Abstract 1032P

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

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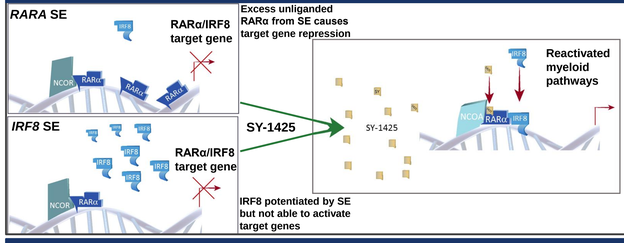
Abstract

Background: SY-1425 (tamibarotene) is an oral, potent and selective synthetic RARα agonist previously approved for the treatment of relapsed/refractory acute promyelocytic leukemia (APL) in Japan. Given preclinical evidence of SY-1425 sensitive AML cell lines and patient samples with RARA pathway activation defined by elevated RARA or IRF8, SY-1425 is being investigated in a Phase 2 study of biomarker selected non-APL AML and MDS patients. DHRS3 is a direct RARα target gene with rapid and robust mRNA upregulation in both AML blasts and PBMCs in response to SY-1425. Here we present the first report of SY-1425 plasma levels with DHRS3 based evidence of RARα target engagement from AML and MDS patients enrolled in the Phase 2 study (NCT02807558).
Methods: Patients positive for RARA pathway biomarkers (RARA, IRF8, or both) initiated continuous treatment with SY-1425 at 6 mg/m2/day 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 5-8 hours post dose on day 1 and once on day 15. DHRS3 expression was assessed by qPCR in PBMCs.
Results: PK data in 16 patients showed SY-1425 plasma levels were consistent with those observed in Japanese APL patients based on day 1 Cmax and day 15 steady state exposure. In 19 PD evaluable patients, upregulation of DHRS3 at 5-8 hours had a greater than 2-fold increase in 84% (16/19). Induction was consistent for AML and MDS, including patients positive for RARA, IRF8, or both biomarkers. DHRS3 expression remained elevated after 15 days of continuous treatment in evaluable patients. Using a parallel exploratory *ex vivo* flow cytometry assay from screening samples, SY-1425 induced differentiation and blast reduction that was correlated with biomarker status.
Conclusion: In a biomarker-selected AML and MDS patients with evidence of RARA pathway activation, SY-1425 agonism of RARα causes strong transcriptional upregulation of DHRS3 target gene, consistent with SY-1425 induced differentiation through myeloid gene activation. The dosing regimen of SY-1425 achieves plasma exposures sufficient to elicit a PD response with direct evidence of RARα target engagement.

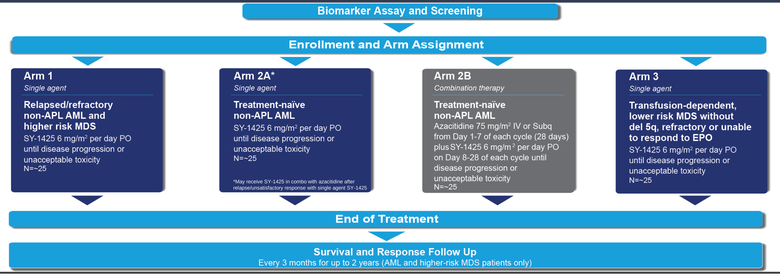
Model of RARA pathway activation by super-enhancer formation and SY-1425 response



SY-1425 agonism of RARα activates target genes for transcription

- Binds excess unliganded RARα and promotes RARα mediated target gene expression
- Enables IRF8 DNA interactions and potentiation of IRF circuits

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



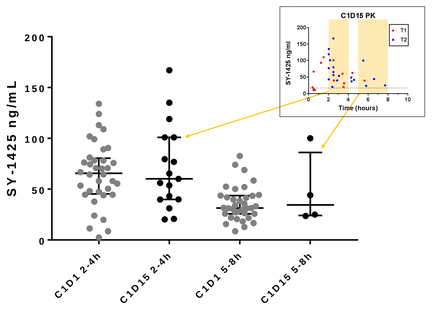
Treatment with SY-1425 6mg/m² BID achieves anticipated exposure in AML and MDS patients

Current Demographics

Category	N=45
Age (y)	
Mean (SD)	74 (12)
Median [Min, Max]	76 [34, 93]
Gender (%)	
Male	27 (60)
Female	18 (40)
Diagnosis (%)	
Relapsed/refractory AML	19 (42)
Relapsed/refractory HR MDS	8 (18)
Transfusion dependent, LR MDS	18 (40)
Prior Tx lines	
1	13 (29)
2	7 (16)
3	6 (13)
4+	11 (24)
Missing	8 (18)
IPSS-R (MDS only) (%)	N=26
Very high	3 (12)
High	5 (19)
Intermediate	3 (12)
Low	15 (58)
Very low	0 (0)

Data as of 8/24/2017

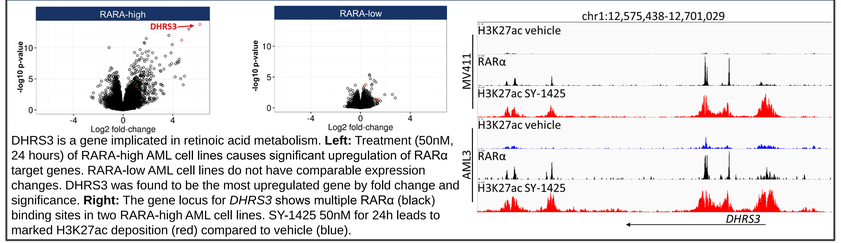
Similar D1 and D15 exposure



Methods:
Only monotherapy patient data were available for analyses. C1D1 SY-1425 PK samples were collected between 2-4h and 5-8h post first dose of SY-1425. On D15, two samples were collected from each patient at least 2h apart for sparse sampling. To allow for comparison to C1D1 data, only D15 data points within 2-4 and 5-8 h windows are presented. Graph plots the median and interquartile ranges. See inset for all D15 datapoints at Time 1 (T1) and Time 2 (T2) which are 2h apart for each patient.

- Demographics of 45 patients enrolled in Study SY-1425-201 (above), including 36 evaluable for PK and 39 evaluable for PD.
- PK at day 1 and steady state showed SY-1425 plasma levels consistent with prior Japanese clinical trial experience (Tobita et al, Blood 1997 90:967-973; Amnolake® label; and Syros data on file).
- No significant accumulation or reduction in exposure after two weeks of SY-1425 at 6 mg/m2 BID.

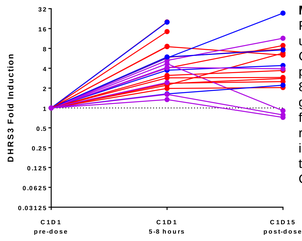
DHRS3 is a SY-1425 dependent measure of RARα target engagement



DHRS3 is a gene implicated in retinoic acid metabolism. **Left:** Treatment (50nM, 24 hours) of RARA-high AML cell lines causes significant upregulation of RARα target genes. RARA-low AML cell lines do not have comparable expression changes. DHRS3 was found to be the most upregulated gene by fold change and significance. **Right:** The gene locus for *DHRS3* shows multiple RARα (black) binding sites in two RARA-high AML cell lines. SY-1425 50nM for 24h leads to marked H3K27ac deposition (red) compared to vehicle (blue).

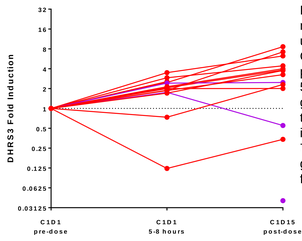
DHRS3 PD assay from patient PBMCs shows target engagement following SY-1425 treatment

R/R AML and HR MDS



AML and HR MDS: The DHRS3 PD marker shows upregulation at C1D1 5-8 hours post dose with 88% (21/24) greater than two fold. 83% remained strongly induced at greater than 2 fold at C1D15.

LR MDS

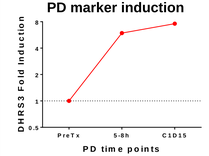


LR MDS: The DHRS3 PD marker shows upregulation at C1D1 5-8 hours post dose with 50% (7/14) greater than two fold. This increased to 79% (11/14) at greater than 2 fold at C1D15.

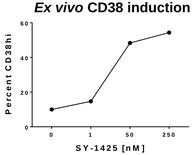
- Robust mechanism based target engagement in R/R AML, HR MDS, and LR MDS in 39 evaluable patient samples
- Induction seen in patients positive for RARA, IRF8 or both biomarkers consistent with their role in RARA pathway activation
- In 6 cases, less than 2-fold induction is noted at C1D15 likely a result of early blood draw soon after dose administration (prior to Cmax) in line with time dependence of target induction

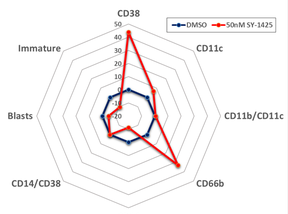
Ex vivo differentiation that supports target engagement can lead to myeloid differentiation

PD marker induction



***Ex vivo* CD38 induction**





Left: DHRS3 is robustly induced in peripheral blood samples from a patient (105-006) treated with SY-1425 6mg/m² BID showing target engagement. **Center:** Base line peripheral blood sample from screening of the same patient (105-006) treated *ex vivo* for 72 hours with SY-1425 shows dose dependent induction of CD38, an RARα target gene and marker of maturation (quantification done with flow cytometry). CD38 induction beings to plateau at 50nM in this patient. **Right:** Analysis of additional markers by multi-channel flow cytometry at 50nM shows evidence of SY-1425 mediated myeloid differentiation.

Ex vivo work done in collaboration with Notable Labs (https://notablelabs.com/)

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 reported in prior Japanese clinical studies.
- No significant accumulation or reduction in SY-1425 exposure after two weeks of continuous dosing, consistent with favorable PK properties 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.
- Similar PD was seen across subgroups: AML and MDS, RARA and IRF8 biomarker positive patients.
- Downstream functional impact of target engagement, including CD38 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.

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