Initial Results from a Biomarker-Directed Phase 2 Trial of SY-1425, a Potent and Selective RARα Agonist, in Combination with Azacitidine in Relapsed/Refractory Acute Myeloid Leukemia

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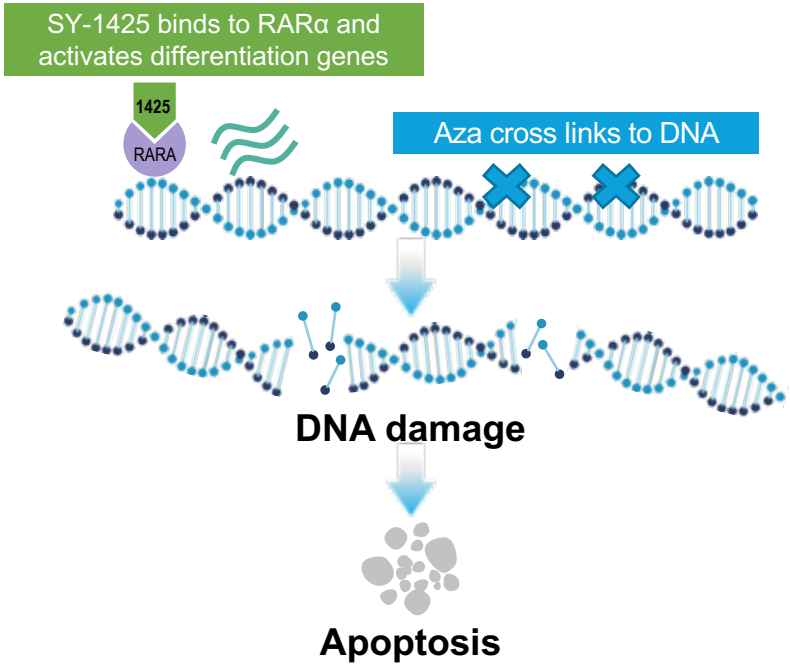
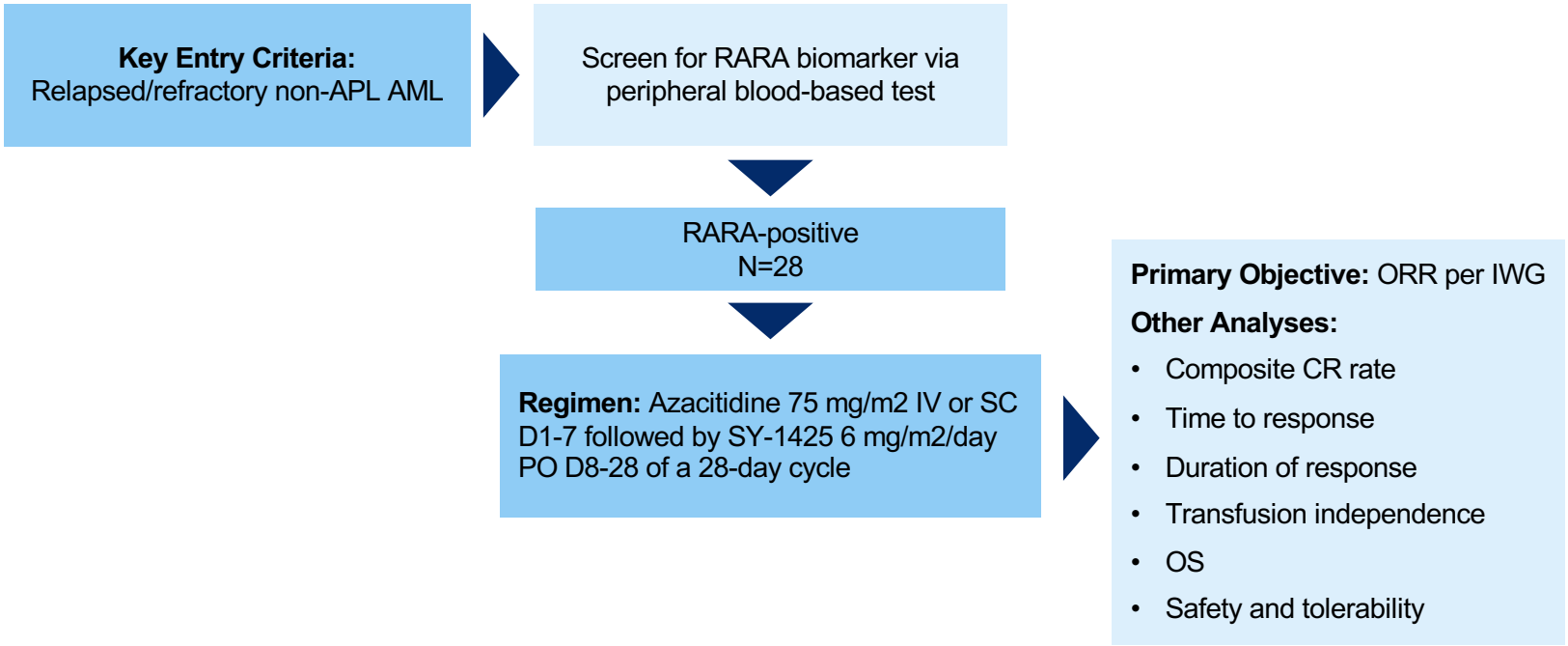
RARA-positive AML is a Novel Patient Subset with an Actionable Target for Treatment with SY-1425, an Oral, Selective RARα Agonist



- Subset of non-APL AML patients are characterized by overexpression of the *RARA* gene
  - Novel blood-based biomarker test identifies patients for treatment with SY-1425, with typical 2 to 3-day turnaround time[1,2]
  - Approximately 30% of AML patients are RARA-positive
- Preclinical synergy of SY-1425 with azacitidine (Aza) supported development of the combination in RARA-positive myeloid malignancies[3]
- Early data of SY-1425/Aza demonstrated a high CR rate and rapid onset of responses in RARA-positive newly diagnosed unfit AML[4,5]
- High unmet need for new effective therapies in R/R AML
  - Survival poor in R/R AML, particularly for those following treatment with venetoclax combinations[6]

[1]McKeown, Cancer Discovery 2017; [2]Vigil, ESH 2017; [3]McKeown, Haematologica 2018; [4]Cook, ASH 2018; [5]de Botton, ESH 2019; [6]Maiti, Haematologica 2020

Study SY-1425-201: A Phase 2, Multi-center, Open-label Trial



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Baseline Demographics and Patient Characteristics

Characteristic	Enrolled Population N=28
Median age, years (range)	74 (30-87)
Male, n (%)	13 (46)
Median prior therapies (range)	2 (1-9)
Type of prior therapy, n (%)	
HMA	18 (64)
Venetoclax combinations	9 (32)
HMA and venetoclax naïve	10 (36)
Intensive induction therapy	14 (50)
Stem cell transplant	6 (21)
AML cytogenetic risk, n (%)	
Favorable	3 (11)
Intermediate	8 (29)
Poor	6 (21)
Missing	11 (39)

Mutations reported for 2 patients at baseline: one with co-occurring ASXL1, RUNX1 and TET2, and one with WT1.
Sixteen patients had no mutations reported. Mutational analysis was not done for 10 patients.

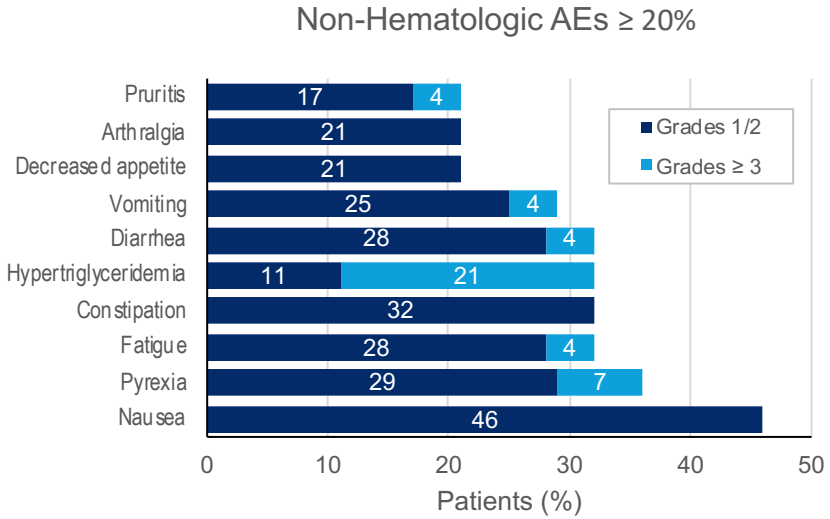
- Older, heavily pretreated patient population
- Exposure to a range of prior therapies, including HMA, venetoclax, cytotoxic chemotherapy and/or SCT

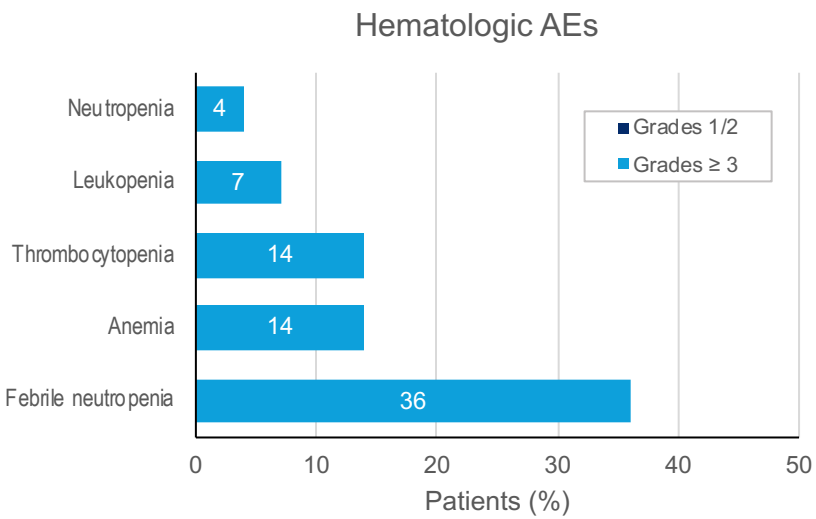
Patient Disposition

Characteristic	Enrolled Population N=28
Discontinued treatment, n (%)	23 (82)
PD	10 (36)
AE	4 (14)
Death	4 (14)
Treatment failure	2 (7)
Non-compliance	1 (4)
Other	2 (7)

Safety Summary

- Combination generally well tolerated with no increased toxicity relative to either single agent SY-1425 or Aza in AML
- Majority of non-hematologic AEs are low grade and reversible
- SAEs were reported for 19 patients; the most frequent (occurring in ≥ 3 pts) included febrile neutropenia (7 pts, with 1 assessed as related to study drug) and sepsis (3 pts, all assessed as not related)





Responses Observed in Heavily Pretreated R/R AML Patient Population

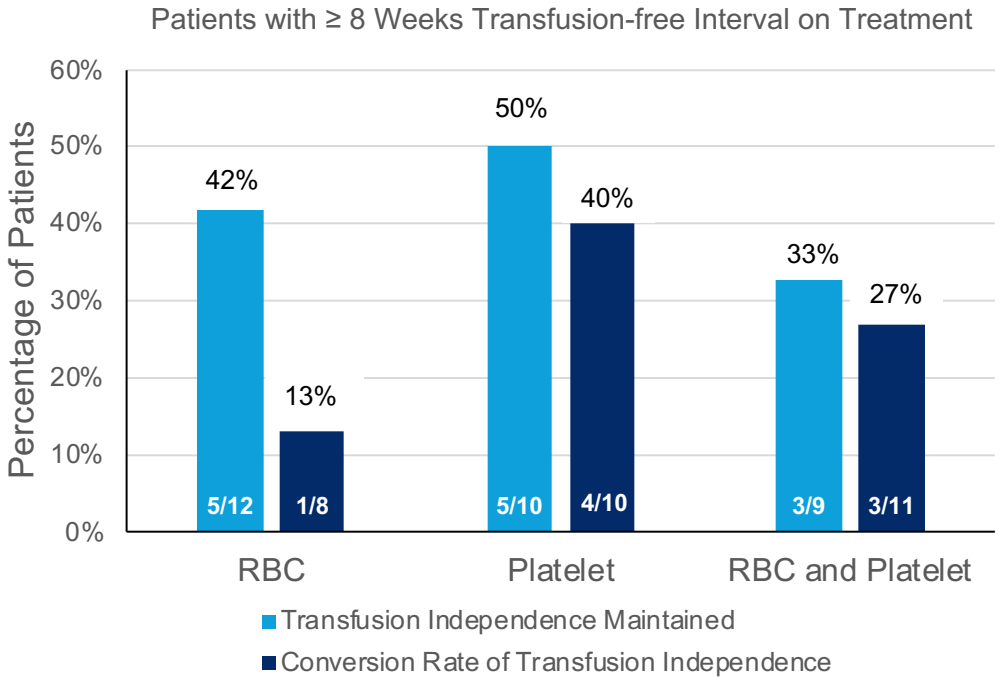
Best IWG Response[1]	Response Evaluable[a] Patients N=21 n (%)
ORR	4 (19)
CR	1 (5)
CRc	1 (5)
CRi	2 (10)
MLFS	1 (5)

[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

- Responses in 4/21 (19%) patients:
  - Median time to response 1.4 months (range 1.0-5.6)
  - 2 patients continue on treatment (1 CRc in month 9 and 1 MLFS in month 8)
  - 2 patients discontinued approximately 1 month after initial response (2 CRi)
- Responses observed in:
  - 3 of 7 (43%) response evaluable HMA and venetoclax naïve patients (1 each CRc, CRi and MLFS)
  - 1 of 8 (13%) response evaluable patients treated with HMA and venetoclax prior to study entry (CRi)

[1]Cheson, JCO 2003

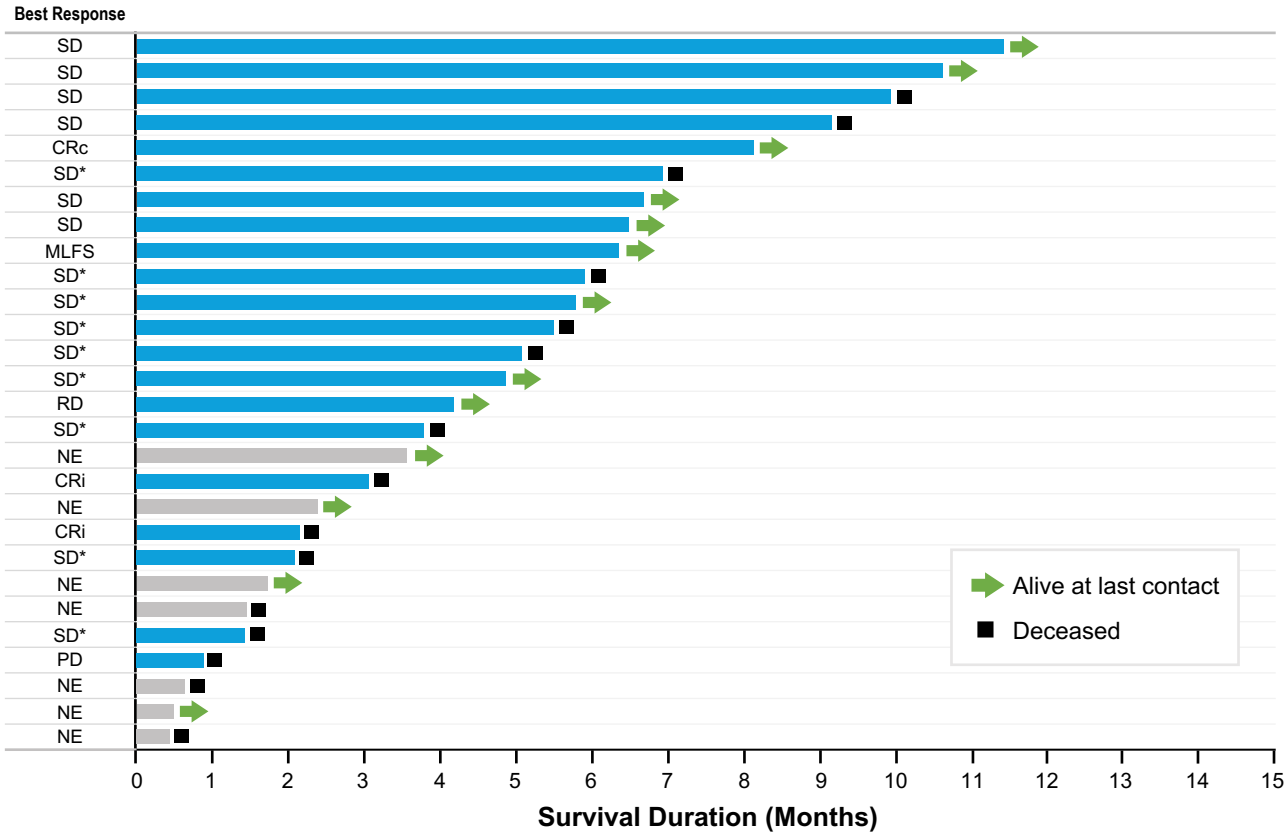
Transfusion Independence



- 30% (6/20) of patients were free of both RBC and platelet transfusions for a ≥ 8-week interval on treatment
- 27% (3/11) of patients dependent on transfusions at baseline converted to transfusion independence during treatment

Patients on treatment ≥56 days evaluable for transfusion independence.
Transfusion independence defined as not requiring RBC or platelet transfusions during any 56-day post baseline period.
Transfusion independence maintained is proportion of patients who were independent at baseline and maintained post-baseline independence.
Conversion rate of transfusion independence is the proportion of patients being post-baseline transfusion independent from baseline dependence.

Overall Survival in Heavily Pretreated R/R AML Population



Median overall survival
5.9 months
(95% CI: 3.1, 9.9)

CRc = Cytogenetic Complete Response
CRi = Complete Response with incomplete blood count recovery
MLFS = Morphologic Leukemia-Free State
NE = Not Evaluable
PD = Progressive Disease
RD = Resistant Disease
SD = Stable Disease

OS analysis includes all enrolled population. *Nine patients with SD achieved reductions in bone marrow blasts ≥ 25% not meeting criteria for IWG response

Conclusions

- Subset of non-APL AML patients are characterized by overexpression of the *RARA* gene
  - Novel blood-based biomarker test identifies patients for treatment with SY-1425, an oral, selective RARα agonist[1,2]
  - Approximately 30% of AML patients are RARA-positive
- SY-1425 in combination with azacitidine was a generally well-tolerated therapy for this R/R RARA-positive AML patient subset
- Clinical activity was observed in this heavily pretreated R/R AML population:
  - Responses in 4/21 (19%) patients overall and in 3/7 (43%) HMA and venetoclax naïve patients
  - Transfusion independence in 6/20 (30%) patients
  - Median OS of 5.9 months (95% CI: 3.1, 9.9)
- Clinical activity supports ongoing development of SY-1425 in RARA-positive myeloid malignancies

[1]McKeown, Cancer Discovery 2017; [2]Vigil, ESH 2017