RS-2023-00282972

Non-clinical development of CYRS1542, a GSPT1 Molecular Glue Degrader, for the treatment of patients with SCLC and AML

Cyrus Therapeutics

ONCOLOGY | **Preclinical**

Product Type	Small Molecule
Indication	Small Cell Lung Cancer (SCLC) and Acute Myeloid Leukemia (AML)
Target	GSPT1
MoA(Mechanism of Action)	**CRBN-dependent GSPT1 degradation / TP53-independent apoptosis through the induction of the Integrated Stress Response** - Cancer cells are generally dependent on transcription and translation processes in order to express elevated levels of oncoproteins - GSPT1, also known as eRF3, acts as a translation termination factor by creating a ternary complex with the ribosome and eRF1. It recognizes a stop codon, facilitating the release of the complete polypeptide chain from the complex - Specific CRBN modulators possess the capability to induce the degradation of GSPT1 via the ubiquitin-proteasome pathway – i.e., GSPT1 molecular glue degrader - GSPT1 degradation leads to a halt in translation termination, activating the Integrated Stress Response (ISR) and subsequently triggering TP53-independent apoptosis
Competitiveness	• **Good to excellent in vitro ADME and safety profiles (e.g., no issues in hERG, AMES, and safety pharmacology panel assays)** • **Favorable safety margin – in normal cells and non-naïve monkeys** • **Stable amorphous solid dispersion formulation identified – excellent PK profiles across species** • **Preferentially effective against highly aggressive neuroendocrine cancers (e.g., SCLC and NEPC)** • **Durable complete responses in mouse CDX models – up to > 3 weeks in H1155 and up to > 7 weeks in HL-60**
Development Stage	Preclinical
Route of Administration	Oral administration

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