RARA Pathway Activation Biomarkers in Study SY-1425-201 Define a New Subset of AML and MDS Patients and Correlate with Myeloid Differentiation Following Ex Vivo SY-1425 Treatment

Carlos E. Vigil1, Joseph Juricic2, Azra Razvi2, Rachel Cook3, Dale Bixby4, Mikkel Sekeres1, David Rizzieri5, Eytan Stein5, Robert L. Redner6, David Steensma7, Gail Roboz1, Michael Savona1, Michael McKeown1, Chris Fiore2, Angela Volkert2, Curran Murphy2, Kristin Stephens2, David A. Roth2, Emmanuelle di Tomaso2, Jorge Cortes1

1University of Iowa, Iowa City, 2Columbia University Medical Center, New York, 3Oregon Health Science Center, Portland, 4University of Michigan Comprehensive Cancer Center, Ann Arbor, 5Cleveland Clinic, Cleveland, 6Duke University Medical Center, Durham, 7Memorial Sloan Kettering Cancer Center, New York, 8University of Pittsburgh Cancer Institute, Pittsburgh, 9 Dana-Farber Cancer Institute, Boston, 10Weill Cornell Medical College, New York, 11Vanderbilt University Medical Center, Nashville, Tennessee

Abstract

Background: We developed an ex vivo approach to profile the gene regulatory landscape of primary AML/MDS patient samples. A novel patient subset defined by RARA pathway activation was identified by super-enhancer (SE) activity in the RARA and IRF8 enhancer. These results were supported by an enhanced separation of biomarker positive and negative patients, suggesting the current cutoff.

Methods: A Clinical Trial Assay (CTA) was developed and Initial FDA Investigational Device Exemption approval for patient enrollment in the Phase 2 study, SY-1425, was obtained. Data from 152 patients (70% AML, 30% MDS) were analyzed for enrichment of SEs present in the RARA and IRF8 gene enhancers of the RARA and IRF8 promoters. The positivity cutoff used was determined using function models characterized by SY-1425 response and retrospective analyses of patient expression data. Use of this positivity cutoff was established using three independent methods: 1) ex vivo differentiation of primary cell lines into microarray enrichment of SEs by SY-1425 treatment, 2) ex vivo differentiation of primary cell lines into microarray enrichment of SEs by SY-1425 treatment, and 3) ex vivo differentiation of primary cell lines into microarray enrichment of SEs by SY-1425 treatment.

Results: Out of 152 patients screened (~70% AML, ~30% MDS), an overall biomarker positive rate of 37.2% was found. Both groups showed similar rates of each biomarker: RARA positive (70%), IRF8 positive (30%), CD38 positive (30%, 7%, and 5%) and RARA/IRF8 double positive (4%, 8%, and 1%). This result shows that the positivity cutoff was established using three independent methods characterized by SY-1425 response and retrospective analyses of patient expression data. Use of this positivity cutoff was established using three independent methods: 1) ex vivo differentiation of primary cell lines into microarray enrichment of SEs by SY-1425 treatment, 2) ex vivo differentiation of primary cell lines into microarray enrichment of SEs by SY-1425 treatment, and 3) ex vivo differentiation of primary cell lines into microarray enrichment of SEs by SY-1425 treatment.

Conclusions: A second approach used an algorithm for scoring differentiation and a negative biomarker patients showed significant differences in degree of differentiation responses to SY-1425. A novel patient subset defined by RARA pathway activation was identified by super-enhancer activity in the RARA and IRF8 enhancers. These results were supported by an enhanced separation of biomarker positive and negative patients, suggesting the current cutoff.

Abstract

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

Clinical trial assay for RARA pathway screening in peripheral blood

Ex vivo analysis of patient samples supports biomarker cut-off in current trial

Example of output from RARA+ patient

Biomarker status associated with myeloid differentiation response

Conclusions

- Syrsys has developed a biomarker assay for AML and MDS patient screening based on preclinical super-enhancer analyses, to evaluate RARA-pathway activation in peripheral blood

- The biomarker test is a qPCR based assay that evaluates RARA and IRF8 gene expression with a rapid turnaround time of less than 3 days on average to report results.

- Evaluation of 201 patients screened for entry into Study SY-1425-201 (evaluable as of 8/31/2017) demonstrated an overall positive biomarker test result in 40% of patients with AML and MDS, and IRF8 expression was consistently one of the most predictive markers in AML and MDS, with expectations from preclinical studies and analyses of historical databases.

- Biomarker test results (positive vs. negative) were significantly associated with differentiation of patient blood samples following ex vivo treatment with SY-1425, suggesting the clinical utility of the biomarker test for patient selection.

- CD38, a marker of myeloid differentiation and target of anti-CD38 directed therapies, is strongly induced following SY-1425 treatment in patient samples ex vivo, and in mouse xenografts in vivo compared to ATRA or vehicle controls. SY-1425 treatment with SY-1425 treatment, suggesting the clinical utility of the biomarker test for patient selection.

- Conclusions: A second approach used an algorithm for scoring differentiation and a negative biomarker patients showed significant differences in degree of differentiation responses to SY-1425. A novel patient subset defined by RARA pathway activation was identified by super-enhancer activity in the RARA and IRF8 enhancers. These results were supported by an enhanced separation of biomarker positive and negative patients, suggesting the current cutoff.

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

- Clinical trial assay for RARA pathway screening in peripheral blood

- Ex vivo analysis of patient samples supports biomarker cut-off in current trial

- Conclusions: A second approach used an algorithm for scoring differentiation and a negative biomarker patients showed significant differences in degree of differentiation responses to SY-1425. A novel patient subset defined by RARA pathway activation was identified by super-enhancer activity in the RARA and IRF8 enhancers. These results were supported by an enhanced separation of biomarker positive and negative patients, suggesting the current cutoff.

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

- Clinical trial assay for RARA pathway screening in peripheral blood

- Ex vivo analysis of patient samples supports biomarker cut-off in current trial

- Conclusions: A second approach used an algorithm for scoring differentiation and a negative biomarker patients showed significant differences in degree of differentiation responses to SY-1425. A novel patient subset defined by RARA pathway activation was identified by super-enhancer activity in the RARA and IRF8 enhancers. These results were supported by an enhanced separation of biomarker positive and negative patients, suggesting the current cutoff.