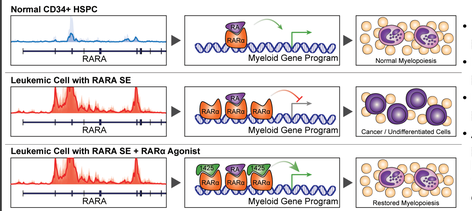
Introduction

- AML and MDS are related hematological disorders associated with impaired differentiation of myeloid progenitor cells; overall survival is poor, and new agents are still needed.
- Super-enhancers (SE), highly active chromatin regions that define cell identity and differentiation state, in patient tumor tissues were used to identify new non-APL AML and MDS patient subsets characterized by RARA pathway activation (McKeown et al, Cancer Discovery, 2017).

Model for SY-1425 activity in RARA pathway activated AML & MDS

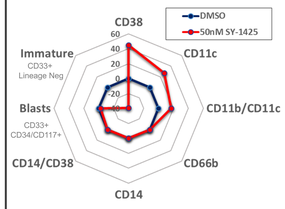


- Binds excess unliganded RARα and promotes RARα target gene expression.
- Enables IRF8-DNA interactions and potentiation of IRF circuits in RARA pathway.
- Promotes terminal differentiation of RARA pathway addicted leukemic cells.
- AML preclinical models indicate that RARA pathway activation (increased RARA and/or IRF8), predict biological response to SY-1425 (tamibarotene), including induction of differentiation and inhibition of proliferation.

- A biomarker test was developed to select non-APL AML & MDS patients for enrollment in a phase 2 study of SY-1425, an oral, potent, and selective RARA agonist previously approved for Relapsed/Refractory APL (R/R APL) in Japan.
- The biomarker test uses qPCR to measure RARA and IRF8 mRNA levels in CD34/CD117 positive PBMCs from patients and demonstrated a positive result in 40% of patients with AML and MDS (Vigil at el ESH 2017).
- SY-1425 PK analyses on day 1 and at steady state showed SY-1425 plasma concentrations that are similar to those in prior Japanese trials (Tobita et al., Blood 1997 90:967-973; Amnolake® label; Syros data on file; and Bixby et al., ESMO 2017).
- AML and MDS patients treated with SY-1425 demonstrated RARα target engagement as measured by DHRS3 (a RARA target gene involved in retinoic acid metabolism) upregulation that persisted in most patients. (Bixby et al., ESMO 2017).
- SY-1425-201 study (NCT02807558) is ongoing and the data presented in this poster is preliminary. All tables shown are derived from an October 30, 2017 data snapshot of monotherapy cohort 1 (R/R AML and HR MDS) and cohort 3 (LR MDS).

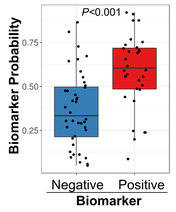
Ex vivo differentiation supports biomarker cutoff

Percent Composition Change



Analysis of patient blood after 72 hours of treatment *ex vivo*. Percent increase and decrease of myeloid cell surface markers relative to control was determined by FACS and demonstrates loss of immature markers and gain of maturation markers in the SY-1425 treated sample.

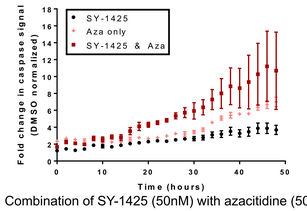
Machine learning using random forest analysis



- Samples from 72 biomarker positive and negative patients were collected at screening in the SY-1425-201 clinical trial. Patients samples were analyzed for differentiation response to SY-1425 *ex vivo*
  - Differentiation across myeloid lineages was observed with concomitant decreases in immature blasts
- Differentiation scores correlated with the biomarker cut-off, as established using preclinical models
  - Positive and negative biomarker samples significantly partition on the basis of flow cytometry changes using two independent methods

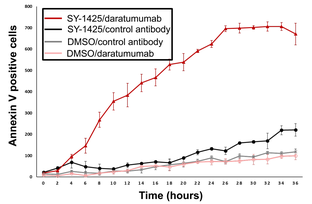
SY-1425 Combinations: two distinct approaches to induce apoptosis

SY-1425 in combination with Azacitidine



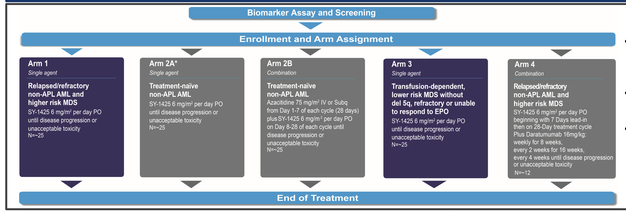
Combination of SY-1425 (50nM) with azacitidine (50nM) leads to DNA damage causing a 10-fold increase in apoptosis compared to DMSO control in OCI-AML3 cells

SY-1425 in combination with Daratumumab



Combination of SY-1425 (50nM) + daratumumab (3μg/mL) induces apoptosis consistent with an upregulation of CD38 on MV411 AML cells (Austgen et al, AACR 2017)

Trial Design



- 58 patients in arms 1 and 3 were enrolled in the study at time of data snapshot.
- 48 patients were response evaluable (Arm 1=23, Arm 3=25).
- Response evaluable is defined as completed at least 1 cycle of treatment and had a response assessment or withdrew prior to cycle 2 day 1 due to disease progression.

Patient Characteristics

Characteristic	R/R AML & HR MDS (N=29)	Lower-Risk MDS (N=29)
Median age (range), years	72 (34-89)	76 (59-93)
Sex, n (%)		
Female	12 (41%)	10 (35%)
Male	17 (59%)	19 (66%)
Diagnosis, n (%)		
R/R AML	21 (72%)	0 (0%)
R/R higher-risk MDS (HR-MDS)	8 (28%)	0 (0%)
Lower-risk MDS (LR-MDS)	0 (0%)	29 (100%)
Prior therapies		
1	16 (55%)	19 (66%)
2	8 (28%)	6 (21%)
3	3 (10%)	2 (7%)
4+	2 (7%)	1 (3%)
Missing	0 (0%)	1 (3%)
AML Cytogenetics, n (%)		
Favorable	3 (14%)	
Intermediate	7 (33%)	N/A
Poor	11 (52%)	
MDS Cytogenetics, n (%)		
Very Good	0	0
Good	2 (25%)	19 (66%)
Intermediate	2 (25%)	7 (24%)
Poor	2 (25%)	1 (3%)
Very Poor	2 (25%)	0
Unknown	0	2 (7%)

Biomarker Results

Biomarker status in 58 enrolled patients	Arm 1 N (%)	Arm 3 N (%)
RARA/IRF8 double positive	13 (45%)	10 (35%)
RARA Positive	10 (34%)	18 (62%)
IRF8 Positive	6 (21%)	1 (3%)
Total	29 (100%)	29 (100%)

Safety Data Overview

TEAEs – All Grades, All Causality[1]

Preferred Term	Any Grade	Grade 3/4
Hypertriglyceridemia	21 (36%)	9 (16%)
Fatigue	18 (31%)	1 (2%)
Dermatologic effects[2]	16 (28%)	2 (3%)
Diarrhea	14 (24%)	0 (0%)
Decreased appetite	12 (21%)	0 (0%)
Edema peripheral	12 (21%)	0 (0%)
Arthralgia	11 (19%)	1 (2%)
Pyrexia	11 (19%)	1 (2%)
Alopecia	10 (17%)	0 (0%)
Anemia	10 (17%)	5 (9%)
Blood alkaline phosphatase increased	9 (16%)	0 (0%)
Cough	9 (16%)	0 (0%)
Dyspnea	9 (16%)	0 (0%)
Nausea	9 (16%)	1 (2%)
Pain in extremity	9 (16%)	1 (2%)

[1]TEAEs occurring in ≥15% of patients regardless of causality. TEAEs were reported for all enrolled patients who received at least one dose of study drug.
[2]Includes preferred terms of rash, rash maculo-papular, pruritis, dermatitis allergic and rash pruritic.

Treatment emergent SAEs, All causality, in 2 or more patients N=58

Adverse Event	N (%)
Febrile neutropenia	6 (10%)
Fall	4 (7%)
Sepsis	4 (7%)
Pneumonia	3 (5%)
Pulmonary embolism	2 (3%)

- Treatment emergent SAEs were reported in 25 (43%).
- Differentiation syndrome was not seen.

Patient Disposition

Patient Disposition	R/R AML & HR MDS	Lower-Risk MDS
Enrolled	29	29
Response evaluable	23	25
Patients on treatment	2	15
Treatment discontinuation	27	14
- Adverse Event	5	4
- Death	2	2
- Lack of efficacy	3	3
- Non-compliance	1	1
- Other	1	0
- Progressive disease	10	0
- Subject withdrawal	5	4

Clinical Activity

Arm 1 & 3: Investigator Reported Hematologic Improvement (N=48)[1]	
R/R AML: (n=16)	4 (25%)
neutrophil	2 (12.5%)
platelet	2 (12.5%)
R/R HR MDS: (n=7)	3 (43%)
neutrophil & platelet	1 (14.3%)*
platelet	1 (14.3%)
erythroid	1 (14.3%)*
LR MDS: (n=25)	2 (8%)
neutrophil	1 (4%)*
platelet	1 (4%)*

- Hematologic Improvement was assessed using the IWG criteria (Cheson et al., Blood 2006).
- 4 patients had confirmed responses greater than 8 weeks*.
- 5 patients had responses with duration less than 8 weeks.

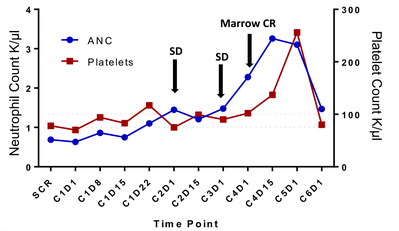
[1] Response evaluable

R/R AML & HR MDS IWG Response Assessment N=29 enrolled, N=23 evaluable

ORR (CR+CRi+PR)	1 (4%)
CR/CRi (includes marrow CR in HR MDS)	1 (4%)
PR	0 (0%)
Anti-leukemic activity that does not meet IWG criteria	
≥50% bone marrow blast reduction to a value of 5-25% with incomplete blood count recovery	3 (13%)
≥25% bone marrow blast reduction	1 (4%)
Stable bone marrow blasts within 25%	13 (57%)
Progressive Disease/Resistant Disease	5 (22%)

- Median treatment duration was 80 days (range, 8 – 238).
  - Arm 1 was 63 days (range, 8 – 238).
  - Arm 3 was 92 days (range, 41 – 232).
- No reports of transfusion independence in Arm 3

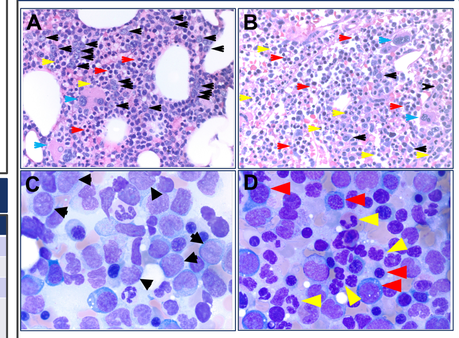
Hematological improvement over time in patient with bone marrow CR Patient A (Arm 1)



- 79 year old with R/R HR MDS (IPSS-R very high-risk) with del(5q) and del(12p) previously treated with azacitidine and lenalidomide
- Initial responses (platelet and ANC) observed on Cycle 1 Day 22, patient remains on treatment past 238 days.

Representative Examples of Biological Activity with Single Agent (Arm 1)

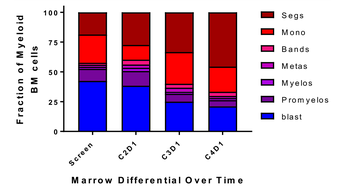
Myeloid Differentiation: Patient B



66 year old male with R/R AML (FAB M5), intermediate risk cytogenetics (normal) and IDH2 mutation. Myeloid differentiation with >25% marrow blast reduction noted at C3D1, continuing through C4D1 (see below).

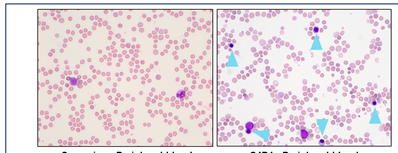
Bone marrow biopsies (H&E) at 40x from screening (A) and C3D1 (B). Bone marrow aspirate (WG stain) at 100x from screening (C) and C3D1 (D). (A) Blasts (black arrows) occur in many small groups. Maturing myeloid cells (yellow arrows), erythroid precursors (red arrows) and megakaryocytes (blue arrows) are also present. (B) Fewer blasts (black arrows) scattered singly with higher number of maturing myeloid cells (yellow arrows), erythroid precursors (red arrows) and megakaryocytes (blue arrows). (C) Black arrowheads = blasts, myeloid and monocytic. (D) Yellow arrowheads = granulocytes, Red arrowheads= erythroid precursors

Shift in marrow myeloid composition for Patient B



Myeloid differentiation was seen at the time of marrow response assessments, with myeloblast percentage of myeloid cells decreasing from 25% to 12% and segmented neutrophils increasing from 12% to 28% between screening and C4D1

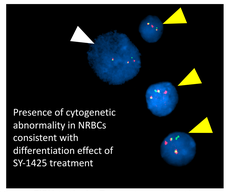
Erythroid Differentiation: Patient C



Screening - Peripheral blood | C4D1 - Peripheral blood

34 year old male, with primary refractory de novo AML and poor risk cytogenetics [t(3;3) and del(7)]. Significant increase in total number of peripheral blood nucleated RBCs (blue arrows above) starting in Cycle 3 of SY-1425 treatment (42.6% NRBCs, 0.92K/cu mm, total WBC of 2.16 K/cu mm).

FISH confirms t(3;3) cytogenetic abnormality in blasts (white arrow) and nucleated RBCs (yellow arrow) using the Abbott MECOM/RPN1 dual fusion probe set. MECOM probe (red), RPN1 probe (green), abnormal dual fusion (yellow).

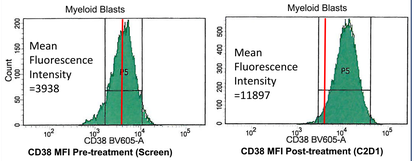


Data from Elie Traer, MD PhD (OHSU)

FISH analysis- Bone marrow aspirate

CD38 upregulation observed in 85% (11 of 13) of patients

Patient D



Red line represents "pre-treatment Mean Fluorescent Intensity" in both panels

- *CD38* gene, a direct target of RARα, is induced by SY-1425 treatment in patients
- Flow cytometry on patient bone marrows at screening and C2D1 was used to assess changes in CD38 expression in 13 patients with available paired samples from Arm 1

Conclusions

- Biomarker status was significantly correlated with differentiation of cells treated *ex vivo* with SY-1425, supporting the predictive value of the biomarker test for patient selection.
- Chronic daily dosing of SY-1425 was generally well tolerated with a median treatment duration of 80 days, and patients treated up to 8 months and remaining on study. The most common adverse events were consistent with the prior clinical experience with SY-1425 (tamibarotene) in APL and included hypertriglyceridemia, fatigue, and dermatologic effects.
- Clinical activity was observed in 10 (43%) R/R AML and R/R HR MDS patients and 2 (8%) LR MDS patients, including:
  - 9 with hematologic improvement
  - 5 with marrow blast reductions including 1 with marrow CR meeting IWG criteria
- Myeloid differentiation based upon morphologic evaluation of marrow, FISH analysis, and immunophenotyping was observed following single agent SY-1425 treatment, consistent with the underlying mechanism of action as a differentiating agent.
  - 85% (11/13) of patients with pre- and post-treatment immunophenotyping samples showed CD38 upregulation in bone marrow after 1 cycle of SY-1425, supporting the anti-CD38 combination cohort recently added to the Phase 2 trial.
- Clinical activity and evidence of differentiation in biomarker-selected AML and MDS patients, together with preclinical combination data and mechanistic rationale, support ongoing development of SY-1425 in combination with HMAs and with anti-CD38 therapy.

Copy of poster is available at Syros.com.