SY-1425 (tamibarotene) is an oral, potent and selective RARα agonist. In preclinical models, RARA pathway activation (increased RARA transcript) was associated with activity of SY-1425 in vitro and in vivo, including induction of differentiation, inhibition of proliferation, and apoptosis.

In patients with R/R AML and high-risk MDS who were biomarker-positive for RARA pathway activation, single-agent SY-1425 was generally well tolerated and demonstrated evidence of biological and clinical activity; 43% showed evidence of hematologic improvement and/or marrow blast reductions; myeloid differentiation was observed including CD34-upregulation.

Rationale for Combination with Azacitidine

SY-1425 was evaluated in combination with a hypomethylating agent, azacitidine, in RARA-high and RARA-low cell lines. Evidence of DNA damage and apoptosis was observed in RARA-high cell lines, but not RARA-low cell lines, and to a far greater extent with the combination than either agent alone. The combination also induced deeper and more durable in vivo responses than either agent alone in a preclinical PDX model.

Rationale for Combination with Daratumumab

SY-1425 activates genes associated with myeloid differentiation in AML. SY-1425 activates CD38 expression in preclinical models of RARA pathway activated AML, and is associated with positive clinical activity, safety and tolerability.

Results: Newly Diagnosed Unfit AML (SY-1425 + Azacitidine)

Clinical activity, safety and tolerability

Eight of ten (80%) patients achieved a clinical response (3 PRi, 1 MR, 1 with SD, and 5 who are not yet response-evaluable due to lack of clinical benefit but was confirmed to have a minor response at that time).

Biomarker-Negative Patients

4/4 evaluable biomarker-negative patients had a response, including 1 patient with an IWG response, 2PRi (1 with MR, 1 with SD), and 2 who are not yet response-evaluable.

Biomarker-Positive Patients

6/8 evaluable biomarker-positive patients had a response, including 5 patients with an IWG response and one who is not yet response-evaluable.

1/6 of the responses were first reported at C1D1, including 3/6 IWG responses.

Duration of IWG responses ranged from 29 to 327 days.

Phase 2 Study Design

SY-1425 + daratumumab in biomarker-positive patients with R/R AML and with initial response generally occurring after 4 treatment cycles in the majority of patients with responses.

Conclusions

SY-1425 in combination with azacitidine, in biomarker-positive newly diagnosed unfit AML, shows evidence of clinical activity with a high response rate and a low rate of response discontinuation. SY-1425 in combination with daratumumab continues to enroll and follow patients to further characterize the clinical activity.

SY-1425 treatment in biomarker-positive patients with R/R AML and HR MDS increased CD34 expression in blasts in the majority of patients.

All profile of the combination was consistent with previously reported for single-agent SY-1425 in AML/MDS or single-agent daratumumab in MM patients, with minor differences: All 2 had to be reported in CR, confirmed by another myeloid response (CRi).

All patients had an AE resulting in dose delay; none reported in >1 patient.

Side effects were generally manageable, with moderate and high-risk MDS and 8 patients had an AE resulting in dose delay; none reported in >1 patient.

Significant hematologic toxicities were 3/9 (33%) in patients with an AE resulting in dose delay; none reported in >1 patient.

Most Common AEs, Regardless of Causality (≥ 3 Patients)

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