**Clinical Pharmacodynamic Markers and Combinations with SY-1425 (tamibarotene) in a Genomiically-Defined subset of non-AML AML**

Michael R McKeown, Chris Fiore, Emily Lee, Matthew L Eaton, Katie Austgen, Darren Smith, Christopher Fritz

Syros Pharmaceuticals, 620 Memorial Drive, Cambridge, MA 02139

---

### Abstract

SY-1425 is a potent and selective agonist of the retinoic acid receptor RARα. It is being investigated in a Phase 1 trial in a novel genomically-defined subset of AML (MYC and/or MLL mutations) that targets gene expression in cell differentiation and proliferation. We identified a super enhancer (SE) at the DHRS3 locus, the gene encoding DHRS3, a protein that regulates a subset of RARα target genes involved in cell differentiation and proliferation. This locus, therefore, represents a promising target for the development of RARα agonists.

#### SY-1425 shows synergy with SOC and emerging therapies in AML

- **Bind by APL target gene (Syros) and emerging therapy (Nat-Co)**
- **DHR35 induction similar to APL**
- **Time to DHRS3 induction**

#### SY-1425 shows synergistic and proliferative effects with current AML standard of care treatments (left: induction) and emerging therapies (right: BFHD inhibitor (ZIP) supporting the potential for addition of SY-1425 to multiple combination treatment regiments)

**SY-1425 induction**

- **Maturation gene CDS9 is bound by RARα and induced by SY-1425 in RARα-high cell lines**
- **DHRS3 mRNA induction by SY-1425**
- **CDS9 mRNA expression changes**

**SY-1425 shows synergistic and proliferative effects with current AML standard of care treatments (left: induction) and emerging therapies (right: BFHD inhibitor (ZIP) supporting the potential for addition of SY-1425 to multiple combination treatment regiments)**

**SY-1425 treatment**

- **Unbound by APL/Target Gene On**
- **Repression and immature state**

**RARA-high predicts for SY-1425 sensitivity**

- **RARα enhancer**
- **RARA-high PDX models respond to clinically relevant doses of SY-1425**

**RARA-high PDX models respond to clinically relevant doses of SY-1425**

- **Tumor burden in bone marrow**
- **A high AML-PDX model responds to SY-1425 sparing non-tumor burden and fewer tumor cells in the peripheral blood at termination. Mouse dose was chosen to match human clinical trial dose with 24 hours post treatment reduction in high-risk bone marrow blasts.**

### Conclusions

- SY-1425 is a first-in-class potent and selective RARα agonist with favorable PK properties and is approved in Japan for the treatment of t(15;17) APL, which is characterized by a balanced APL and promyelocytic leukemia factor gene.
- SY-1425 induces differentiation and anti-proliferative effects in non-AML APL model cells that are highly dependent on a strong RARα expression and increased RARα target gene levels.
- SY-1425 induces a reduction in which can be correlated with alterations in key cellular drug targets.
- DHRS3 and CDS9 are being targeted in an ongoing Phase II clinical trial of SY-1425 to get early assessment of biological activity.
- SY-1425 shows synergy with genomics, hypoxia-targeted agents and novel therapies in in AML and non-AML models, providing evidence for clinical combination strategy in addition to the ongoing single agent strategy.
- SY-1425 is currently being investigated in a biomarker-directed Phase II trial in genomically defined subsets of AML, and MDS patients with high levels of RARα gene expression (clinicaltrials.gov. NCT03875796).