Pharmacodynamic and pharmacokinetic evaluation of SY-1425 (tamibarotene) in biomarker-selected acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) patients

Dale Bixby1, Carlos E. Vigil2, Jose Noriega3, Rachel Cook4, Anna Skerrett2, Colin E. Liberty5, Rachel Vigil3, Gail Roboz5,6, Tamara Moy1, Michael R. McKeown7, Nigel J. Waters2, Kristin Stephens7, Emmanuelle de Sy2,8, David A. Roth9, Eytan Stein1

1University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; 2University of Iowa, Iowa City, IA; 3Columbia University Medical Center, New York, NY; 4Oregon Health Science University, Portland, OR; 5Cleveland Clinic, Cleveland, OH; 6Glake University Medical Center, Durham, NC; 7NOAB Cancer Center, Houston, TX; 8University of Pittsburgh Cancer Institute, Pittsburgh, PA; 9Weill Cornell Medical College, New York, NY; 10Vanderbilt University Medical Center, Nashville, TN. SY-1425 Pharmacokinetics study sponsored by Syros Pharmaceuticals, Cambridge, MA. Memorial Sloan Kettering Cancer Center, New York, NY.

Background
SY-1425 (tamibarotene) is an oral, potent and selective RARα agonist approved previously for the treatment of relapsed/refractory acute promyelocytic leukemia (APL) in Japan. Given preclinical evidence of SY-1425 sensitive AML cell lines and clinical trial experience with SY-1425 in both AML and MDS, SY-1425 is being investigated in a Phase 2 study of biomarker selected non-AML AML and MDS patients. DHRS3 is a direct RARα target gene with rapid and robust mRNA and protein induction in human AML and MDS. A recent study demonstrated that DHRS3 expression is predictive of response to SY-1425 (Bixby et al. 2017, JCO). We present here the first report of SY-1425 plasma levels with DHRS3-based evidence of RARα target engagement from AML and MDS patients enrolled in a Phase 2 study of SY-1425.

Methods
Patients positive for RARA biomarker pathways (RARA, RAR, or both) initiated continuous treatment with SY-1425 at 5 mg/24h in divided doses. Sparse PK was collected twice on day 1 and twice on day 15. PD was sampled before the first dose and at 4 hours (T4) and 8 hours (T8) after dosing and before day 15. DHRS3 expression was assessed by qPCR in PBMCs (lymphocytes, monocytes, neutrophils). 39 evaluable patients were based on day 1 of cycles 1 and 5 steady state exposure. In 19 PD evaluable patients, upregulation of DHRS3 at 5 hours had a greater than 2 fold increase in SY-1425 plasma levels from pre-dose to post-dose. 8 hours post first dose of SY-1425 in evaluable patients with evidence of RARA target engagement.

Conclusion
In a biomarker-selected AML and MDS patient population, SY-1425 agonism of RARα causes strong transcriptional upregulation of DHRS3 target gene, consistent with SY-1425 induced RARα pathway activation. The regimen of SY-1425 achieves plasma exposures sufficient to elicit a PD response with direct evidence of RARα target engagement.

Clinical trial design for SY-1425-201 (NCT02807558)

Demographics of 45 patients enrolled in Study SY-1425-201, including 36 evaluable for PK and 39 evaluable for PD.

• No significant accumulation or reduction in exposure after two weeks of SY-1425 at 6 mgBID.

Results
• Robust mechanism based target engagement in SY-1425 and MDS. SY-1425 is 3 evaluable patient samples.
• Induction seen in patients positive for RARA, RARα, and both biomarkers who achieved anticipated plasma exposures (prior to dose administration) and upregulated DHRS3 expression in myeloid cell subsets.

Conclusions
• AML and MDS patients treated in Study SY-1425-201 achieved anticipated SY-1425 drug exposures based on this initial PK evaluation, consistent with those observed in prior Japanese clinical studies.
• No significant accumulation or reduction in SY-1425 exposure after two weeks of dosing, consistent with favorable PK/PD relationship in comparison to historical data with ATRA.
• AML and MDS patients treated with SY-1425 demonstrated RARα target engagement as measured by robust DHRS3 upregulation that persisted in the majority of patients. SY-1425 was seen across subgroups: AML, MDS, RARα and RARβ biomarker positive patients.
• Downstream functional impact of target engagement, including CDD8 induction, could be assessed in a 3 day ex vivo assay measuring myeloid differentiation. SY-1425-201 enrollment is ongoing, with a target of 100 patients anticipated to provide complete PK/PD analysis.