Trial in Progress: First-in-Human Study of ATX-559, an Oral Inhibitor of DHX9, in Patients with Advanced or Metastatic Solid Tumors, and Molecularly Defined Cancers

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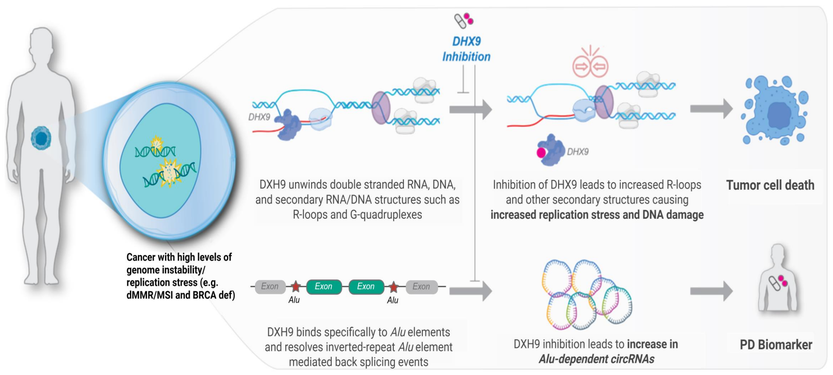
BACKGROUND

DHX9 Mechanism of Action

- DHX9 is a multifunctional RNA helicase that is involved in the maintenance of genomic stability by resolving RNA/DNA secondary structures that otherwise lead to DNA replication stress and DNA damage

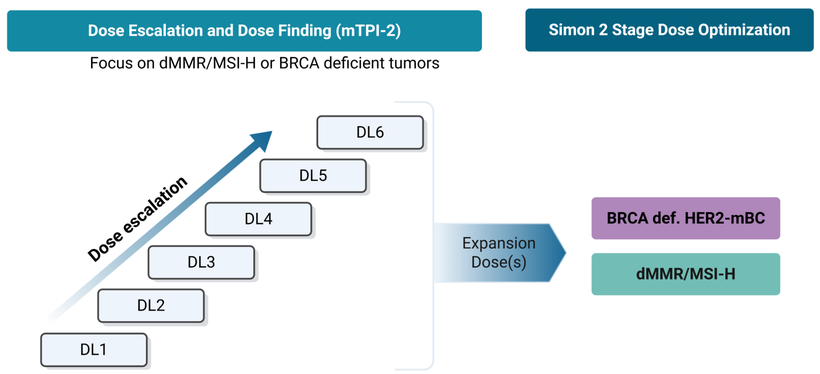


- ATX-559, a novel and selective oral inhibitor of DHX9, has been shown to induce robust anti-tumor activity in preclinical models of solid tumors including models with BRCA deficiency and microsatellite instability-high (MSI-H) and/or deficient mismatch repair (dMMR)
- In preclinical studies, ATX-559 treatment leads to accumulation of R-loops and G-quadruplexes resulting in DNA replication fork stalling and increased replication stress, subsequent DNA damage, and cell death selectively in cancer models with high genomic instability and elevated replication stress (Castro, 2025)

ATX-559 PHASE I CLINICAL TRIAL

Study Design

- This is a first-in-human, Phase 1, open-label, single-arm, dose-escalation and expansion study to evaluate the safety profile of ATX-559 and determine the recommended phase 2 dose (RP2D) in subjects with locally advanced or metastatic solid tumors with genomic instability. including models with BRCA1/2 alterations or deficiency (BRCA deficient) and microsatellite instability-high (MSI-H) and/or deficient mismatch repair (dMMR)



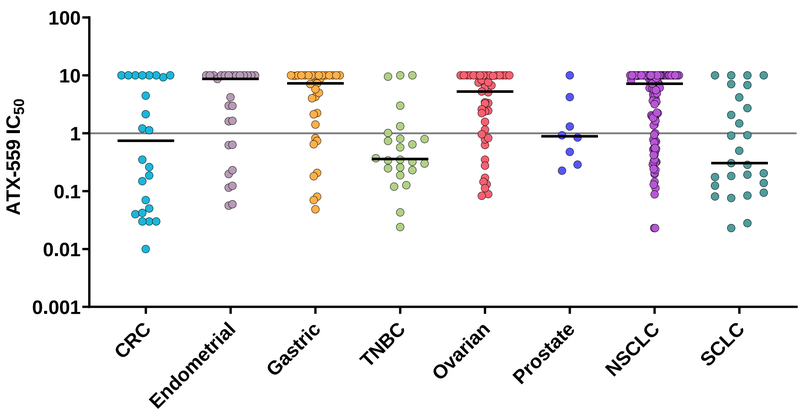
- The study will be conducted in two parts: dose escalation, followed by dose expansion
- Participant enrollment and continuous safety assessment will be guided by a mTPI-2 design (Guo, 2017) to identify an acceptable dose
- To assess evidence of preliminary antitumor activity, a Simon 2-stage design (Simon, 1989) will be used during dose expansion
- A randomized Project Optimus cohort and Biopsy Sub-study are also included in the protocol design

Key Eligibility Criteria

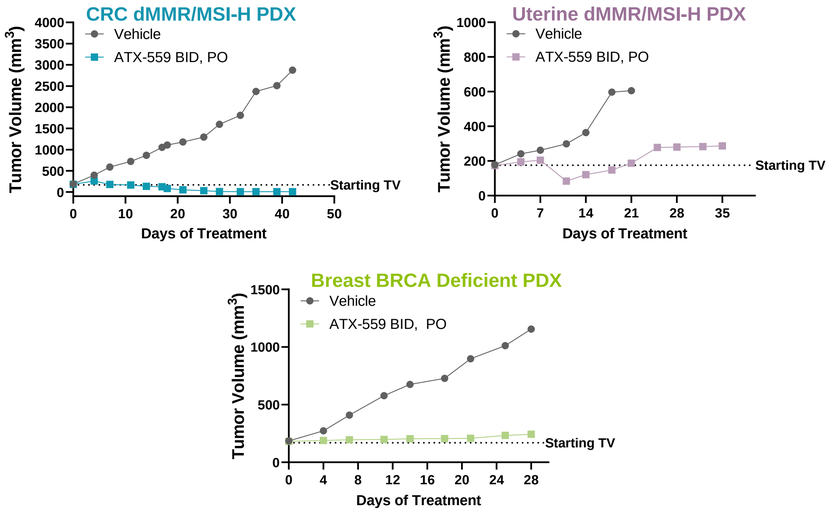
- For dose escalation: adults with histologically confirmed solid tumors who have locally recurrent or metastatic measurable or evaluable disease per RECIST v1.1, enriched for expansion cancer types of interest
- For the expansion cohorts, participants must have histological confirmation and measurable disease of the specified tumor types:
  - **BRCA 1 or 2 deficient, HER2 negative metastatic breast cancer**
  - **dMMR or MSI-H with unresectable or metastatic solid tumor**
- Refractory to or relapsed after all standard therapies with proven clinical benefit, unless refused; no limit to lines of therapy
  - Includes PARP inhibitor and endocrine treatment (if appropriate) for BRCA def. breast cohort
  - Includes checkpoint inhibitor and chemotherapy for dMMR/MSI-H solid tumor cohort
- Time since the last dose of prior therapy to treat underlying malignancy (including other investigational therapy):
  - Systemic cytotoxic chemotherapy: ≥ the duration of the most recent cycle of the previous regimen (≥ 2 weeks for all, except ≥ 6 weeks for systemic nitrosourea or mitomycin-C);
  - Biologic therapy (e.g., antibodies): ≥ 3 weeks;
  - Small molecule therapies: ≥ 5 × half-life, excluding hormone ablation
- ECOG 0-1
- Available archival tumor tissue identified
- Adequate organ function
- No concurrent antineoplastic treatment except for allowed local radiation of lesions for palliation (to be considered non-target lesions after treatment) and hormone ablation
- Medical issue that limits oral ingestion or impairment of gastrointestinal function is excluded

ATX-559 Preclinical Validation

ATX-559 Exhibits Robust Anti-Proliferative Activity In Cancer Cell Lines from Multiple Indications



dMMR/MSI-H & BRCA def. Breast PDX Tumors are Sensitive to ATX-559



- ATX-559 is well tolerated *in vivo*, leading to robust and dose dependent tumor growth inhibition and regression in dMMR/MSI-H and BRCA deficient breast patient derived xenograft (PDX) models

Current Status

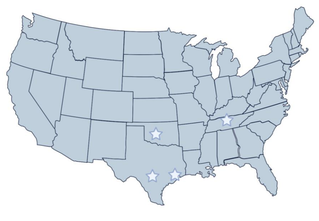
Phase I enrollment is active and ongoing

We see what's next ONCOLOGY — San Antonio, TX

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center — Making Cancer History® — Houston, TX

SCRI Sarah Cannon Research Institute — Nashville, TN

OU Health Stephenson Cancer Center — Oklahoma City, OK



+4 more USA sites

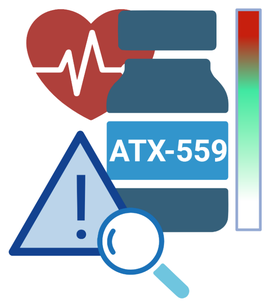
NCT06625515

References

- Castro, J. et al, ATX-559, a First in Class DHX9 Inhibitor, and Targeted Therapeutic for Molecularly Defined Tumors with Genomic Instability and Replicative Stress. AACR. 2025 April; Chicago, IL
- Guo, W. et al., A Bayesian interval dose-finding design addressing Ockham's razor: mTPI-2. Contemp Clin Trials. 2017 Jul;58:23-33.
- Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989 Mar;10(1):1-10.

Study Objective

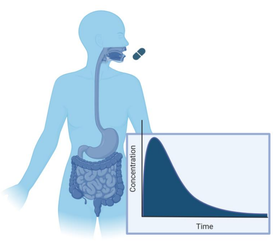
Primary Objectives



- To determine the recommended phase 2 dose (RP2D) and/or maximum tolerated dose (MTD) and to characterize the dose-limiting toxicities (DLTs) of ATX-559 using mTPI-2 to identify a dose that is deemed acceptable
- To evaluate safety and tolerability of ATX-559 at expected pharmacologically active dose(s) and/or schedule(s) by frequency and severity of adverse events (AEs) overall, by grade, relationship to study treatment, time-of-onset, duration of the event and concomitant medications administered

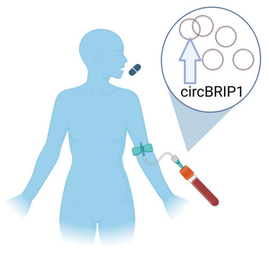
Secondary Objectives

Pharmacokinetics (PK)



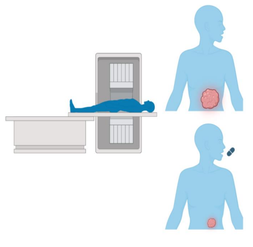
- Maximum observed concentration (C_{max})
- Time to reach maximum observed concentration (T_{max})
- Area Under Concentration-time curve (AUCO-t)

Pharmacodynamics (PD)



- Measurement of circBRIP1 RNA levels in blood over time (target engagement marker produced by DHX9 inhibition in all cells)

Anti-Tumor Activity



- Preliminary antitumor activity endpoints per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)