Mechanistically informed combinations of SY-1425, a potent and selective RARα agonist, with hypomethylating or anti-CD38 targeted agents in AML and MDS

Michael R McKeown, Kathryn Austgen, Chris Fiore, Emily Lee, Darren Smith, Christian Fritz, Tracey Lodie, Emmanuelle de Tomaso, Eric Olson

Syros Pharmaceuticals, 620 Memorial Drive, Cambridge, MA 02139

Abstract

The complex pathogenesis of acute myeloid leukemia (AML) necessitates the development of novel therapeutic strategies to optimize patient benefit. Thus, we investigated novel combinations of SY-1425 (synergy agent) and other agents to build on the therapeutic strategy used in SY-1425 in biologic synergy with HDACi and DNA damaging agents. Based on the ability of SY-1425 to reactivate upstream RARA and downstream CD38, we investigated prior work showing preclinical synergistic effects between SY-1425 and hypomethylating agents (HMAs) and CD38 induction was explored. We sought to investigate mechanistically informed combinations of SY-1425 with ATRA and with potential novel agents in AML. We also investigated the effects of SY-1425 on the tumor microenvironment and primary AML patient samples (commercially obtained) similar to what is observed in an SY-1425 resistant cell line (MV4-11) with CD38 upregulated in response to SY-1425. We also explored SY-1425 in combination with daratumumab (Dara) as a marker of myeloid cell maturation, as a direct target gene of RARα, and as an activator of CD38-mediated reprogramming. SY-1425 drives the expression of CD38 in RARA-high AML cells to levels comparable to those of MM cell lines that are responsive to SY-1425 treatment. RARA-high AML cells become more sensitive to SY-1425 (3mpk BID) and ATRA synergies were observed in combination treatment of the NK and RARA high AML cell line, indicating that a combination of SY-1425 and ATRA will be demonstrated in an increased level of synergy in CD38.

Model for HMA priming of SY-1425 mediated reprogramming

CD38 is upregulated in response to SY-1425. SY-1425 induces CD38 expression in RARA-high AML cells to levels comparable to those of MM cell lines that are responsive to SY-1425 treatment. RARA-high AML cells become more sensitive to SY-1425 (3mpk BID) and ATRA synergies were observed in combination treatment of the NK and RARA high AML cell line, indicating that a combination of SY-1425 and ATRA will demonstrate an increased level of synergy in CD38.

Conclusions

• SY-1425, an oral and selective RARα agonist, induces differentiation in RARA-high AML cell lines and patient samples but not in RARα-low.
  - Currently approved in Japan for the treatment of relapsed/refractory APL.
  - Cancer pathogenesis is complex and often optimally treated through multiple combined mechanisms
  - By identifying alteration in gene regulation, Syros platform uncover de novo liabilities for tumor cells leading to novel targeted combinations with therapeutic potential.

• Hypomethylating agents identified as promising combination agents with SY-1425.
  - Synergies seen in RARA-high AML cell line and in vivo models
  - Synergy based on combined gene activation and differentiating mechanisms of the respective drugs
  - AML in vitro studies identified a regimen to maximize tumor suppression and tolerability, supporting a clinical combination strategy
  - SY-1425 is being investigated as a monotherapy and in combination with azacitidine in a biomarker-directed Phase 2 trial in biomarker defined subsets of AML and MDS patients (clinicaltrials.gov, NCT02045758)

• CD38, a marker of maturation, is upregulated in response to SY-1425.
  - The CD38 gene is a direct target of RARα leading to potent and specific upregulation.
  - SY-1425 induces CD38 expression in biomarker-high AML cell lines at a level comparable to that observed in MM.
  - SY-1425 induces AML cell lines becomes more sensitive to daratumumab, a known effective agent in MM.
  - SY-1425 + daratumumab combination is more active than either single agent in AML models.

This data supports the clinical exploration of the combination of SY-1425 and daratumumab in RARA positive AML patients.

EHA Annual Meeting 2017