SY-1425 (tamibarotene), a selective RARα agonist, shows synergetic anti-tumor activity with hypomethylating agents in a biomarker selected subset of AML

Michael R McKeown, Emily Lee, Chris Fiore, Matthew L Eaton, Christian Fritz, Eric Olson

Syros Pharmaceuticals, 620 Memorial Drive, Cambridge, MA 02139

Abstract

In patients with acute myeloid leukemia (AML) (10 years) and myelodysplastic syndrome (MDS), the use of hypomethylating agents (HMAs) may extend survival, but cure rates are very low and new treatment approaches are needed. HMAs, such as azacitidine, work by inhibiting DNMT1, leading to depletion of DNA methylation in the tumor cells. Hypomethylating agents synergize with agents that upregulate expression of genes associated with differentiation and growth arrest. We have recently explored the potent and selective RARα agonist SY-1425 in a genetically defined subset of AML. SY-1425 binds to RARα and causes a transcriptional transition from repression to strong activation of target genes, thus reprogramming the tumor cells toward terminal maturation in RARA-high AML models, supporting our recently released Phase 2 trial in a biomarker selected subset of AML and MDS (NCT02797050). Based on synergistic effects of SY-1425 in combination with HMAs, we investigated the preclinical efficacy of these agents in a biomarker selected, newly diagnosed AML patient subset. The combination of SY-1425 and azacitidine showed synergistic antiproliferative effects in AML xenograft (PDX) mouse models of RARA-high AML cell lines, with combination indices less than 0.5 over a range of concentrations from 0.10 to 1000X of SY-1425 and 1 to 11 Y of HMAs. SY-1425 and azacitidine were also co-administered in a disseminated patient-derived xenograft (PDX) mouse model of RARA-high AML and showed synergistic antiproliferative effects in this model. SY-1425-mediated gene induction. It was observed that the two agents work cooperatively to promote terminal differentiation and decrease proliferation of the AML tumor cells, with the potential for genomic reprogramming to strong activation of target genes, thus reprogramming the tumor cells toward terminal maturation in RARA-high AML models. RARA-high AML models resulted in strong and specific induction of genes bound by RARs. It was hypothesized that azacitidine acts to prime the tumor cells for reprogramming by SY-1425. The loss of methylcytosine residues following azacitidine treatment modulates gene enhancer activity, providing a strong rationale for a planned study of this combination in biomarker selected, newly diagnosed AML patients.

Abstract

In patients with acute myeloid leukemia (AML), the leukemia suppressive agent PTSN was upregulated and the pro-growth gene CAMK2B was downregulated more after combination treatment than single agent treatment in our xenograft mouse models but not in RARA-low high AML cell line treated with combination therapy. Combination therapy including the missense marker CD33 and the RARA signaling PD1 inhibitor SIRPα monoclonal antibody and factor binding motifs had increased azacitidine-genome wide combination treatment.

Conclusions

• SY-1425, a potent and selective oral RARα agonist (currently approved in Japan for the treatment of relapsed refractory APL) shows synergy with hypomethylating agents.

• Synergy seen in RARA-high AML cell line and in vivo in a mouse model but not in RARA-low

• Synergy based on complementary gene activation and differentiating mechanisms of the respective drugs.

• Preclinical studies identified a regimen to maximize tumor suppression highlighting the potential of optimal combination strategy.

• Current platforms are complex and often optimized through multiple combined mechanisms.

• 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: NCT02807050).