Abstract #526282 First-in-human clinical evaluation of ST-01156, an optimized and selective degrader of RNA-binding motif 39 (RBM39): A phase 1 study in advanced solid malignancies with a focus on RBM39-dependent cancers

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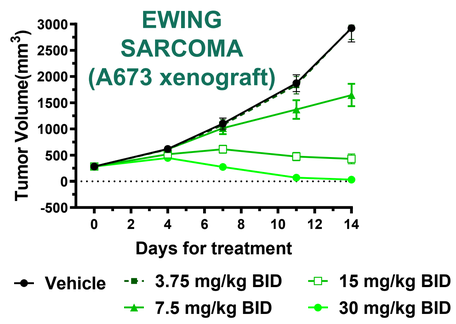
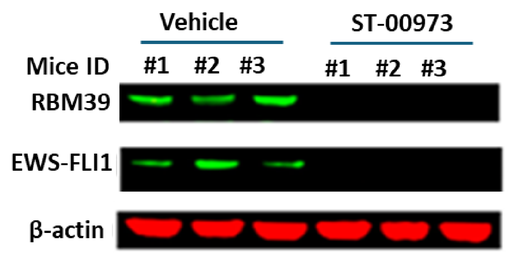
Abstract

Introduction: ST-01156 is a small molecule designed to degrade RBM39, a protein that splices RNA into mRNA and is upregulated in cancer. ST-01156 has entered clinical evaluations for the treatment of several cancer types supported by its novel mechanism of action (MOA) and preclinical data. Lead optimization maximized degradation selectivity, potency, metabolic stability (e.g deuteration) and other drug-like properties. Its potential to achieve meaningful and selective effects is exemplified by complete degradation of RBM39 within hours *in vitro,* accompanied by downstream mis-splicing of pathogenic transcripts, most notably the *EWSR1-FLI1* fusion "driving" Ewing sarcoma (ES). ST-01156 also depletes proteins involved in DNA damage repair (DDR), supporting the potential for synthetic lethality in cancers depending on proficient DDR. In addition, RBM39 regulates KRAS isoforms essential for the proliferation and survival of cancer stem cells, providing a MOA distinct from current KRAS inhibitors. RBM39 is highly expressed in advanced hepatocellular carcinoma (aHCC), acting as an arginine sensor to support oncogenic metabolism. ST-01156 is highly active in PDX models of neuroblastoma, biliary tract carcinoma (BTC), and endometrial carcinoma (EC). Highly proliferative Heme and GI tissues were most susceptible to RBM39 inhibition in preclinical toxicology studies.

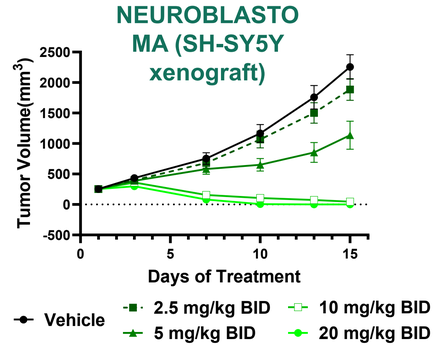
Methods: In this first-in-human study, ST-01156 doses are being adaptively escalated based on the rate and severity of adverse events in subjects with advanced solid malignancies. ST-01156 is administered orally once daily (QD) for 5 days every 7 days, with an option to adapt to a QD schedule. Backfilling of safe dose levels with high priority malignancies is allowed. In addition to safety and tolerability endpoints, dose escalation and Phase 2 dose derivation is based on pharmacokinetic (PK) endpoints and real-time RBM39 targeting measured in peripheral blood mononuclear cells. After an optimal dose is determined from safety, PK and pharmacodynamic data, ST-01156 will be evaluated in the following expansion cohorts: ES, aHCC; *KRAS*-mutant cancers, and an adaptive cohort of cancers projected to be susceptible to RBM39 inhibition including BTC, EC, and cancers with DDR aberrations.

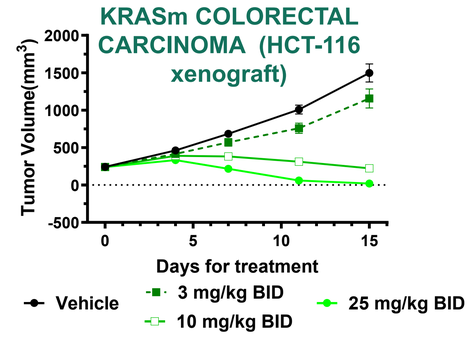
ST-00156: Robust activity against RBM39 dependent cancers





Treatment of human A673 Ewing sarcoma xenograft in NOD/SCID mice with ST-01156 on a twice daily schedule results in tumor regression, with complete regression at 30 mg/kg (left). Mean ± SEM plotted. Western blots of RBM39, EWS-FL1, and β-actin from tumor lysates show complete elimination of RBM39 and the EWS-FL1 fusion protein on day 3 of treatment of A673 Ewing sarcoma xenograft with ST-00937, a nondeuterated precursor of ST-01156, compared to vehicle (right). Measurements with vehicle control and ST-00937 performed in triplicate (3 lanes each).



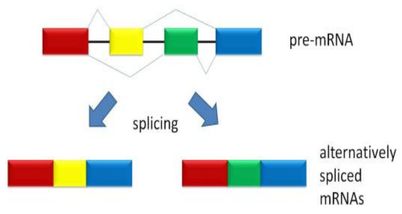


Treatment of human SH-SY5Y neuroblastoma xenograft in NOD/SCID mice with ST-01156 on a twice daily x 5 every 7-day schedule results in tumor regression with complete regression (left). Mean ± SEM plotted. Treatment of HCT-116 KRAS (G13D) mutated colorectal cancer xenograft with ST-00937, a nondeuterated precursor of ST-01156, results in complete regression (right). Measurements with vehicle & ST-00937 performed in triplicate (3 lanes each).

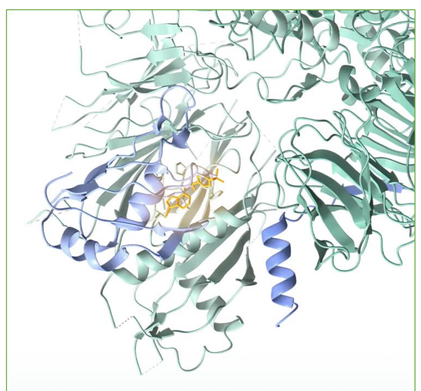
RBM39, critical for RNA splicing and oncogenic proteins in many cancers, is selectively inhibited by ST-01156

BIOLOGY: Why does it matter?

- Master regulator of oncogenic RNA splicing programs essential for tumor survival.
- Splicing machinery is non-enzymatic and historically undruggable.

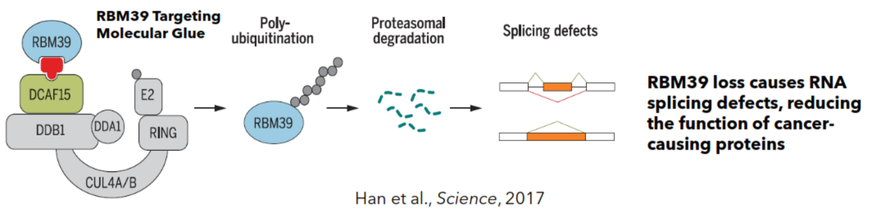


- RBM39 is involved in specific splice site selection, including splicing that generates mature oncogenic fusion proteins, such as Ewing sarcoma EWS/FL1 fusion.



RBM39–DCAF15 complex structure has been solved, enabling discovery of next-generation precision degraders

- RBM39 is degraded by "gluing" to DCAF15 and facilitating its ubiquitarian and degradation.



Han et al., *Science*, 2017

MECHANISM: How does ST-0156 work?

- ST-01156 facilitates molecular glue-mediated degradation via DCAF15, selectively eliminating RBM39.
- ST-01156 Induces lethal mis-splicing in cancer but spares normal cells due to redundancy.
- ST-01156 causes mis-splicing in a small proportion of specific transcripts, indicating that splicing errors are not global, thereby suggesting a potential safety benefit.

VALIDATION: Why is RBM39 as a target and ST-01156 de-risked?

- ST-01156 eliminates the EWS/FL1 fusion, which causes 90% of Ewing sarcoma; treatment results in complete regression in established models of Ewing sarcoma.
- Genetic and pharmacologic degradation of RBM39 drives strong anti-tumor effects.
- Broad dependency across Ewing sarcoma and multiple solid malignancies.

SEED THERAPEUTICS

NCT07197554

Phase 1/Dose expansion clinical study design

OBJECTIVES

- Primary:
  - Characterize the safety and tolerability of ST-01156
  - Determine the optimal dose of ST-01156 and recommend a dose for phase 2 studies (RP2D).
- Secondary
  - Characterize the pharmacokinetics of ST-01156 in real-time
  - Evaluate the effects of ST-01156 on RBM39 levels in PBMCs
  - Detect preliminary antitumor activity.

TREATMENT ARMS AND DOSE ESCALATION SCHEME

- Single-arm, open-label, N = 30–50 adults (age, 18+ for advanced solid cancer or age 16+ for Ewing sarcoma)
- ST-01156 orally on a once daily x 5-day every week schedule with option to modify to a continuous daily dosing schedule
- 3-6 patients/cohort with further expansion at relevant dose levels
- Variable dose escalation increments based on the severity and incidence of adverse events
- Backfilling of prior dose levels with RBM39-dependent cancers (Ewing sarcoma, KRAS mutant, hepatocellular carcinoma, DNA repair aberrant cancers, others [biliary tract, endometrial]).

DOSE EXPANSION DESIGNED TO DETECT AND QUANTIFY ANTITUMOR ACTIVITY

Expansion Cohorts at RP2D

- 6–35 subjects per cohort.
- Simon 2-stage with futility

- **Ewing sarcoma (Age 12+)**
- **Hepatocellular carcinoma (advanced)**
- **KRAS mutant cancer (colorectal, lung, other)**
- **RBM39-dependent cancer (endometrial, biliary tract, DNA repair aberrations, others)**
- **Pediatric dose escalation (Age 12+) (staggered with the adult study)**