SY-1425, a Potent and Selective RARα Agonist, in Combination with Azacitidine Demonstrates a High Complete Response Rate and a Rapid Onset of Response in RARA-positive Newly Diagnosed Unfit Acute Myeloid Leukemia

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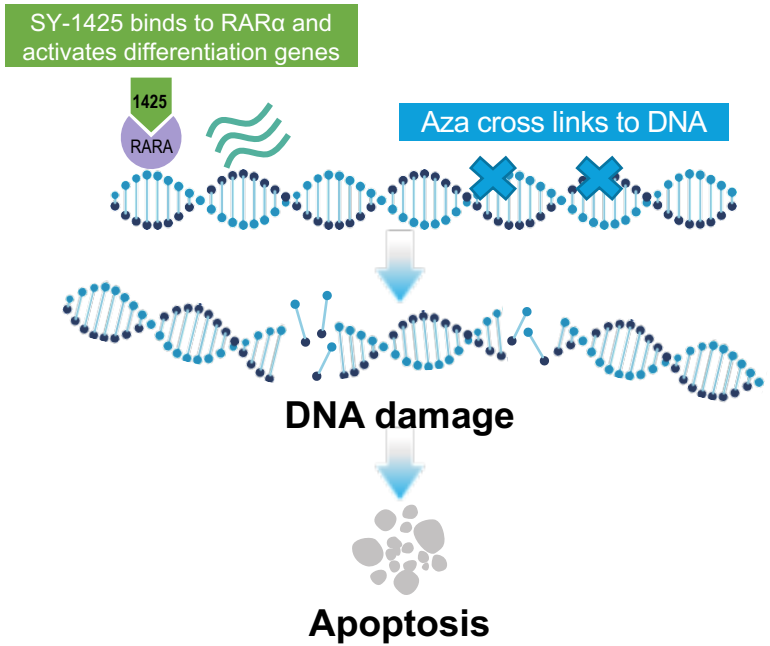
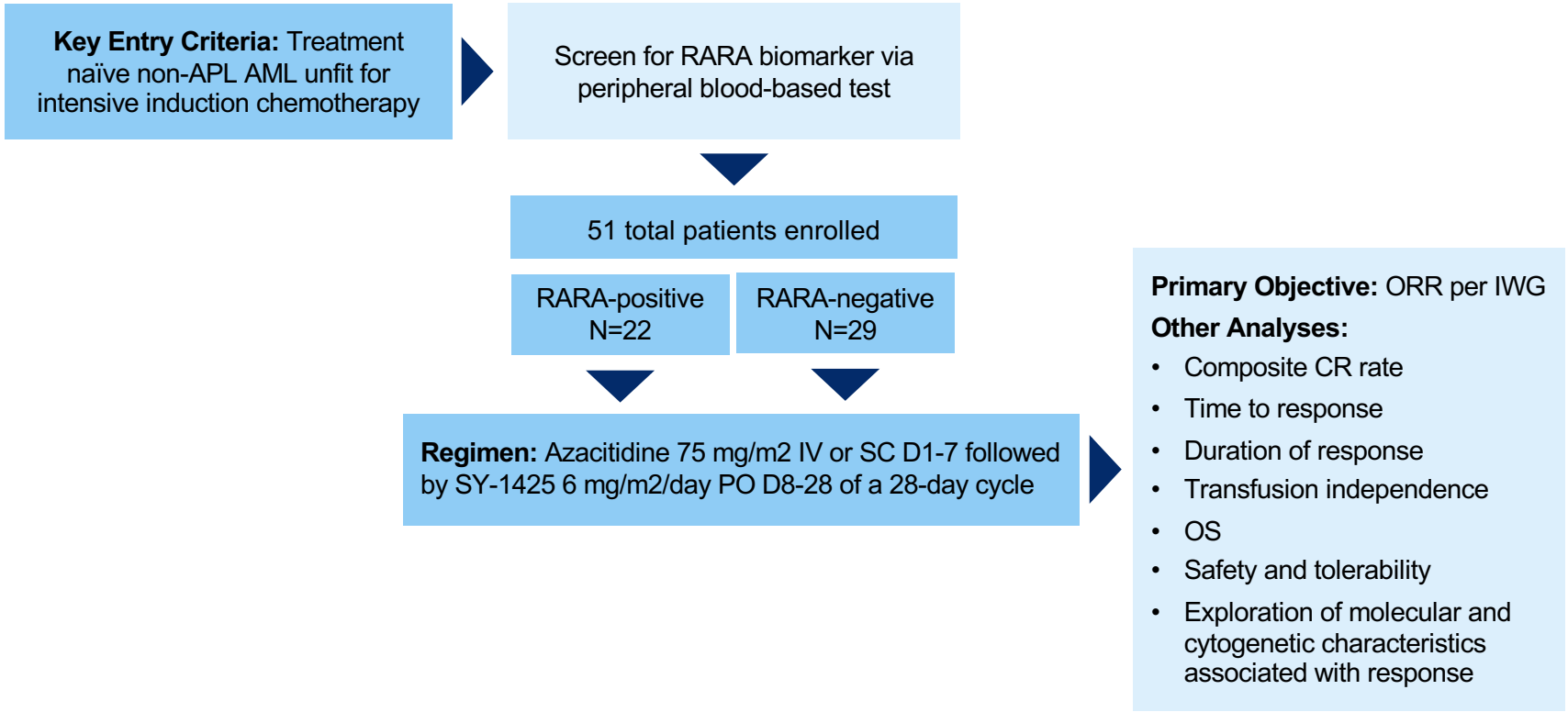
RARA-positive AML is a Novel Patient Subset with an Actionable Target for Treatment with SY-1425, an Oral, Selective RARα Agonist

- Subset of non-APL AML patients 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 high CR rate and rapid onset of responses in RARA-positive newly diagnosed (ND) unfit AML[4,5]
- Unmet need for new well-tolerated therapies remains, for example, one-third of ND unfit AML patients do not respond to upfront treatment with venetoclax/Aza, and a majority of responders eventually relapse[6]



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

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



NCT02807558

Baseline Demographics and Patient Characteristics

Characteristic	RARA-positive (N=22)	RARA-negative (N=29)
Median age, years (range)	77 (60-91)	76 (64-86)
Male, n (%)	13 (59)	19 (66)
Diagnosis, n (%) De novo AML Secondary AML Evolved from antecedent hematologic malignancy Associated with treatment from prior malignancy	 16 (73) 6 (27) 6 (27) 0 (0)	 13 (45) 16 (55) 13 (45) 3 (10)
AML cytogenetic risk, n (%) Intermediate Poor Not done	 16 (73) 6 (27) 0 (0)	 18 (62) 10 (34) 1 (3)
Baseline bone marrow blasts, n (%) ≤ 30% >30%	 7 (32) 15 (68)	 11 (38) 18 (62)

- Elderly patient population
- Large proportion with high blast counts and poor risk features

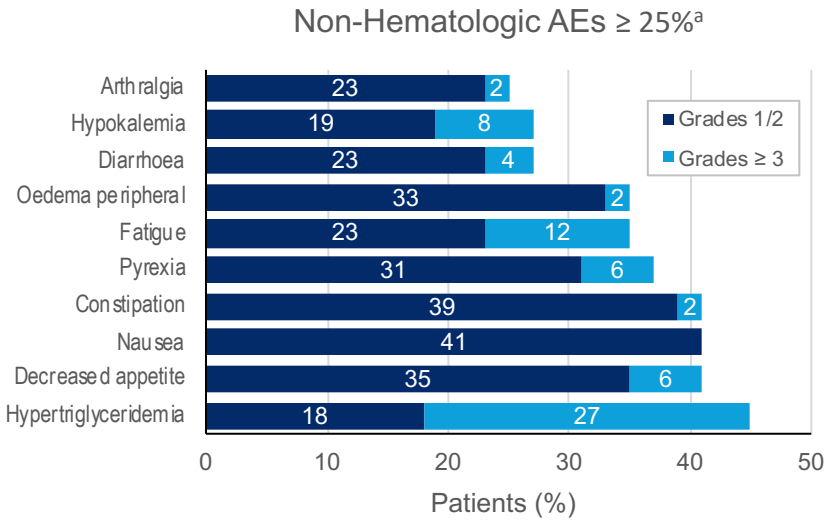
Patient Disposition

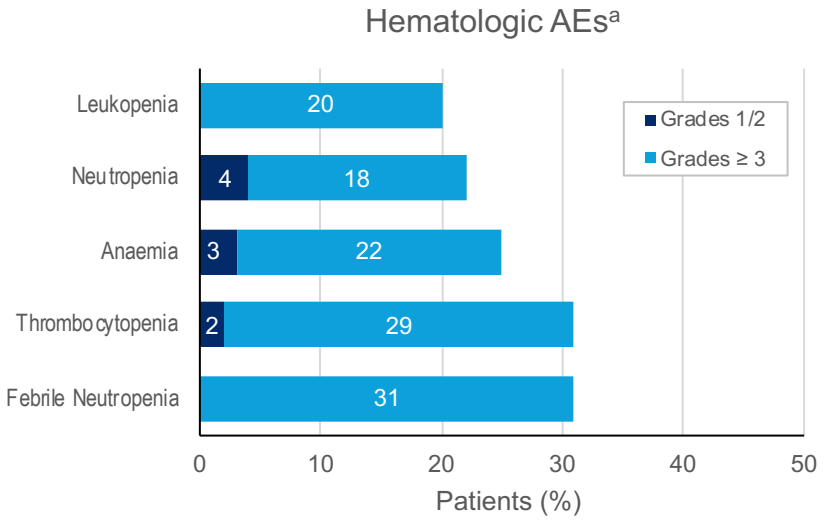
Characteristic	Enrolled Population N=51
Discontinued treatment, n (%)	46 (90)
AE[a]	16 (31)
PD	14 (27)
Treatment failure	3 (6)
Withdrawal of consent	3 (6)
Lack of clinical benefit	1 (2)
Death	1 (2)
Other	8 (16)

[a]Includes 2 patients who discontinued treatment prior to first dose of SY-1425. Of the 16 patients who discontinued due to AE, 2 were due to AEs assessed as related to study drug.

Safety Summary

- Combination generally well tolerated with no increased toxicity relative to either single agent SY-1425 or Aza in AML
- Myelosuppression comparable to reports of single agent Aza in this population
- Majority of non-hematologic AEs are low grade and reversible
- SAEs were reported for 42 patients; the most frequent (occurring in ≥ 5 pts) included febrile neutropenia (14 pts), pyrexia (6 pts), pneumonia (6 pts) and sepsis (5 pts)





[a]Includes all enrolled patients, N=51.

RARA-positive Patients Have a High Complete Remission Rate with a Rapid Time to Response

Best IWG Response[1]	RARA-positive n (%)	RARA-negative n (%)
Response Evaluable, N[a]	18	28
ORR	**12 (67)**	**12 (43)**
CR/CRi	**11 (61)**	**9 (32)**
CR	**9 (50)**	**7 (25)**
CRm	4 (22)	3 (11)
CRc	4 (22)	3 (11)
CRi	2 (11)	2 (7)
MLFS	1 (6)	1 (4)
PR	0 (0)	2 (7)

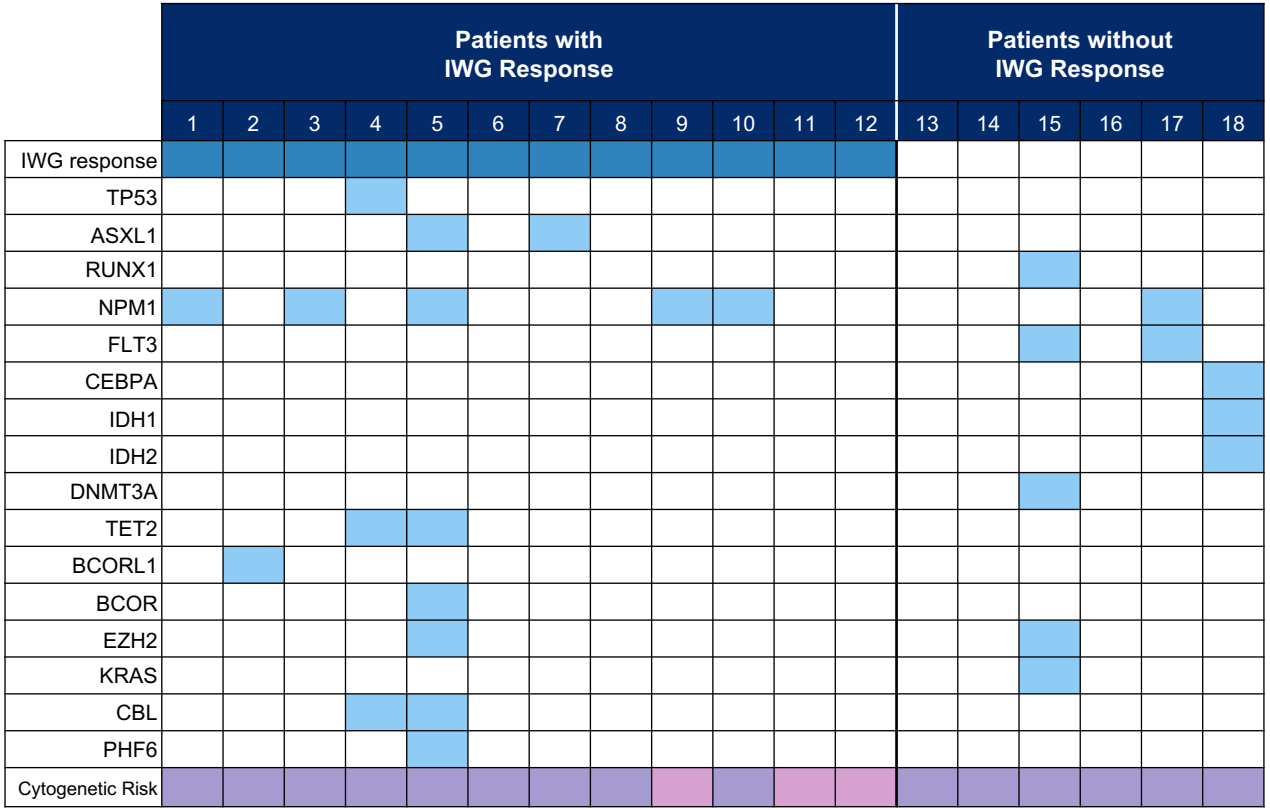
[a] Only response evaluable patients are included, defined as all patients who completed one cycle of treatment with at least one post-baseline response evaluation or discontinued earlier due to disease progression, and who have not had any major protocol violations. There were 4 non-response evaluable RARA-positive patients (2 discontinued prior to first dose of SY-1425 and 2 discontinued prior to completion of cycle 1 due to AE not related to study drug) and 1 non-response evaluable RARA-negative patient (discontinued due to clinical progression without post-baseline response evaluation).

- RARA-positive patients:
  - High CR/CRi response rate
  - Deep CR with 8/9 (89%) CRm or CRc
  - Rapid time of onset of initial complete response[b] with median 1.2 months
  - Median duration of complete response[b] 10.8 months (95% CI: 2.9, 15.2)
- RARA-negative patients:
  - Response rates comparable to historical response rates for single agent Aza[2-4]
  - Median time to initial complete response[b] delayed relative to RARA-positive patients at 3.0 months
  - Median duration of complete response[b] 10.3 months (95% CI: 3.1, NE)

[b]Complete response includes CR, CRi, CRh

[1]Cheson, JCO 2003; [2]Fenaux, JCO 2010; [3]Dombret, Blood 2015; [4]VIDAZA® Prescribing Information

Responses Observed in RARA-positive Patients Irrespective of Mutation or Cytogenetic Risk



Achieved IWG response

Presence of the indicated molecular mutation

Cytogenetic Risk[a]

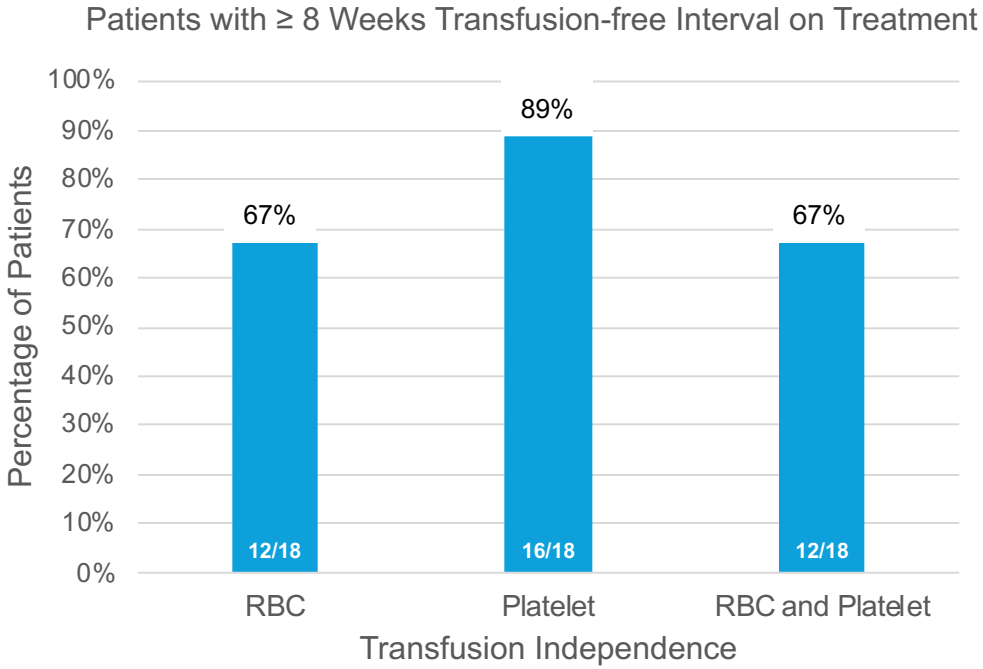
Intermediate

Poor

*Data shown for the 18 response evaluable patients

[a]Cytogenetic risk per NCCN AML guidelines 2018

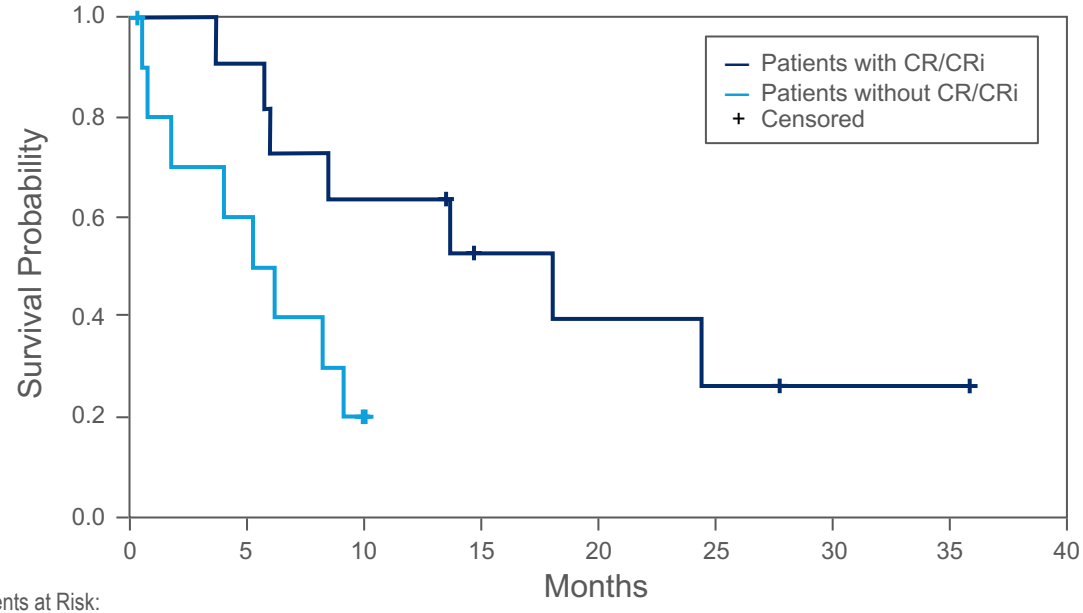
Transfusion Independence



- High proportion of RARA-positive patients achieved or maintained transfusion independence:
  - 67% (12/18) of patients were free of both RBC and platelet transfusions for a ≥ 8-week interval on treatment
  - 86% (6/7) 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.

Overall Survival in RARA-positive Patients Stratified by Response Status



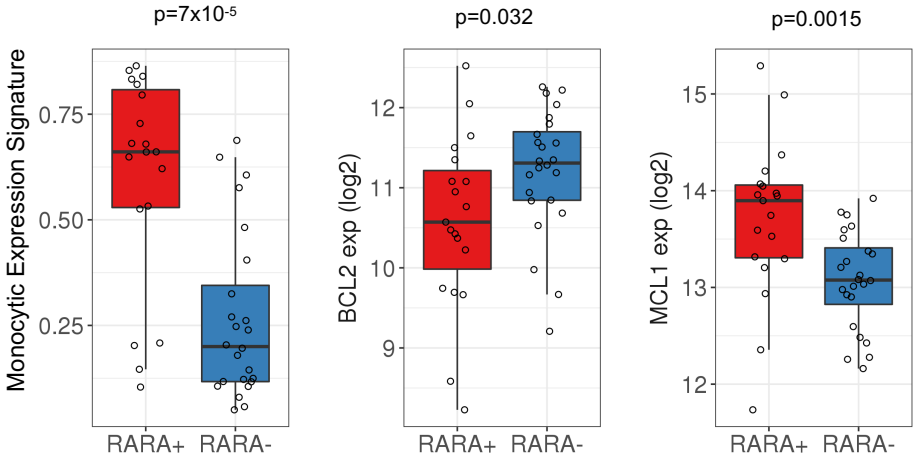
Patients at Risk:								
Patients with CR/CRi	11	10	7	4	3	2	1	0
Patients without CR/CRi	11	6	0					

- RARA-positive patients with CR/CRi (N=11):
  - Median OS 18.0 months (95% CI: 5.7, NE)
- RARA-positive patients without CR/CRi (N=11)[a]
  - Median OS 5.6 months (95% CI: 0.4, 9.0)
- Total enrolled RARA-positive patients (N=22):
  - Median OS 8.4 months (95% CI: 5.2, 18.0)

[a] RARA-positive patients without CR/CRi included 4 non-response evaluable patients (2 discontinued prior to first dose of SY-1425 and 2 discontinued prior to completion of cycle 1 due to AE not related to study drug).

RARA-positive ND Unfit AML Patients Including Those with Response to SY-1425 Plus Aza are Enriched for Features Associated with Venetoclax Resistance

Analyses of Patient Samples from Clinical Trial



- Multiple recent studies report venetoclax resistance is associated with a monocytic phenotype[1-3]
- A monocytic expression signature was developed using 9 well-established monocytic and primitive gene expression markers[4]
- ~80% of RARA-positive ND unfit AML trial patients have monocytic phenotype associated with venetoclax resistance, which includes lower BCL2 and higher MCL1 expression[4]
- Majority of RARA-positive ND unfit AML patients who achieved CR/CRi with SY-1425/Aza have this monocytic phenotype[4]

Selection of RARA-positive Newly Diagnosed Unfit AML Patients with Elevated *RARA* Gene Expression Enriches for Features Associated with Primary Resistance to Venetoclax and Clinical Response to SY-1425, a Potent and Selective RARα Agonist, plus Azacitidine (abstract # 137323) to be presented in Session 616 AML: Novel Therapy, excluding Transplantation: Poster III on Mon, Dec 7

[1]Zhang, Blood 2018; [2]Kuusanmäki, Haematologica 2020; [3]Pei, Cancer Discovery 2020; [4]Fiore, ASH 2020

Conclusions

- SY-1425/Aza demonstrates high CR rates including the majority with molecular and cytogenetic CRs in RARA-positive AML, a novel subset of AML characterized by *RARA* overexpression
  - Rapid onset of response
  - Responses observed across cytogenetic risk groups and mutations
  - Majority achieved or maintained transfusion independence
  - Median OS for responders was 18.0 months, suggesting clinically meaningful benefit
- SY-1425/Aza was generally well-tolerated with no evidence of increased toxicity relative to either as a single agent
  - Rates of myelosuppression were comparable to single-agent Aza
- ~80% of RARA-positive ND unfit AML trial patients have monocytic phenotype associated with venetoclax resistance, which includes lower BCL2 and higher MCL1 expression[1]
  - Majority of RARA-positive ND unfit AML patients who achieved CR/CRi with SY-1425/Aza have this monocytic phenotype, suggesting the potential for combination treatment with SY-1425 to address significant unmet need in ND unfit AML, including in those who may be resistant to venetoclax[1]
- Further development is warranted in RARA-positive AML and other myeloid malignancies

[1]Fiore, ASH 2020