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POSTER ABSTRACTS

604.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: MYELOID NEOPLASMS

Sgr-2921, a Potent CDC7 Inhibitor, Demonstrates Significant Anti-Leukemic Responses in Patient-Derived AML Models Representing Difficult-to-Treat Disease

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Introduction: Elevated replication stress (RS) is a common feature of many highly proliferative cancers including AML. CDC7 has been shown to activate key components of the RS response, including ATR, and the BRCA1 and cohesin complexes, thereby mitigating accumulation of DNA damage and genomic instability. Inhibition of CDC7 in cancer cells results in an impaired response to RS, leading to accumulation of DNA damage and cell death.
SGR-2921 is a potent inhibitor of CDC7 and a clinical trial to evaluate the safety, tolerability and preliminary antitumor activity of SGR-2921 in patients with AML and MDS is expected to begin in 2023 (NCT 05961839).
We have previously shown that SGR-2921 has potent anti-proliferative activity in 12 out of 16 patient-derived AML samples *ex vivo*. Importantly, 6 out of 6 AML patient samples with mutations in TP53 responded to SGR-2921. Here we show that SGR-2921 results in potent, dose-dependent, anti-leukemic activity in multiple disseminated in vivo AML patient-derived xenograft (PDX) models representing difficult-to-treat disease.
Methods: NOG-EXL mice were inoculated with primary human AML blast cells after sublethal irradiation. Engraftment of human AML blast cells were measured in surrogate mice by flow cytometry using human CD45 vs. mouse CD45 markers. When human CD45 engraftment reached >20% of bone marrow cells in surrogate mice, the study mice were randomized based on weight and dosed with vehicle, SGR-2921 at 3 dose levels or a standard of care agent. SGR-2921 was administered via oral gavage (PO) twice daily in cycles of 5 days of dosing followed by 9 days of no compound dosing over 2 cycles. In a separate study, phosphorylated MCM2 (a direct substrate of CDC7) was measured in the same cohort of mice engrafted with human AML cells following 3 doses of SGR-2921 to determine target engagement.
Results: *In vivo*, SGR-2921 showed strong anti-leukemic activity in the AML PDX models at tolerated doses. Specifically, engrafted AML cells derived from a patient with TP53 mutated AML, a relapsed and refractory patient and a patient with KTM2a rearrangements showed significant and dose-dependent reduction in human CD45 positive AML blast cells. The reduction of blast cells was observed in both peripheral blood and bone marrow. The reduction in human CD45 positive blast cells were associated with an increase in mouse CD45 positive cells. In addition, SGR-2921 demonstrated dose-dependent inhibition of phosphorylated MCM2 in the spinal cord and spleen of the AML PDX models as surrogates of the bone marrow and extravascular compartments, respectively.
Conclusions: Our data show remarkable dose-dependent *in vivo* activity of SGR-2921 in AML PDX models, including in those representing difficult-to-treat disease. Direct inhibition of CDC7 by SGR-2921 in AML blasts was demonstrated by a dose-dependent reduction of phosphorylated MCM2. Together, these data demonstrate that SGR-2921-mediated CDC7 inhibition is an attractive novel treatment opportunity in AML, with potential utility in patients with high risk mutations and relapsed and refractory AML.

Disclosures Izadi: *Schrödinger:* Current Employment. **Wang:** *Schrödinger:* Current Employment. **Atsriku:** *Schrödinger:* Current Employment. **Konst:** *Schrödinger:* Current Employment. **Levinson:** *Schrödinger:* Current Employment. **Piccotti:** *Schrödinger:* Current Employment. **Pirie-Shepherd:** *Schrödinger:* Ended employment in the past 24 months. **Tang:** *Schrödinger:* Current Employment. **Weiss:** *Schrödinger:* Current Employment. **Akinsanya:** *Schrödinger:* Current Employment. **Wright:** *Schrödinger:* Current Employment. **Jensen:** *Schrödinger:* Current Employment.

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