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)

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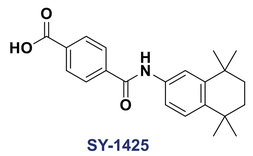
Background

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 state 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 (tamibarotene), 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 (Tamibarotene)

- 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

- 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) [3, 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

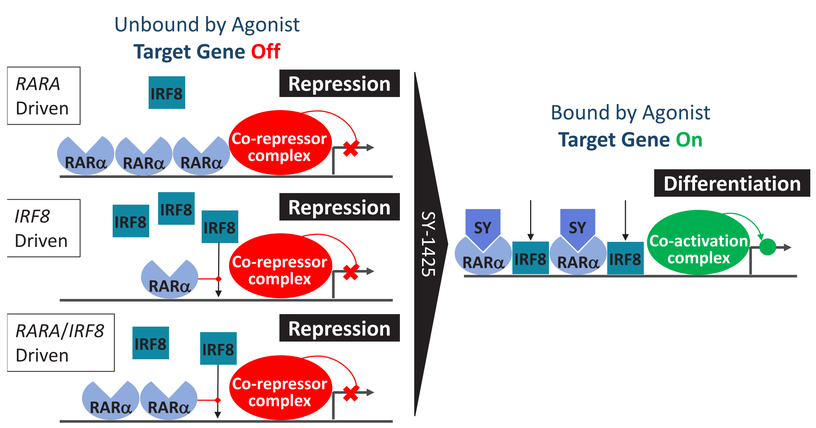
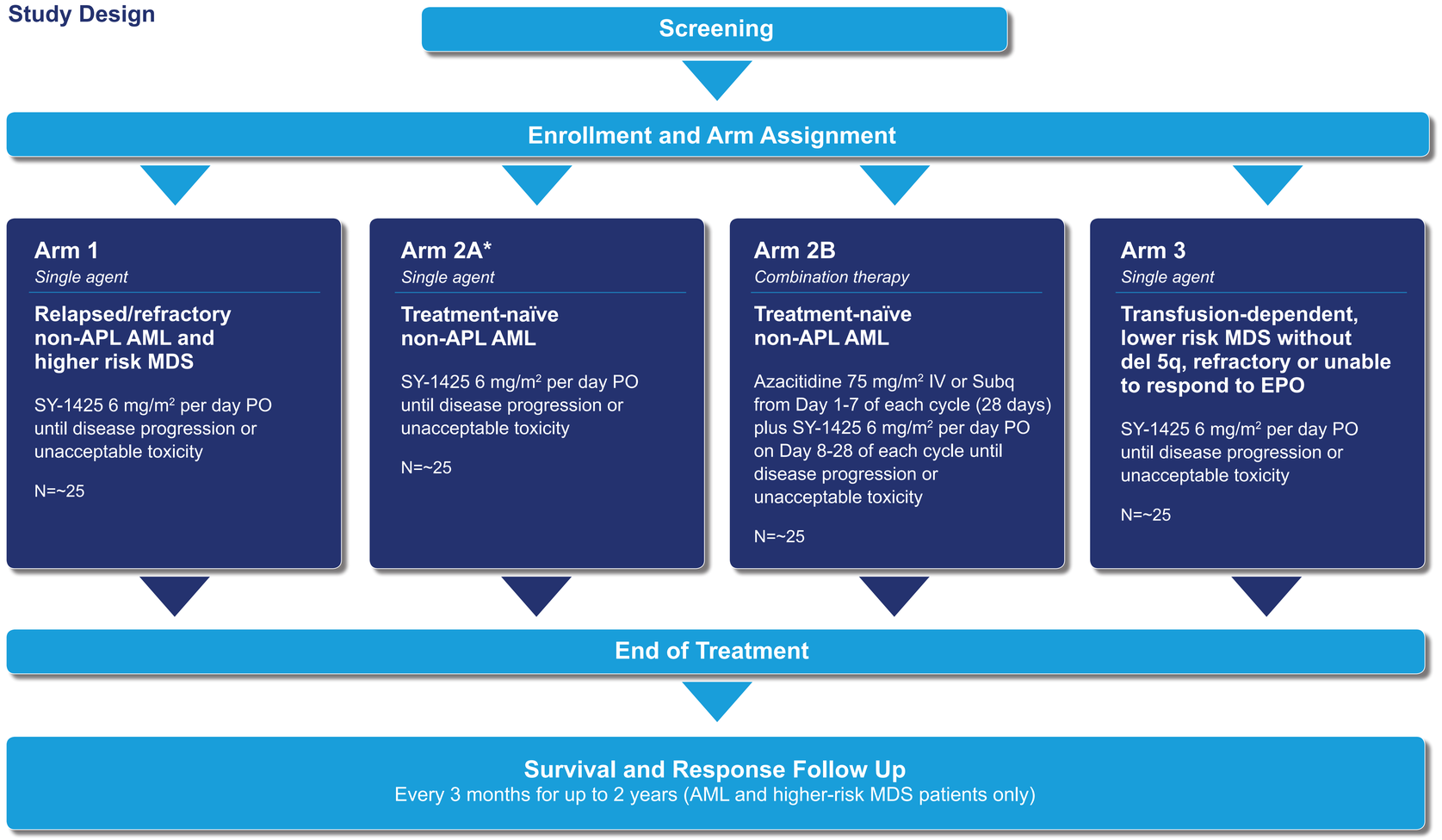


Figure: Model of RARA pathway activation. The presence of an SE or upregulated mRNA for RARA and/or IRF8 is an indication of a differentiation blocked state. SY-1425 reverses this effect to re-activate myeloid maturation genes, leading to differentiation and inhibiting proliferation.

Study Design



*Patients in Arm 2A may receive SY-1425 in combo with azacitidine after relapse/unsatisfactory response with single agent SY-1425

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 • PK/PD relationship

Response Assessments and Criteria

- Response measured via changes in peripheral blood counts and bone marrow aspirate
- Bone marrow aspirates: Day 1 of Cycles 2, 3, and 4, then by every third cycle from Cycle 7 Day 1; additional aspirates collected when clinically indicated or to establish CR or disease progression.
- AML: IWG response criteria (Cheson 2003)
- MDS: IWG criteria (Cheson 2006)

Key Inclusions

- Biomarker positive for RARA pathway activation (RARA and/or IRF8)
- Amenable to serial bone marrow aspirates 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 10^9/L) at study entry
  - These patients may be treated with hydroxyurea and enroll when the leukocyte count falls below 25 x 10^9/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

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