Inhibition of CDC7 with SGR-2921 in AML models results in enhanced DNA damage and anti-leukemic activity as monotherapy and in combination with standard of care agents.

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Introduction
CDC7 is a protein kinase that maintains DNA replication during the cell cycle S-phase by phosphorylating MCM proteins of the DNA helicase complex. CDC7 plays a critical role in the replication stress response by generating a platform for ATR checkpoint signaling and by activating components of the BRCA1-A (MERIT40) and Cohesin complexes (PDS5B), which are critical for protection and restart of stalled DNA replication forks. Inhibition of CDC7 disrupts the ability of cancer cells to overcome replication stress and DNA damage.

Acute myeloid leukemia (AML) is a rapidly proliferating cancer and is characterized by high replication stress and DNA damage.

CDC7 inhibitors, and other agents that target replication stress and DNA damage response pathways, represent novel therapeutic opportunities in AML.

SGR-2921 is a selective and potent inhibitor of CDC7

A potent and selective CDC7 inhibitor, SGR-2921, was identified using Schrödinger’s physics-based computational platform. SGR-2921 is potent in biochemical and biophysical assays and in cell-based target engagement and cell viability assays. SGR-2921 is a low molecular weight inhibitor with good aqueous solubility, as well as desirable cell permeability and kinase selectivity.

SGR-2921 shows potent anti-proliferative activity in AML cell lines

300 cancer cell lines representing various tumor types were screened for sensitivity to SGR-2921. Leukemia was most sensitive to SGR-2921 relative to other cancer types. Within leukemia, AML cell lines were the most sensitive to SGR-2921.

SGR-2921 shows dose-dependent anti-tumor activity and target engagement in the MV-4-11 AML xenograft model

SGR-2921 shows dose-dependent anti-tumor activity and target engagement in the MOLM-16 AML xenograft model

SGR-2921 maintains tumor growth control with intermittent dosing in MOLM-16 CDX model

SGR-2921 demonstrates tumor growth control with intermittent dosing in the MV-4-11 disseminated model

SGR-2921 in combination with Venetoclax shows synergistic effect on cell viability and apoptosis markers in MV-4-11 cells

SGR-2921 in combination with Venetoclax combination is well tolerated and shows robust tumor growth inhibition in MV-4-11 CDX model

SGR-2921 demonstrates synergy with other agents in MV-4-11 cells

Conclusion
- AML models are more sensitive to SGR-2921 treatment relative to other cancer types, possibly due to high replication stress in this cancer type.
- SGR-2921 demonstrates single agent tumor growth inhibition in vivo in multiple AML models at tolerated doses and shows synergistic effects on cell viability in combination with standard of care agents.
- Patient-derived AML samples are sensitive to SGR-2921 independently of genetic drivers and pre-treatment.
- SGR-2921 is active in AML models that are resistant to standard of care agents.

References

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