Trial in Progress: A Phase 1/2 First-in-Human Study of ATX-295, an Oral Inhibitor of KIF18A, in Patients with Advanced or Metastatic Solid Tumors, Including Ovarian Cancer

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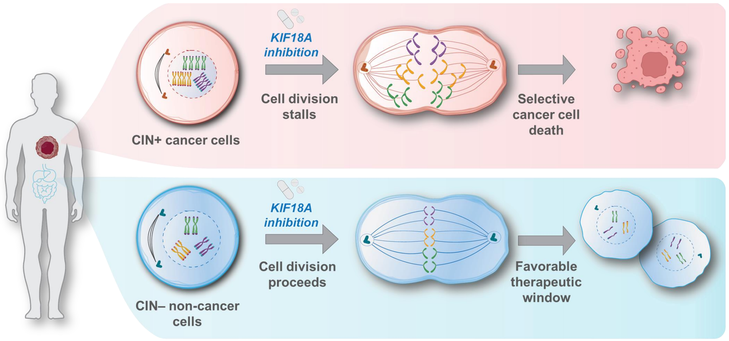
BACKGROUND

ATX-295 Mechanism of Action and Profile

- KIF18A is a plus-end directed kinesin that facilitates chromosome alignment and spindle microtubule dynamics during mitosis
- Cells with ongoing chromosomal segregation defects are vulnerable to disrupted mitosis when KIF18A is lost; thus, KIF18A is a compelling synthetic lethal target in chromosomally instable (CIN+) cancers
- KIF8A inhibition leads to robust anti-proliferative activity solid tumor cell lines, as well as marked anti-tumor activity in *in vivo* models of ovarian, squamous non-small cell lung cancer (sqNSCLC), and triple negative breast cancer (TNBC)



ATX-295 is a proprietary Accent Therapeutics clinical candidate that potently and selectively inhibits KIF18A

Orally bioavailable with clear differentiation vs. competitor inhibitors

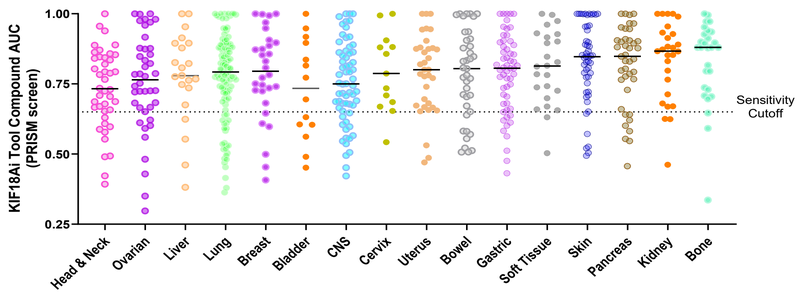
Robust monotherapy activity and therapeutic margins in preclinical models

Highly selective against other kinesins and 98 targets in a safety pharmacology panel

ATX-295 Preclinical Validation

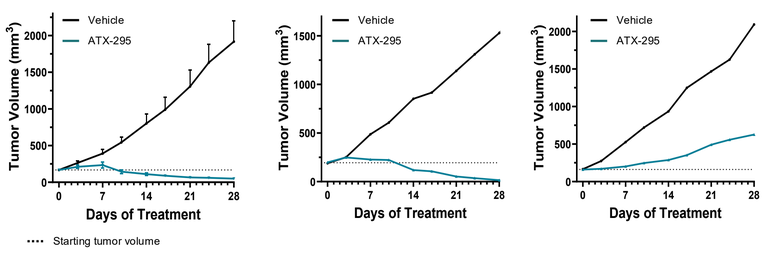
KIF18A offers a large patient impact opportunity across multiple high unmet need indications

PRISM screen with Accent KIF18A chemical matter



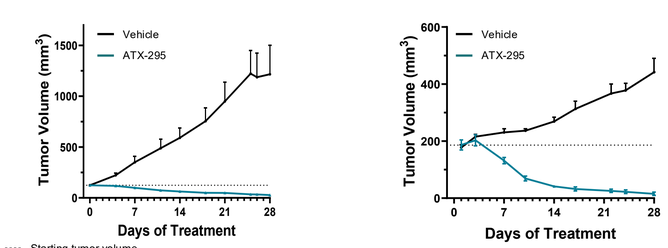
ATX-295 shows robust response in TP53 LOF ovarian CDX and PDX models

OVCAR-3 CDX | **Ovarian PDX**



ATX-295 inhibits tumor growth in TP53 LOF sqNSCLC and TNBC PDX models

sqNSCLC PDX | **TNBC PDX**



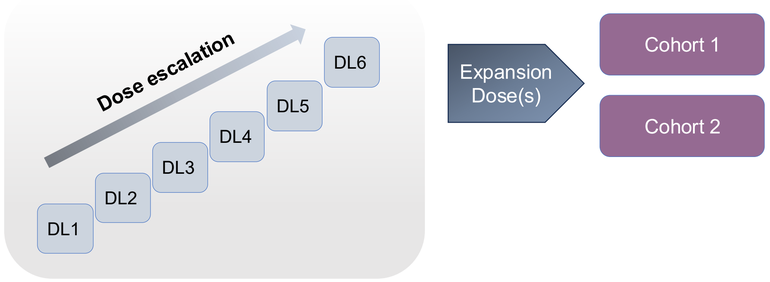
- ATX-295 is well tolerated *in vivo*, leading to robust tumor growth inhibition and regression in ovarian CDX and PDX models, as well as sqNSCLC, and TNBC PDX models

ATX-295 PHASE 1/2 CLINICAL TRIAL

Study Design

- This is a first-in-human, Phase 1, open-label, single-arm, dose-escalation and Simon's 2-Stage expansion study to evaluate the safety profile of ATX-295 and determine the recommended phase 2 dose (RP2D) in participants with Locally Advanced or Metastatic Solid Tumors, including High-Grade Serous Ovarian Cancer

Dose Escalation and Dose Finding (mTPI-2) | **Simon's 2-Stage Dose Optimization**



- 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's 2-stage design (Simon, 1989) will be used during dose expansion
- A 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
- Refractory to or relapsed after all standard therapies with proven clinical benefit, unless refused; no limit to prior lines of therapy
- For the expansion cohorts, participants must have histological confirmation and measurable disease of the specified tumor types:
  - Platinum-resistant, platinum-refractory, or platinum-intolerant HGSOC
- ECOG 0-1
- Available archival tumor tissue identified
- Adequate organ function
- No use of other concurrent anti-cancer treatment, except for hormonal blockade
- No clinically unstable central nervous system (CNS) tumors or brain metastasis
- No clinically significant (i.e., active) or uncontrolled cardiovascular disease
- No medical issue that limits oral ingestion or impairment of gastrointestinal function is excluded
- No use of proton pump inhibitors on study or H2-receptor antagonists for the dose escalation portion of the study
- Able to transition off strong or moderate CYP3A4 inhibitors or strong inducers
- No pregnancy or intent to breastfeed or conceive a child within the projected duration of treatment

Current Status

Phase I enrollment is active and ongoing

Florida Cancer Specialists & Research Institute — Sarasota, FL

The University of Texas MD Anderson Cancer Center — Making Cancer History® — Houston, TX

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

SCRI Sarah Cannon Research Institute — Nashville, TN

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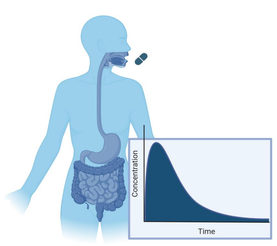
Study Objectives

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-295 using mTPI-2 to identify a dose that is deemed acceptable
- To evaluate safety and tolerability of ATX-295 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

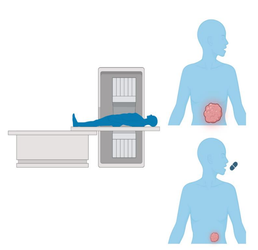
Secondary objectives

Pharmacokinetics (PK)



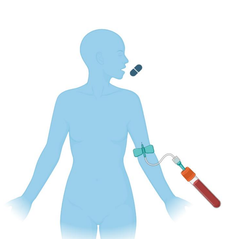
- Maximum observed concentration (C_{max})
- Time to reach maximum observed concentration (T_{max})
- Area under the concentration-time curve (AUC_{0-t})

Anti-tumor activity



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

Pharmacodynamics (PD)



- Measurement and comparison of the levels of pathway PD biomarkers downstream of ATX-295

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