# A Biomarker-Directed Phase 2 Study of SY-1425, a Selective Retinoic Acid Receptor Alpha Agonist, in Adult Patients with Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

Rachel Cook\(^1\), Eytan Stein\(^2\), David Steensma\(^3\), Mikkael Sekeres\(^4\), Dale Bixby\(^5\), David Rizzieri\(^6\), Joseph Jurcic\(^7\), Carlos E. Vigil\(^8\), Robert Redner\(^9\), Gail Roboz\(^10\), Michael Savona\(^11\), Michael R. McKeown\(^12\), Kristin Stephens\(^13\), David A. Roth\(^12\), Jorge Cortes\(^13\)

\(^1\)Oregon Health Science Center, Portland, OR; \(^2\)Memorial Sloan Kettering Cancer Center, New York, NY; \(^3\)Dana-Farber Cancer Institute, Boston, MA; \(^4\)Cleveland Clinic, Cleveland, OH; \(^5\)University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; \(^6\)Duke University Medical Center, Durham, NC; \(^7\)Columbia University Medical Center, New York, NY; \(^8\)University of Iowa, Iowa City, IA; \(^9\)University of Pittsburgh Cancer Institute, Pittsburgh, PA; \(^10\)Weil Cornell Medical College, New York, NY; \(^11\)Vanderbilt University Medical Center, Nashville, TN; \(^12\)Syros Pharmaceuticals, Cambridge, MA; \(^13\)MD Anderson Cancer Center, Houston, TX

Abstract No:T187071
Poster Board Number:268b

## Background

**RARA Pathway Activation in AML and MDS**

- AML and MDS are related common hematological disorders; therapeutic responses are often not durable, and new agents to extend survival and improve quality of life are needed in both disorders.
- Syros characterized super-enhancers (SE), highly active chromatin regions that define cell identity and differentiation stage in normal and cancer cells, in patient tumor tissues and identified new AML and MDS patient subsets characterized by RARA pathway activation\(^1\).
- AML preclinical models indicate that RARA pathway activation (increased RARA and/or IRF8), predict biological response to SY-1425 (tamiobarotene), including induction of differentiation and inhibition of proliferation; based on these results, Syros developed a biomarker test that quantifies RARA pathway activation.
- Genome-wide ChIP-seq and expression studies of RARA-high blasts treated with SY-1425 identified DHRS3 mRNA induction as a PD marker in AML and MDS.
- Preclinical combination studies of SY-1425 and azacitidine showed synergy in RARA-high AML models, but not in RARA-low AML models.

**SY-1425 (Tamiabarotene)**

- SY-1425 is an oral, potent and selective synthetic RARα agonist previously approved for the treatment of relapsed/refractory APL in Japan\(^2\).
- Potential advantages over all-trans retinoic acid (ATRA):
  - More potent and selective for RARα (≥100 x more selective over RARβ and RARγ) in preclinical studies
  - Improved PK with longer half-life (5 vs 0.6 hours)
  - Not metabolized by CYP26A1, leading to higher sustained blood levels with continuous dosing
- SY-1425 monotherapy resulted in 58% CR rate in APL patients who relapsed after ATRA, consistent with results in APL patients relapsing after both ATRA and ATO (64% CR/CRi)\(^2,4\).
- As add-on to ATO therapy, higher CR rates were observed with SY-1425 vs ATRA (80% vs 54%), including higher molecular CR rates with SY-1425 (23% vs 3%)\(^5\).

## Azacitidine

- Pyrimidine analogue, approved for MDS in the US and EU; SOC in US for AML, and approved in EU for AML.

## Study Rationale

- The mechanism of RARα-mediated differentiation block in the tumor and consequent response to SY-1425 is similar to that described with retinoids in APL.
- Syros has initiated a Phase 2, multicenter, biomarker-directed study (SY-1425-201; ClinicalTrials.gov NCT02807558) in AML and MDS, utilizing a clinical trial assay (CTA) to measure RARA pathway activation.

## Study Design

### Arm 1

- **Single agent**
- **Relapsed/refractory non-APL AML and higher risk MDS**
- SY-1425 6 mg/m² per day PO until disease progression or unacceptable toxicity
- N=25

### Arm 2A*

- **Single agent**
- **Treatment-naïve non-APL AML**
- SY-1425 6 mg/m² per day PO until disease progression or unacceptable toxicity
- N=25

### Arm 2B

- **Combination therapy**
- **Treatment-naïve non-APL AML**
- Azacitidine 75 mg/m² IV or Subq from Day 1-7 of each cycle (28 days) plus SY-1425 6 mg/m² per day PO on Day 8-28 of each cycle until disease progression or unacceptable toxicity
- N=25

### Arm 3

- **Single agent**
- **Transfusion-dependent, lower risk MDS without del 5q, refractory or unable to respond to EPO**
- SY-1425 6 mg/m² per day PO until disease progression or unacceptable toxicity
- N=25

## Key Endpoints

### Primary

- ORR in patients with AML or higher-risk MDS
- Transfusion independence rate (TIR) in patients with lower-risk MDS

### Secondary

- Event-free survival, relapse-free survival, duration of response, OS, and hematologic improvement
- Safety and tolerability
- PK parameters
- Changes in pharmacodynamic (PD) markers including DHRS3 induction and myeloid differentiation markers

### Exploratory

- Health-Related Quality of Life
- PKPD relationship

## Key Inclusions

- Biomarker positive for RARA pathway activation (RARA and/or IRF8)
- Ablenam to serial bone marrow aspirations and peripheral blood sampling
- Adequate organ function as defined by:
  - Total bilirubin ≤ 1.5 x the ULN
  - ALT and AST ≤ 3 x ULN or ≤ 5 x ULN if documented liver infiltration with leukemia cells
  - Serum creatinine ≤ 2.0 x ULN or calculated creatinine clearance ≥ 40 mL/min per Cockcroft-Gault

## Key Exclusions

- APL (M3 subtype of AML) or patients with a t(9;22) cytogenetic translocation
- Hyperleukocytosis (leukocytes ≥ 25 x 10⁹/L) at study entry
  - These patients may be treated with hydroxyurea and enroll when the leukocyte count falls below 25 x 10⁹/L
- Refractory to platelet or packed red cell transfusions or refusal of blood product support
- Prior treatment with ATRA or systemic retinoid for hematologic malignancy
- Patients with hypertriglyceridemia defined as >1000 mg/dL

## References

2.Amirole Product Label (Japan)

---

For more information on this study, please contact:
Kristin Stephens
Tel: 617-744-1340 ext. 309
Email: kstephens@syros.com

---

Figure: Model of RARA pathway activation. The presence of an SE or upregulated mRNA for RARA and/or IRF8 is an indication of a differentiation blocked state. SY-1425 reverses this effect to re-activate myeloid maturation genes, leading to differentiation and inhibiting proliferation.