SY-1425, A POTENT AND SELECTIVE RARA AGONIST, REPROGRAMS AML CELLS FOR DIFFERENTIATION ALONG DISTINCT LINEAGES, UNCOVERING PD MARKERS FOR CLINICAL STUDIES

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Abstract

SY-1425 is a potent and selective RARA agonist with favorable PK properties approved in Japan for the treatment of R/R APL, which is characterized by fusions between RARA and other transcription factor genes. SY-1425 induces differentiation and anti-proliferative effects in non-APL AML preclinical models that have a high dependence on RARA pathway activation. SY-1425 activates target genes as predicted by SY-1425 treatment and using ex vivo patient samples. This presentation will provide an overview of the SY-1425 mechanism of action.

Results:

1. RARA pathway activation defines a subset of AML patients

2. The enhancer landscape is associated with the AML lineage state

3. AML lineage state is linked to distinct enhancer landscapes

4. Shift in enhancer landscape by SY-1425 indicates AML cell differentiation

5. The gene regulatory circuitry response to SY-1425 in RARA-high AML

Conclusions:

SY-1425 is a potent and selective RARA agonist with favorable PK properties.

Approved in Japan for the treatment of R/R APL, which is characterized by fusion between RARA and other transcription factor genes.

SY-1425 induces differentiation and anti-proliferative effects in non-APL AML preclinical models that have a high dependence on RARA pathway activation.

RARA and IRF8 have a significant role in the gene regulatory circuitry of SY-1425 response.

Differentiation response to SY-1425 is mediated by cell state changes in the TF usage, chromatin, and expression.

Evidence of differentiation found in cell lines, PDX models, and ex vivo patient samples.

A biomarker-directed phase 2 trial (NCT02807558) of SY-1425 is currently ongoing in genomically defined subsets of AML and MDS patients.