Novel Combinations Leveraging RARα Targeting with SY-1425 in AML and MDS

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Disclosures

Company Name	Research Support	Employee	Consultant	Stockholder	Speakers Bureau	Advisory Board	Other
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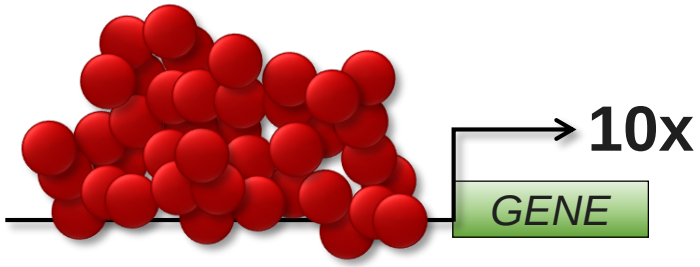
AbbVie	×						
Astellas	×						
AstraZeneca			×				
Celgene	×						
Daiichi Sankyo	×						
Forma Therapeutics	×						
Genentech	×						
Kura Oncology	×						
Novartis			×				
Syros Pharmaceuticals	×						

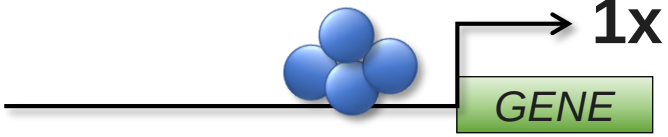
- SY-1425 (tamibarotene) is an investigational drug in development for use in AML and MDS in the US and EU
- This presentation includes no reference to off-label or investigational use of an approved product in the US or EU

In a subset of tumors, a super-enhancer drives the *RARA* gene

Super-Enhancer (1-5% of genes)



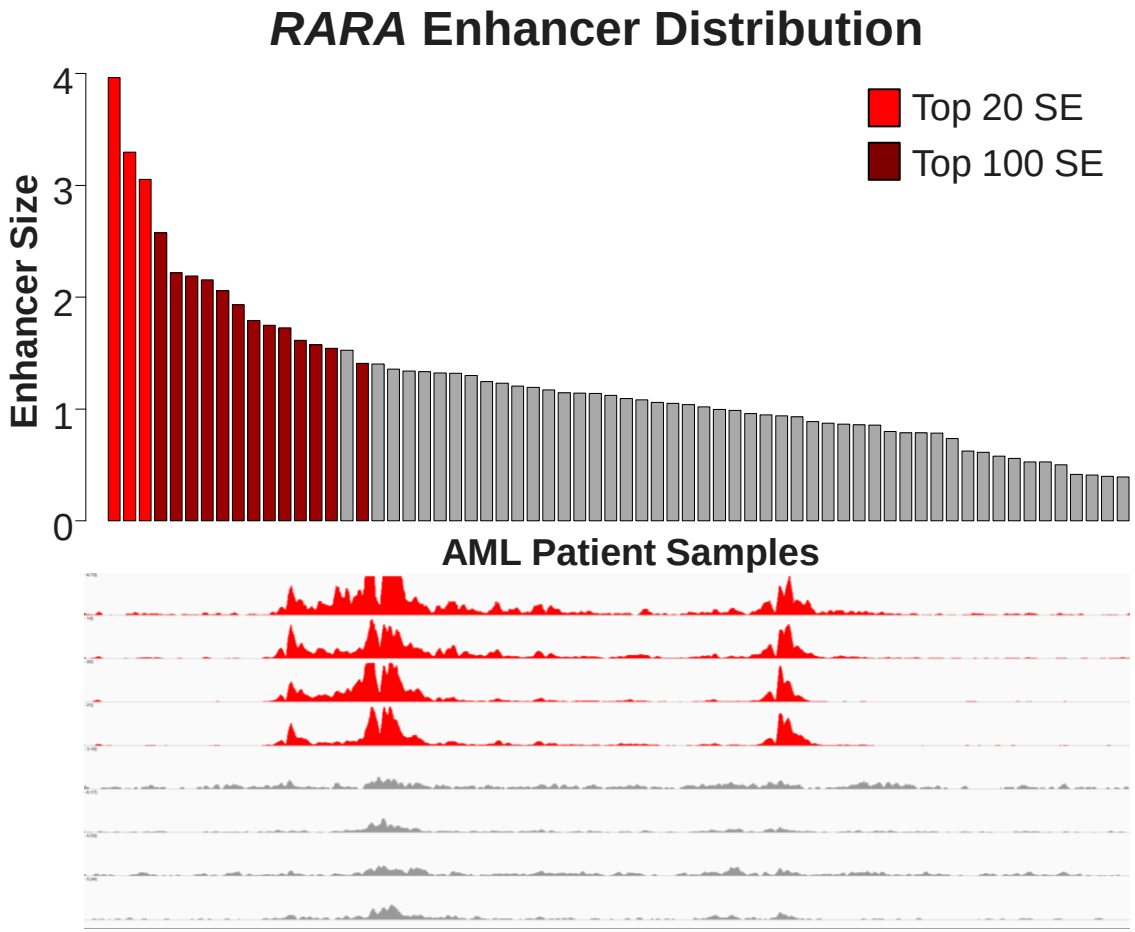
Typical Enhancer

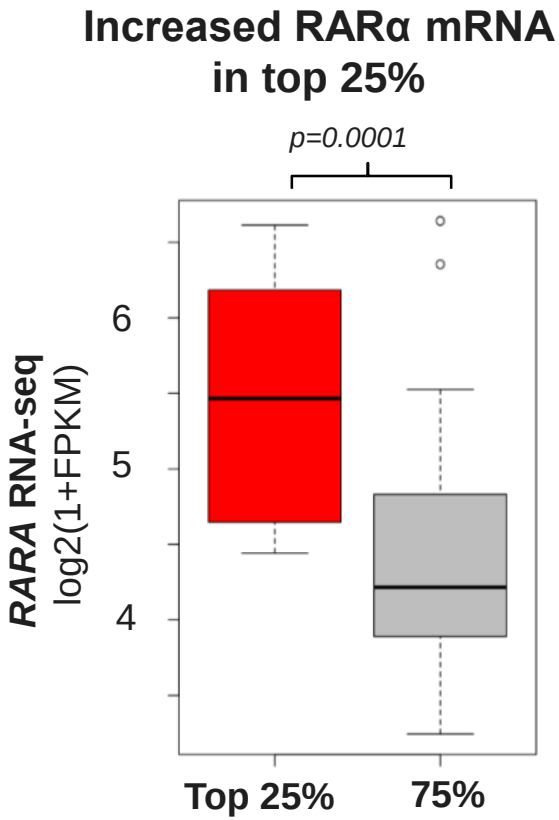


- Super-enhancers (SE) are large clustered enhancer regions in the human genome
- Control expression of genes critical for determining cell fate, differentiation, and malignant transformation
- Genome-wide profiling identified a SE at the *RARA* gene locus regulating *RARA* expression in ~1/3 of 1º AML patient samples

Data presented in June 2016 at the 21st Congress of the European Hematology Association (EHA)
McKeown MR *et al. Cancer Discov* 2017; 7:1136-1153.

A subset of non-APL AML patients have an *RARA* SE





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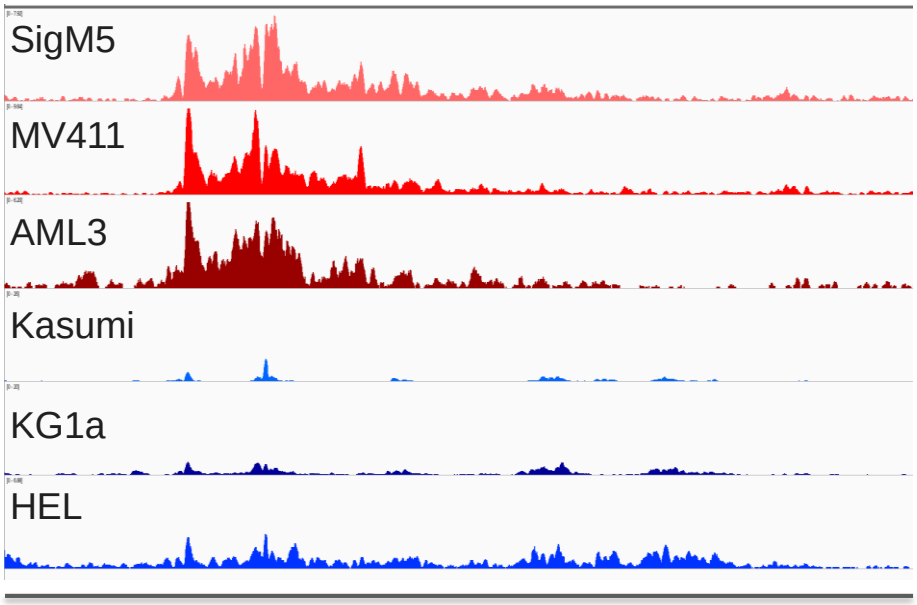
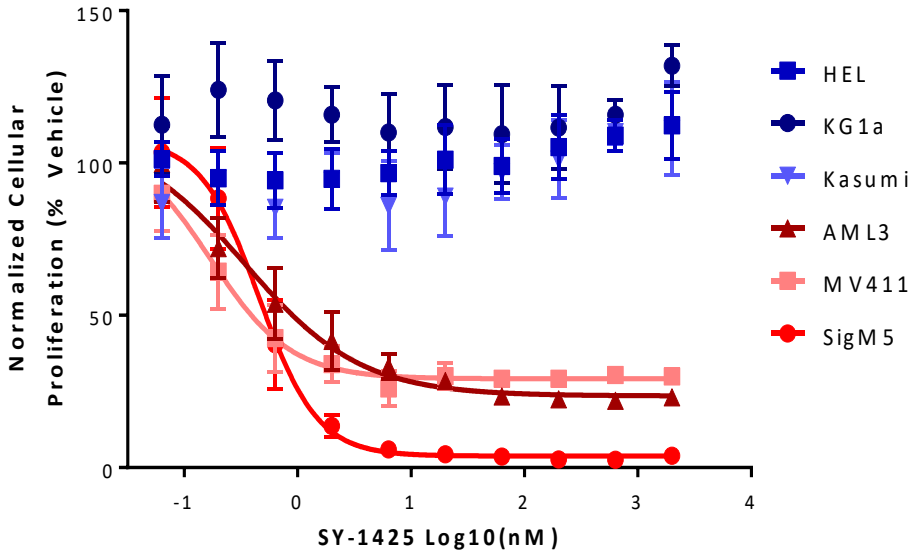
RARA SE predicts sensitivity to an RARα agonist in non-APL AML cell line models

RARA Enhancer



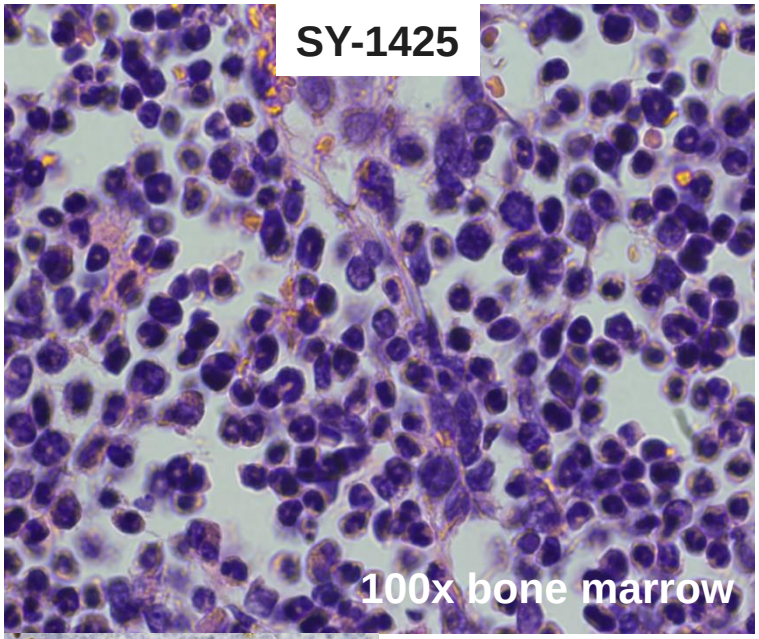
***RARA* gene locus**

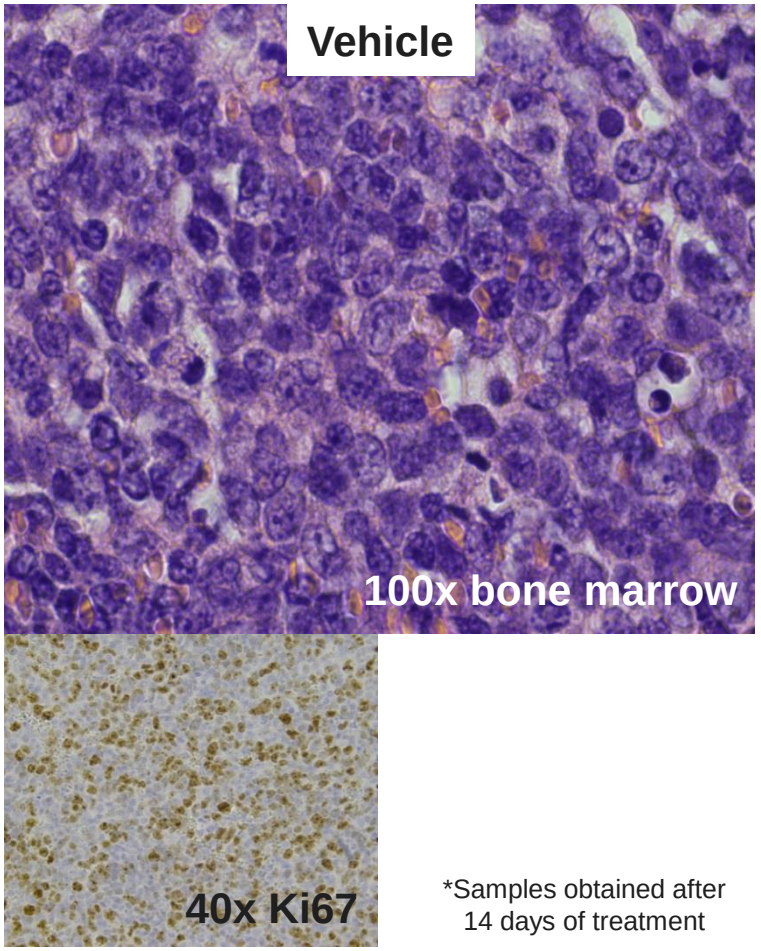
SY-1425 Anti-Proliferative Effect



Data presented in June 2016 at the 21st Congress of the European Hematology Association (EHA)

SY-1425 induces differentiation in non-APL AML *RARA*-positive PDX models





*Samples obtained after 14 days of treatment

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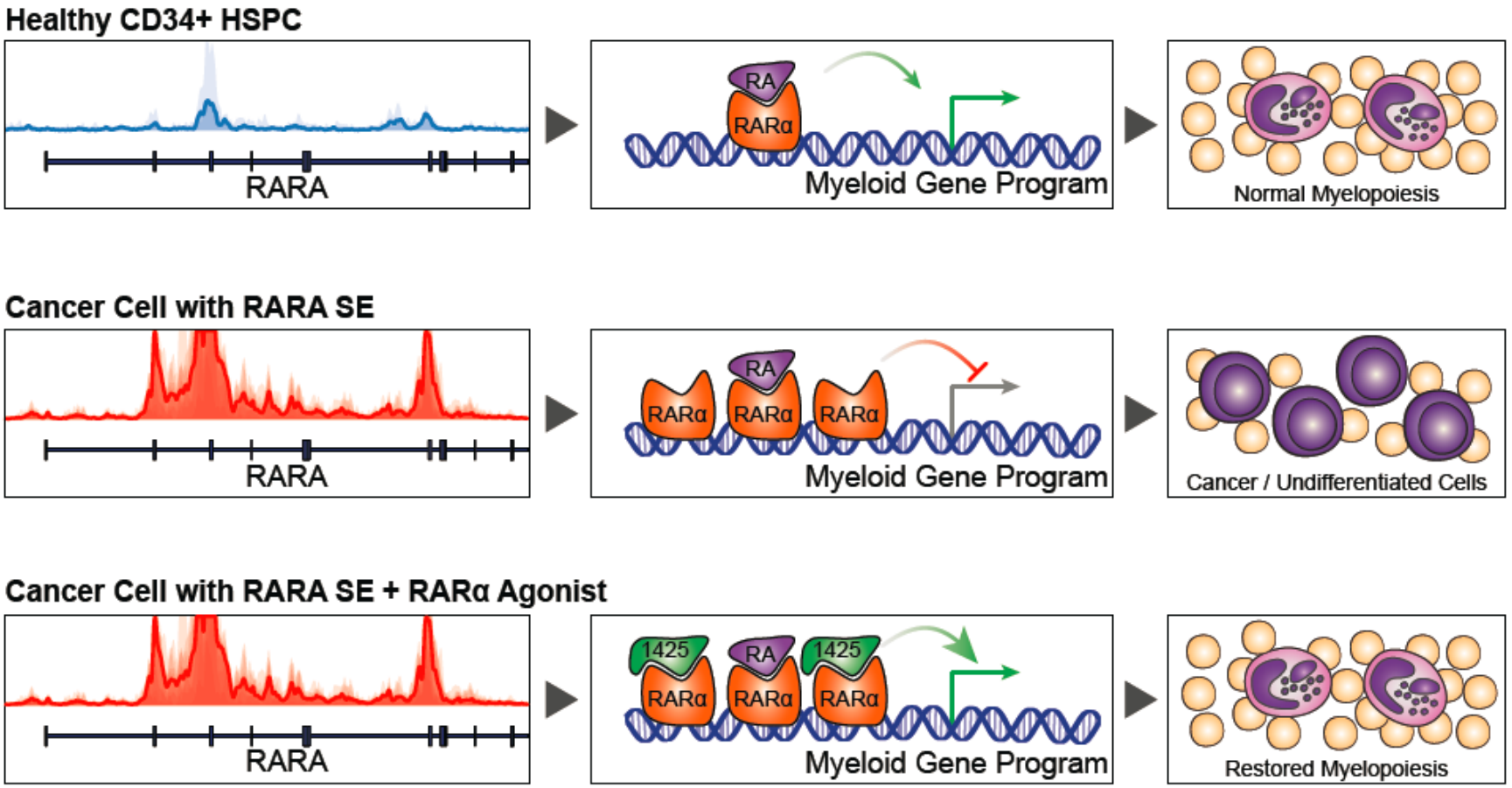
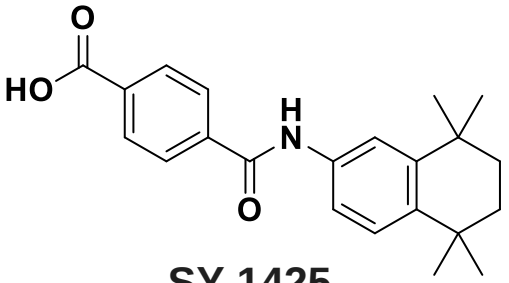
McKeown MR *et al. Cancer Discov* 2017; 7:1136-1153.

Proposed model of SY-1425 action in *RARA*-positive AML promoting differentiation and restoring myelopoiesis



SY-1425 is a first-in-class selective RARα agonist



SY-1425

- Developed to overcome liabilities associated with ATRA
- Very potent and selective for RARα
  - 0.26 nM binding on RARα
  - Greater than 100x selectivity for RARα over RARβ and RARγ
- Oral drug with improved pharmacokinetic properties
  - Longer half-life (5 vs. 0.6 hours)
  - Not metabolized by Cyp26A1
  - High sustained blood levels
- In clinical development as an investigational agent in AML and MDS patients selected for *RARA* pathway activation using RARA and/or IRF8 biomarkers (NCT02807558)

Clinical and biologic activity seen with single-agent SY-1425 in difficult-to-treat AML and high-risk MDS patients

Phase 2 data in biomarker-selected patients showed myeloid differentiation, improved blood counts and reduced bone marrow blasts

- Biomarker status significantly correlated with differentiation of cells treated *ex vivo* with SY-1425, supporting the predictive value of the biomarker test for patient selection
- Clinical activity observed in 43% (10/23) R/R AML and high-risk MDS and 8% (2/25) low-risk MDS patients
  - 9 with hematologic improvement
  - 5 with marrow blast reductions, including 1 with marrow CR meeting IWG criteria
- 57% (13/23) R/R AML and high-risk MDS patients had stable disease
- Myeloid differentiation observed, including induction of CD38 in 85% (11/13) of evaluable patients

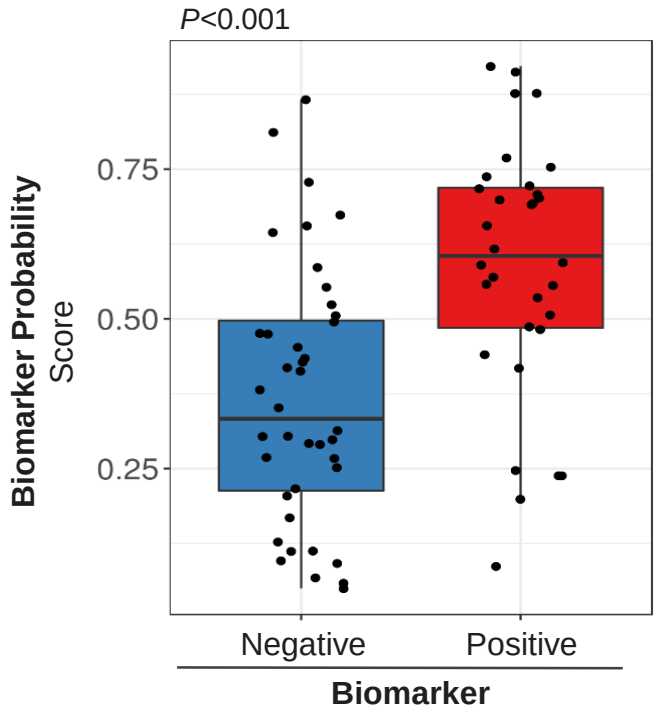
Generally well-tolerated with manageable and/or reversible side effects

- 58 R/R AML or high-risk MDS and low-risk MDS patients treated for median duration of 80 days; patients treated up to 8 months and remaining on study
- Most common AEs consistent with prior experience:
  - Hypertriglyceridemia
  - Fatigue
  - Dermatologic effects
- Majority of AEs were low-grade

Data presented in December 2017 at the 59th American Society of Hematology (ASH) Annual Meeting

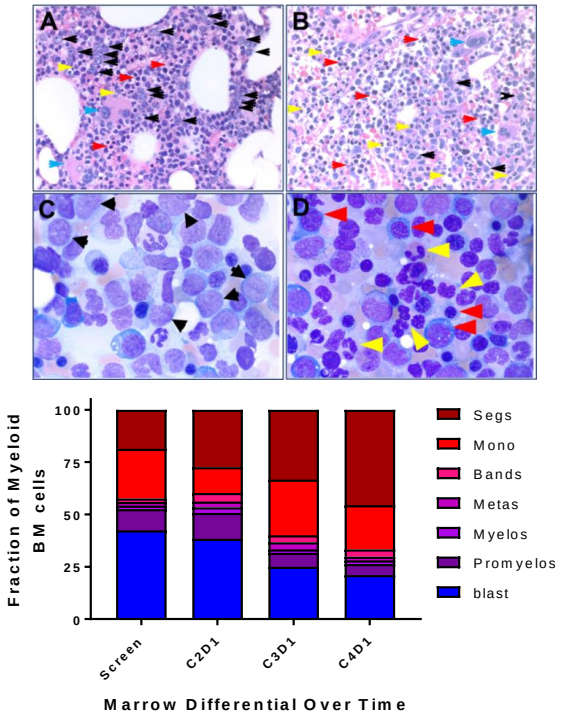
Differentiation observed in biomarker-positive patient samples and clinical trial patients treated with SY-1425

Unbiased machine learning approach using Random-Forest analysis



Data presented in October 2017 at the European School of Haematology (ESH) 4th International Conference on AML

66-year-old male with R/R AML



Myeloid differentiation starting after one cycle, with marrow blast reduction >25% beginning after two cycles and continuing to the start of the fourth cycle

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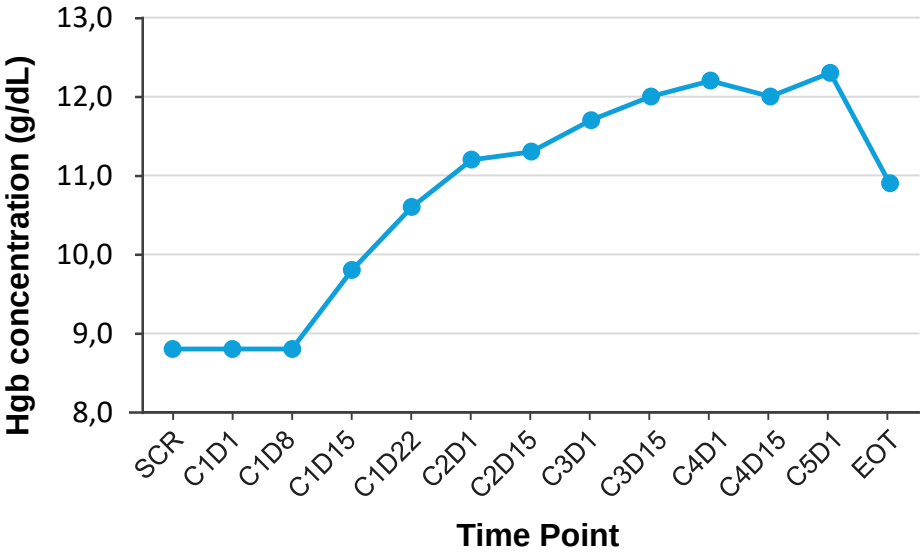
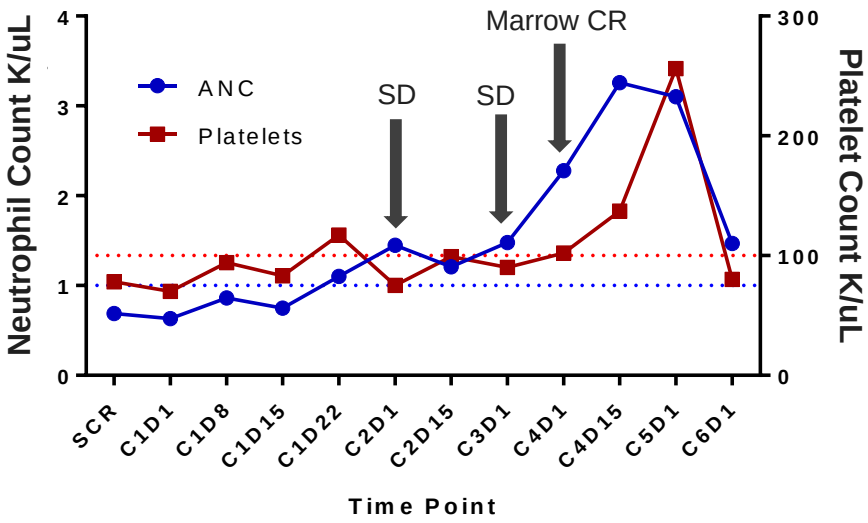
Clinical activity observed in relapsed/refractory patients

Erythroid response in R/R HR MDS patient



Initial response observed two weeks after starting treatment and lasting through five months without blood transfusions

Marrow CR in R/R HR MDS patient



Initial responses (platelet and ANC) observed on cycle 1 day 22, patient remains on treatment past 238 days

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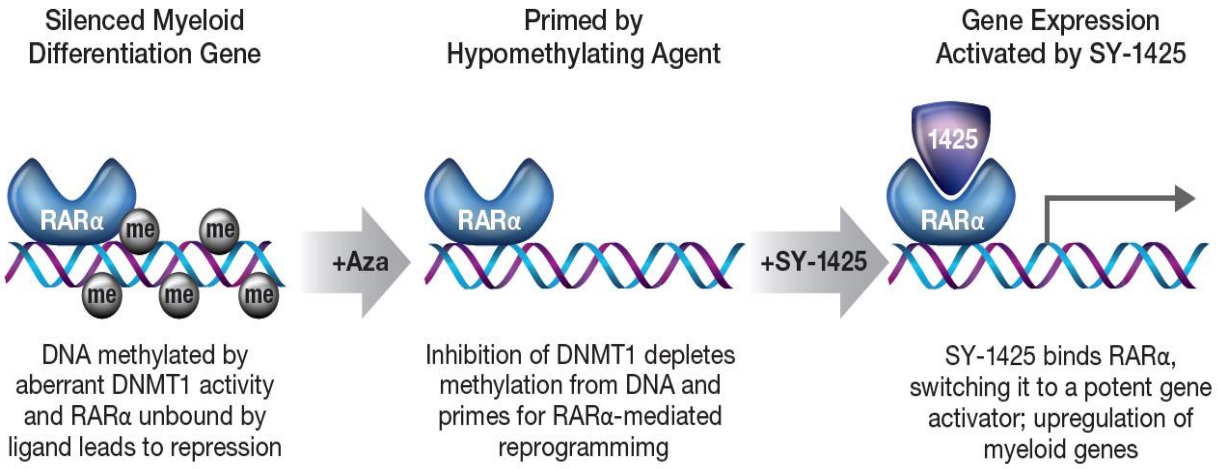
Ongoing Phase 2 trial evaluating SY-1425 combinations in genomically-defined AML and MDS patients

Phase 2 Clinical Trial Design

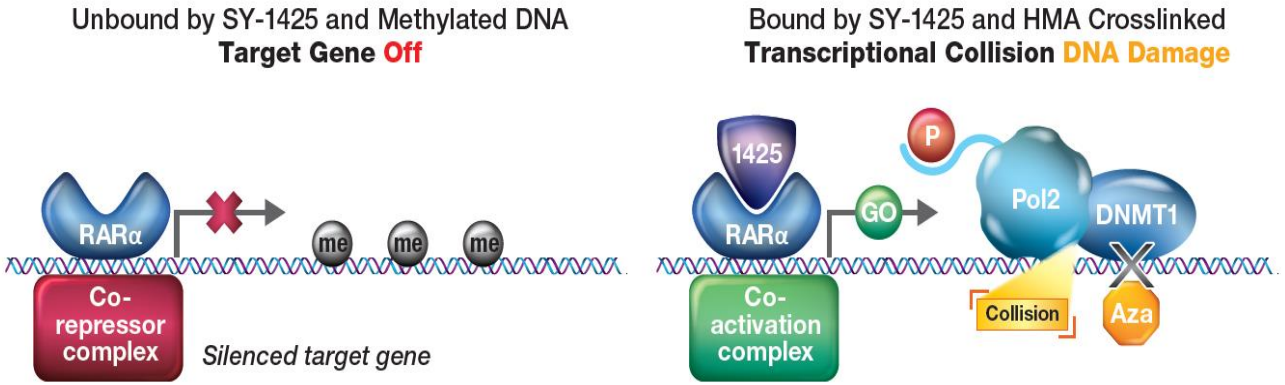
Patient Population	Combo Agent	Primary Purpose
Biomarker-positive newly diagnosed, unfit AML *(25 patients)*	Azacitidine	• Assess safety and efficacy
Biomarker-positive R/R AML and higher-risk MDS *(12 patient pilot)*	Daratumumab	• Demonstrate CD38 induction • Assess safety and efficacy
Biomarker-negative newly diagnosed, unfit AML *(25 patients)*	Azacitidine	• Support development of commercial companion diagnostic

SY-1425 plus azacitidine leads to tumor cell death: Potential mechanisms for combination synergy

1. Demethylation by AZA could prime SY-1425 agonism of formerly repressed RARα target genes

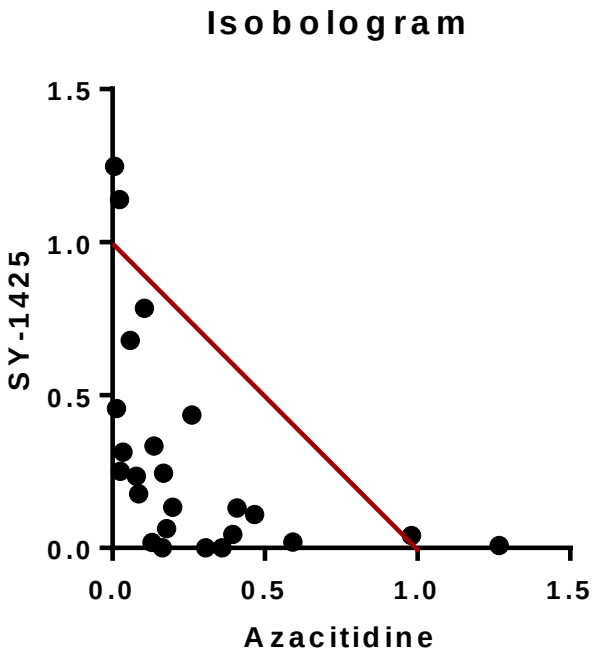


2. SY-1425-mediated gene activation in the context of AZA crosslinked to DNMT1 leads to DNA damage and apoptosis

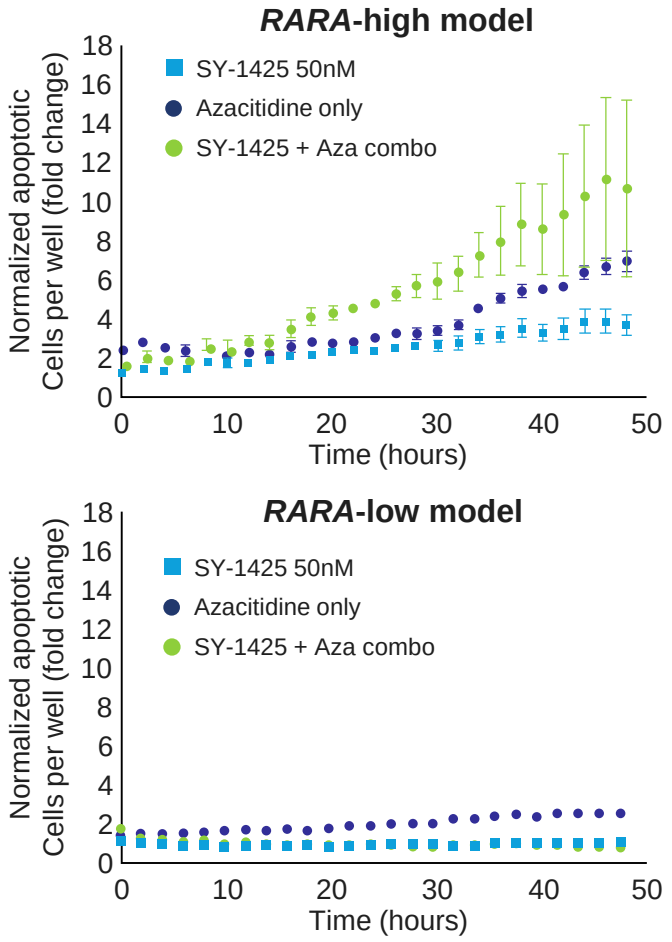


SY-1425 plus azacitidine demonstrates combination synergy and induces apoptosis preclinically

Combo demonstrates in vitro synergy in *RARA*-high cell line models



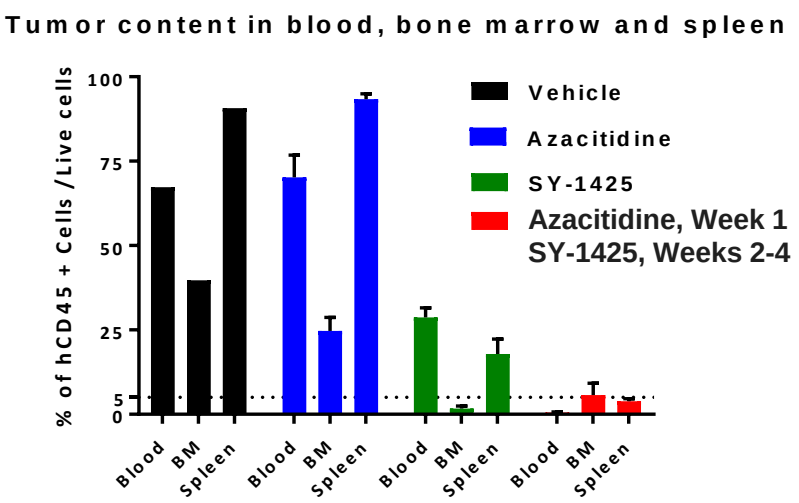
Combo induces apoptosis in *RARA*-high cell lines



Data presented in April 2017 at the American Association for Cancer Research (AACR) Annual Meeting

SY-1425 plus azacitidine induces increased tumor reduction and deeper, more durable responses *in vivo*

Combo leads to increased reduction in tumor burden in preclinical PDX model



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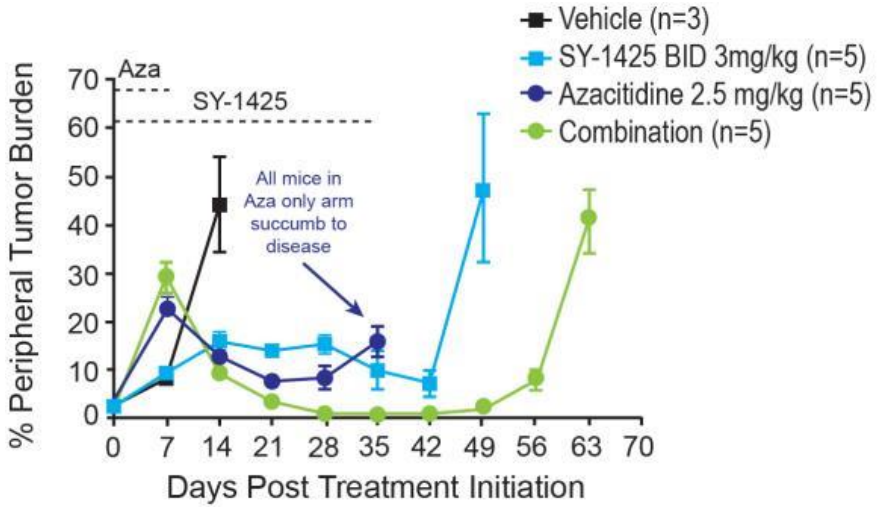
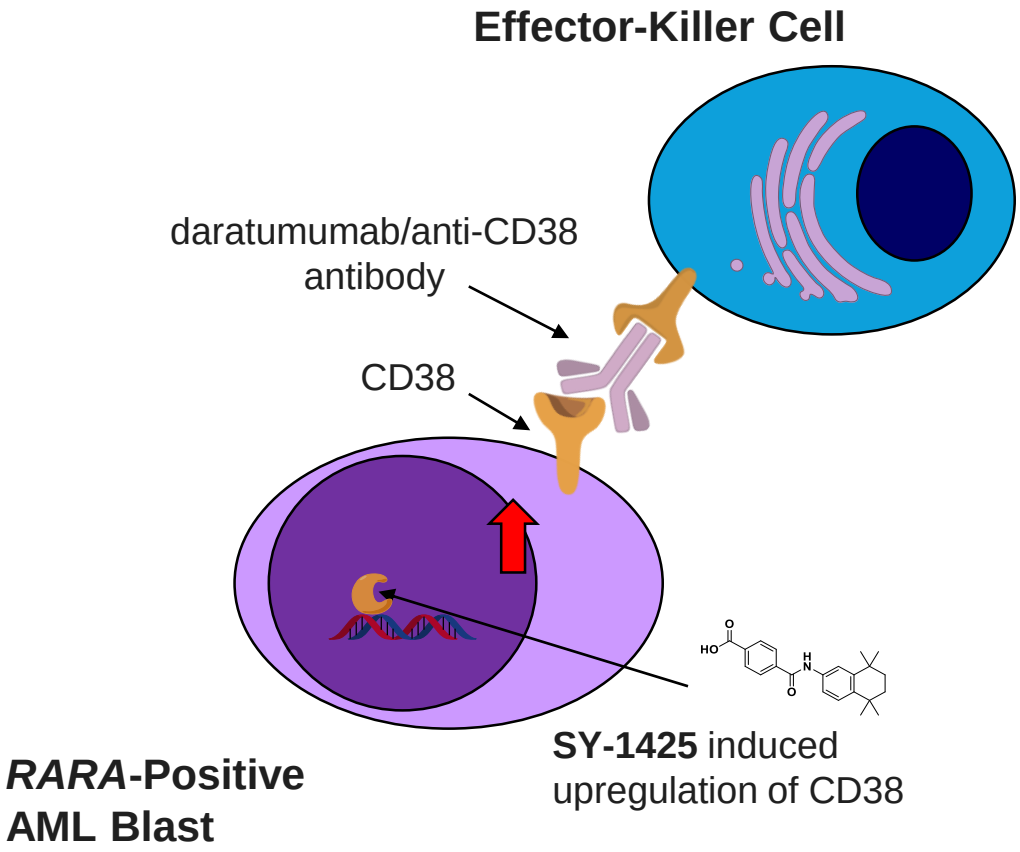
Combo leads to deeper and more durable response in preclinical PDX model



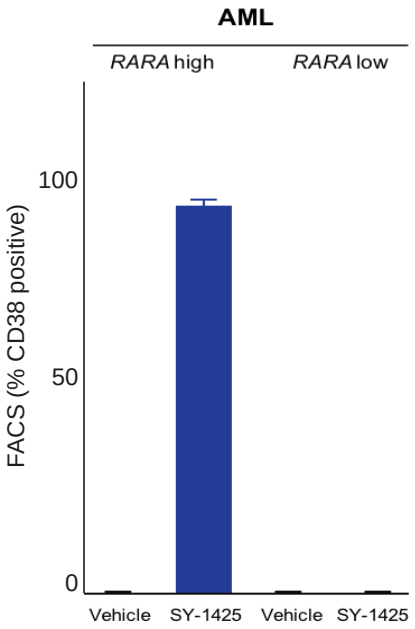
Data presented in December 2016 at the 58th American Society of Hematology (ASH) Annual Meeting

SY-1425 induces high levels of CD38 expression in *RARA*-positive AML supporting a CD38 targeting strategy

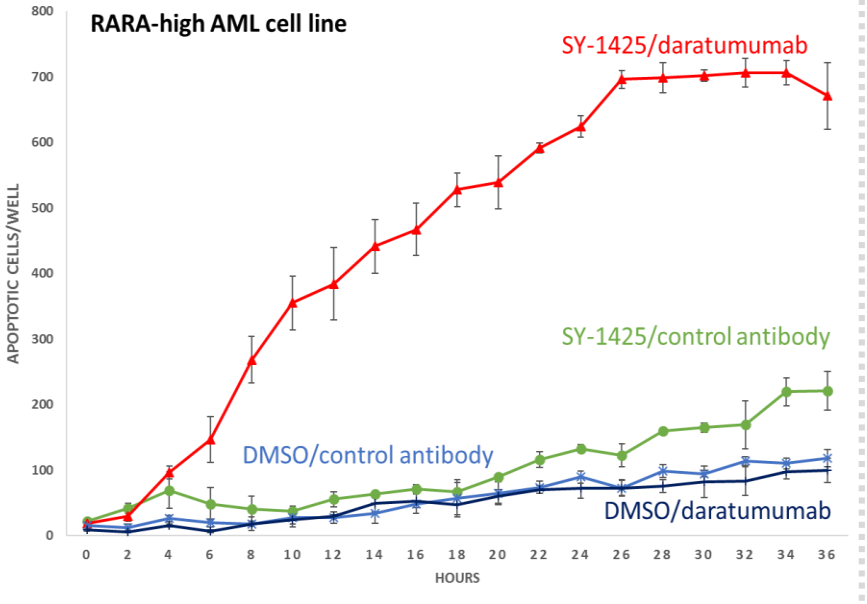


SY-1425 induces CD38 expression in preclinical models and patients; Anti-CD38 combination induces immune-mediated cell death *in vitro*

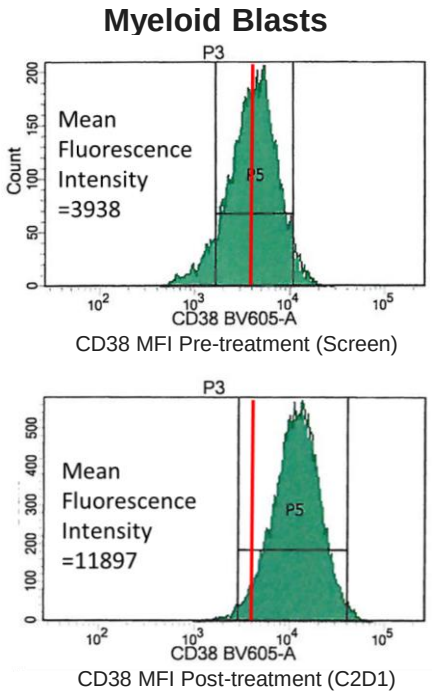
SY-1425 induces CD38 cell surface expression



SY-1425 in combination with daratumumab induces immune-mediated cell death



CD38 induction seen in 85% of evaluable clinical trial patients



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Conclusions

- SY-1425 is a first-in-class selective, oral RARα agonist that has been generally well-tolerated to date in AML and MDS clinical study patients
- SY-1425 demonstrated single-agent clinical and biological activity in novel AML and MDS patient subsets as defined by biomarkers of *RARA* pathway activation
- Preclinical data support multiple mechanisms of combination synergy to induce leukemic cell death in AML models
- An ongoing Phase 2 study is evaluating SY-1425 in combination with azacitidine and with daratumumab