Discovery of potent, selective, and orally bioavailable GSPT1 degraders and their pre-clinical anti-tumor activity in acute myeloid leukemia and solid tumors

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Introduction

- Molecular glue degraders (MGDs) of neo-substrates that function by hijacking the CRBN E3 ligase have been clinically validated as therapeutics for the treatment of hematological malignancies.
- In particular, MGDs of GSPT1, a translation termination factor, can induce abnormal protein translation termination and subsequent TP53-independent apoptosis in acute myeloid leukemia (AML) cells through activation of the integrated stress response (ISR).
- In addition, the dysregulation of translation termination has been found to be cytoxic specifically to MYC-driven cancer cells.
- Phase 1 clinical trials of three novel GSPT1 MGDs have recently been launched for the treatment of patients with AML and/or MYC-driven solid tumors (NCT02948091, NCT04336982, NCT05546268, and NCT05144334).

In this study, we present novel GSPT1 MGDs and their pre-clinical data in AML and solid tumors.

Results

Discovery of potent and durable GSPT1 MGDs

In vitro anti-leukemic activity

Preferential activity of GSPT1 MGDs in specific solid tumor cell lines

Differential pharmacodynamics of CYRS1542 in lung cancer cells

In vivo anti-tumor efficacy

Conclusion

- CYRS1542, a novel GSPT1 MGD, was identified as a development candidate for the treatment of AML and solid tumors and the INDI-enabling study has been initiated.
- CYRS1542 showed good safety profiles in various normal cells when compared to other known GSPT1 degraders (data not shown).
- CYRS1542 showed strong anti-leukemic and anti-tumor activity with preferential activity against specific cancer types in solid tumors.
- In mouse models of AML and lung cancers, excellent efficacies were observed with good tolerability and significant survival benefit.

Disclosures

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