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Activity of the Novel KIF18A Inhibitor, ATX-295, is Enriched in Whole Genome Doubled Ovarian Cancer Pre-Clinical Models

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Disclosure Information

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Presenter: Maureen Lynes (mlynes@accenttx.com)

I have the following relevant financial relationships to disclose:

Employee and shareholder of: Accent Therapeutics

I have no additional financial relationships to disclose.

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KIF18A Kinesin is a Selective Dependency in Chromosomally Instable (CIN) Tumors

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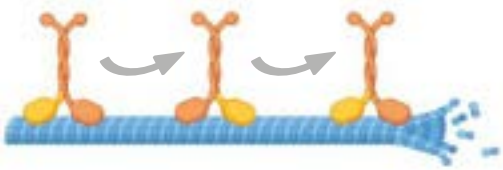
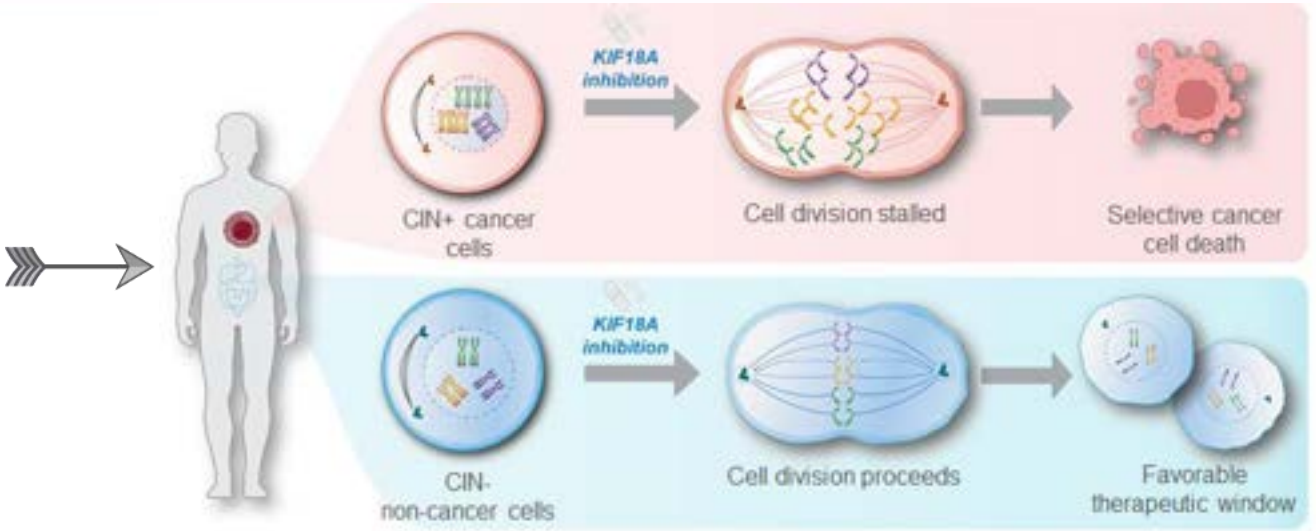
KIF18A is a mitotic kinesin that facilitates chromosome alignment and kinetochore attachment





nature

Aneuploidy renders cancer cells vulnerable to mitotic checkpoint inhibition

nature

Whole-genome doubling confers unique genetic vulnerabilities on tumour cells

ARTICLE

Chromosomally unstable tumor cells specifically require KIF18A for proliferation

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KIF18A: Large Patient Impact Opportunity Across Multiple Indications

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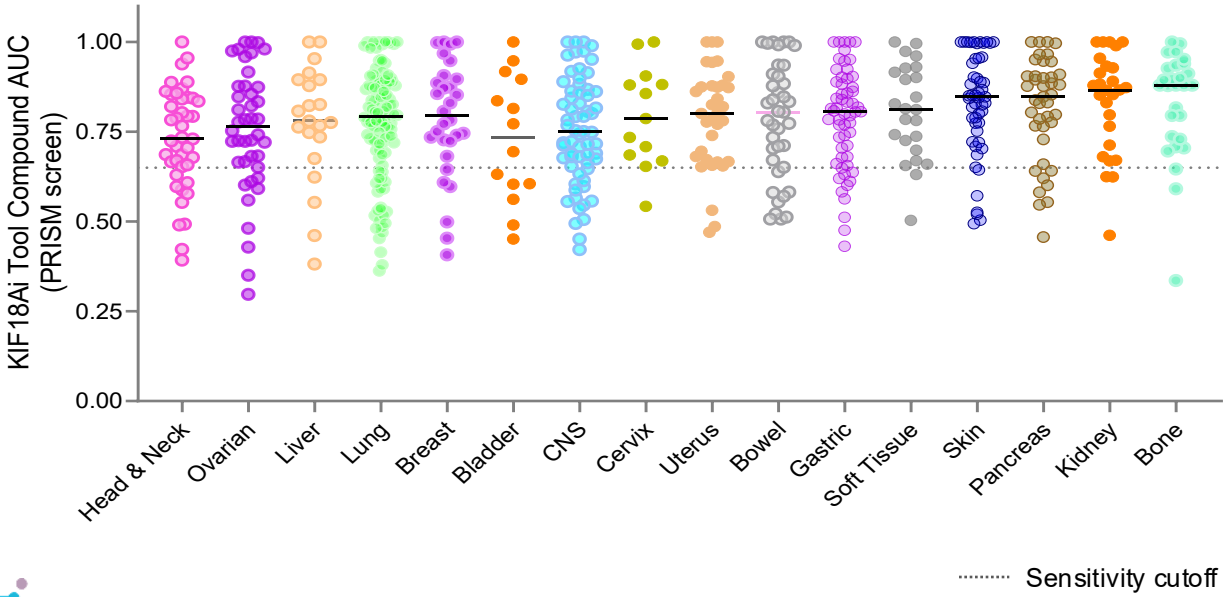
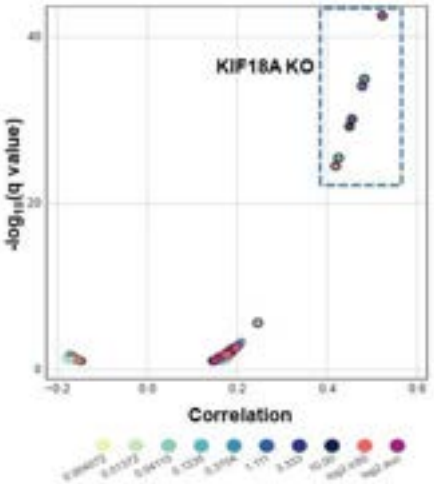
PRISM Screen with Accent KIF18A chemical matter



KIF18Ai Sensitivity Profile is Highly Correlated to KIF18A KO



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ATX-295 is a Potent and Selective Inhibitor of KIF18A

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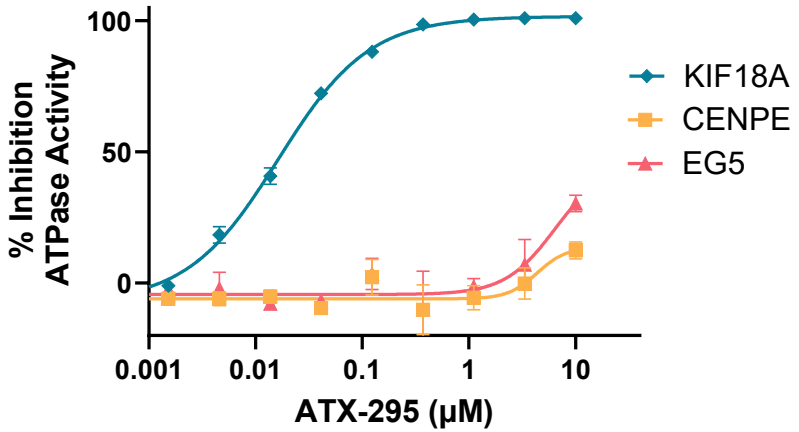

- ATX-295, a proprietary Accent development candidate, inhibits KIF18A biochemical activity with an IC_{50} of 16 nM
- ATX-295 is selective for KIF18A over other mitotic kinesins

Kinesin	KIF18A	CENPE	EG5
IC_{50} (nM)	16	4366	6413

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ATX-295 Selectively Induces Mitotic Arrest and Apoptosis in CIN+ Cells

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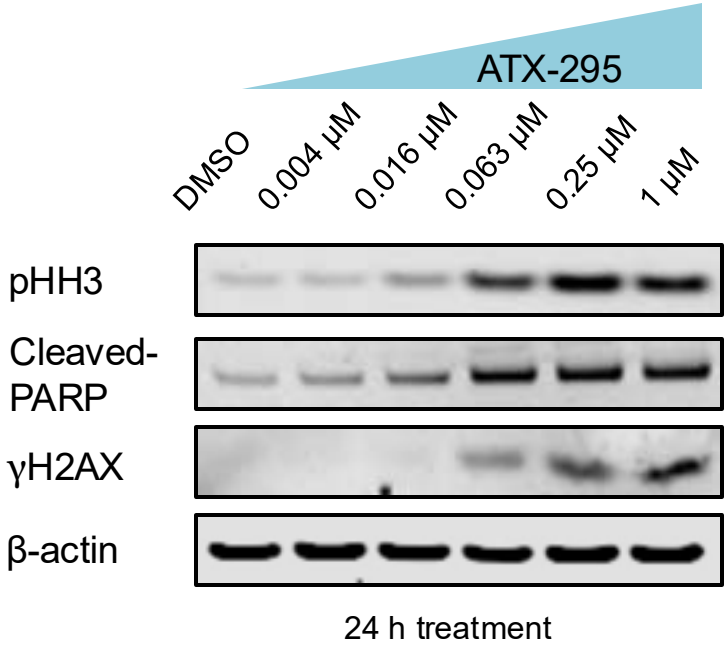
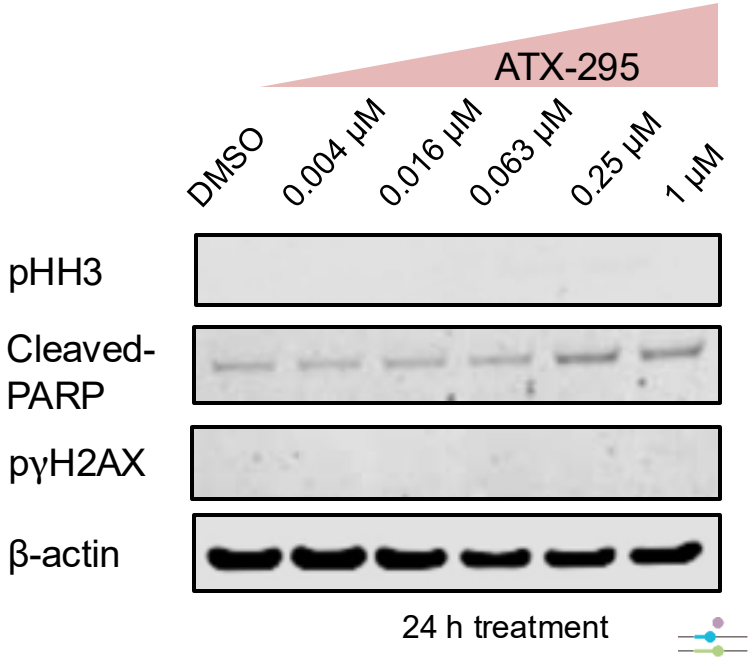
CIN+ OVCAR-3 cells



CIN- A2780 cells



ATX-295 Alters Microtubule Dynamics Leading to Mitotic Catastrophe & Cell Death

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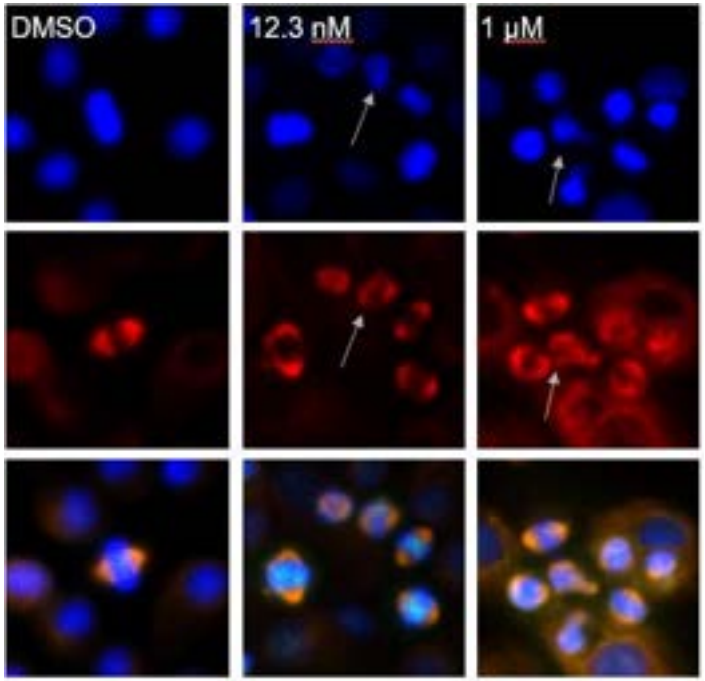
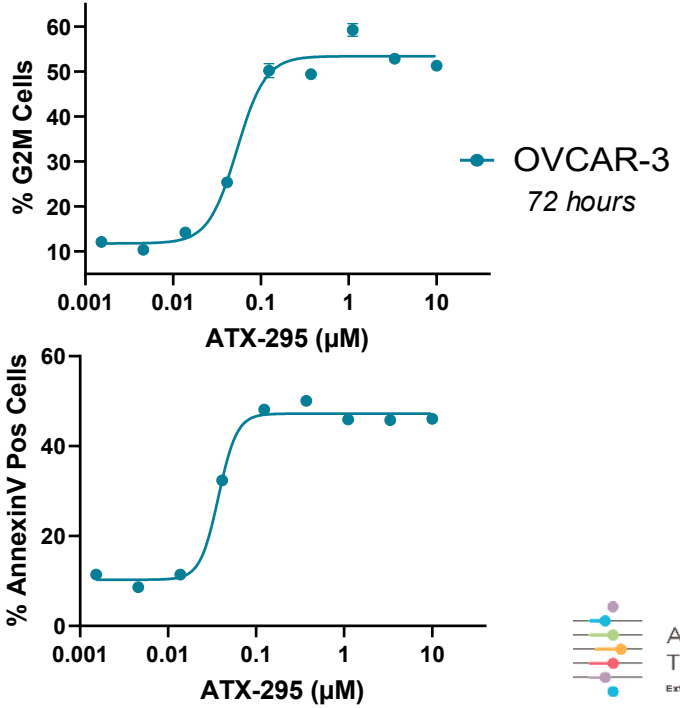
Altered Spindle Dynamics in ATX-295 Treated OVCAR-3 cells



ATX-295, 24 hours

ATX-295 Induces Robust G2M Arrest and Apoptosis



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ATX-295 Exhibits Robust Anti-Proliferative Activity in HGSOC and TNBC Cell Lines

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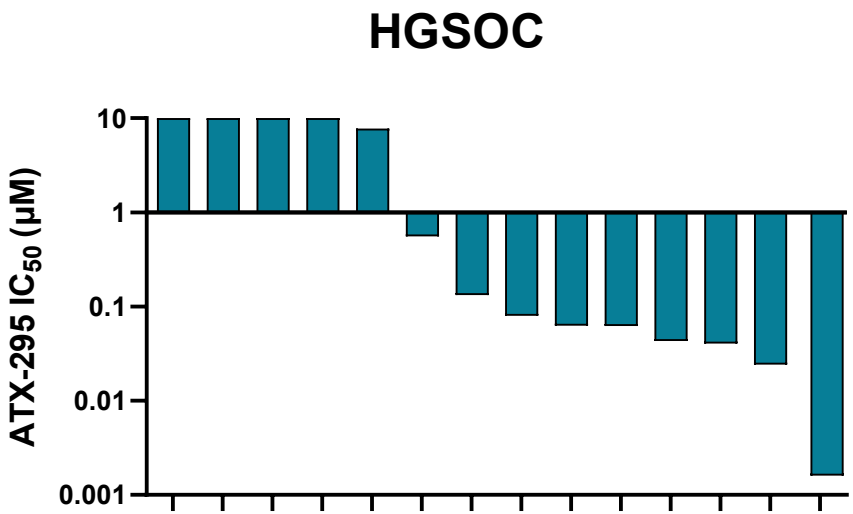

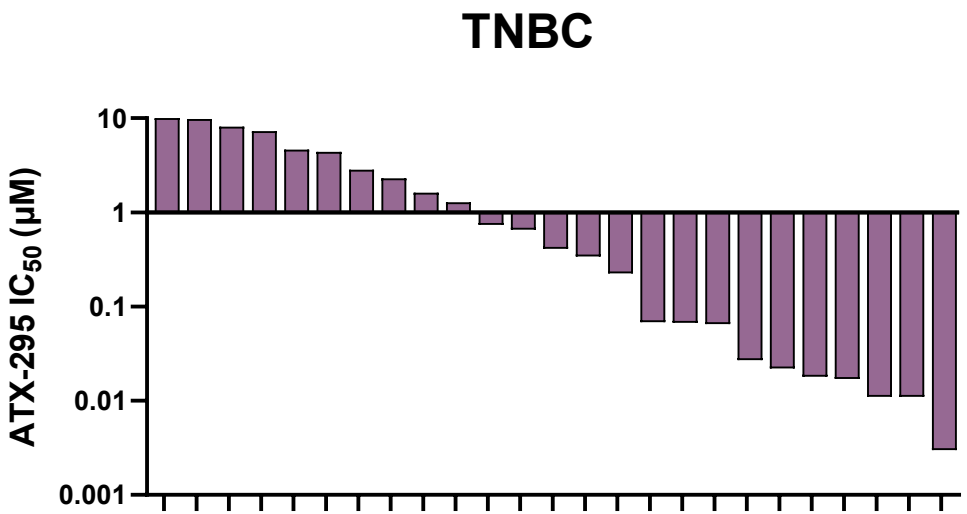

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Chromosomal Instability Can be Inferred from Surrogate Measurements

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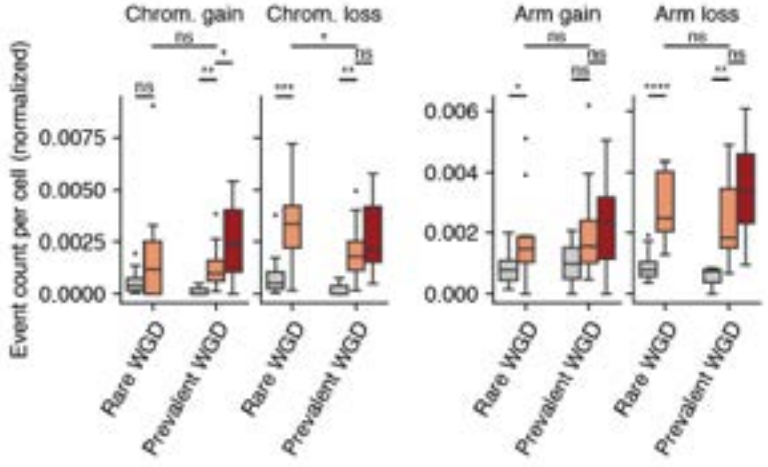
- A subset of CIN tumors is dependent on KIF18A (estimated 20% of solid tumors)
- Surrogates of CIN such as fraction genome altered, aneuploidy score, and whole genome doubling were assessed for their ability to predict ATX-295 sensitivity
- WGD is a prevalent CIN marker in HGSOC[1,2] and in TNBC[2]

WGD+ HGSOC Tumors Exhibit High Rates of CIN Events



[1]McPherson, Shah Biorxiv 2024
[2]Bielski, Nature Genetics 2018

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Correlates of CIN Enrich for ATX-295 Sensitivity in HGSOC & TNBC

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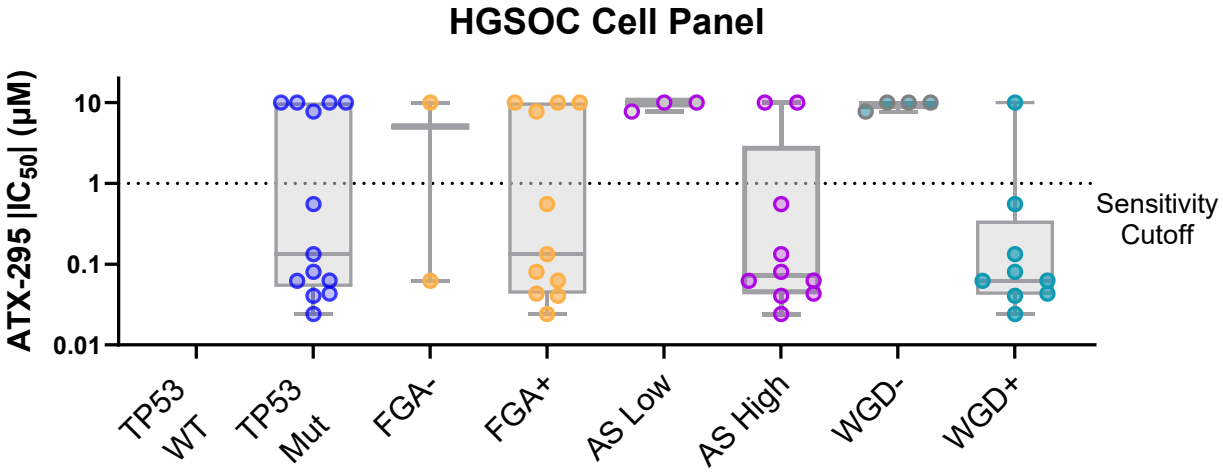

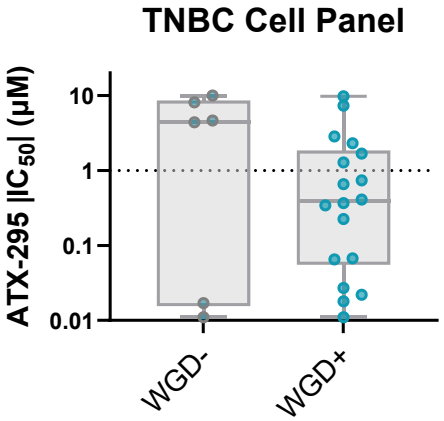

FGA = fraction genome altered
AS = aneuploidy score
WGD = whole genome doubling

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ATX-295 Induces Robust Tumor Growth Inhibition in a WGD+ CDX Model

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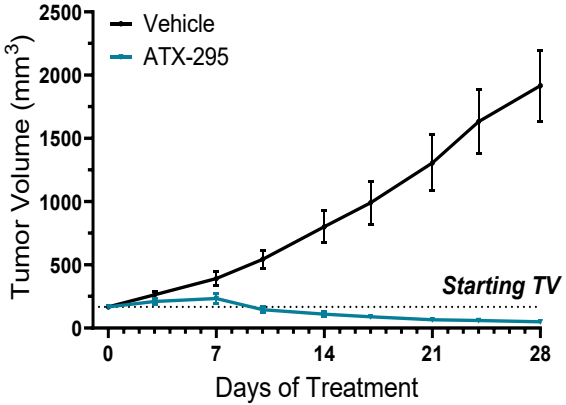
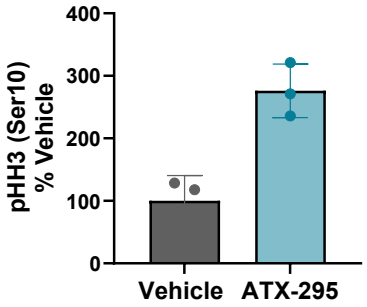
WGD+ Xenograft Model (OVCAR-3)

ATX-295 Leads to Regression in an OVCAR-3 Xenograft Model



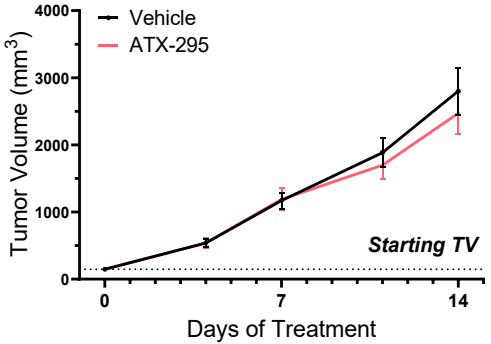
ATX-295 Induces Intratumoral pHH3



ATX-295 treatment well tolerated

WGD- Xenograft Model (OVK18)

Lack of Tumor Growth Inhibition in OVK18 Xenograft Model



Limited activity in predicted insensitive ovarian cancer model; pHH3 not induced

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WGD is Enriched in ATX-295 Responsive Ovarian PDX Models

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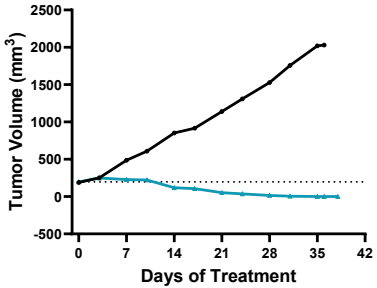
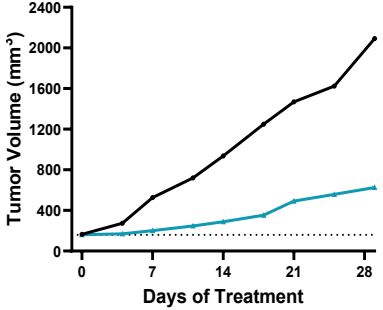
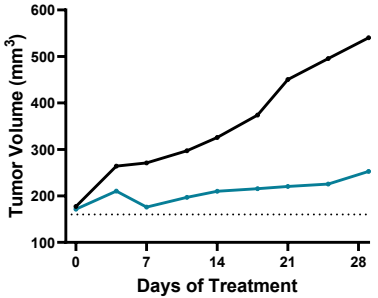
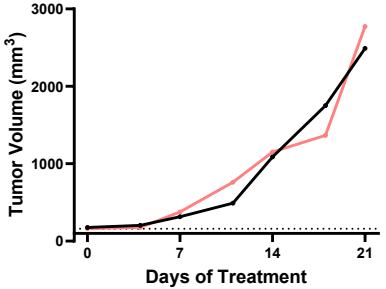
WGD+ Ovarian PDX







WGD- Ovarian PDX



75% of WGD+ PDX models exhibited anti-tumor activity* with ATX-295 treatment (n=18)

- Vehicle
- ATX-295
- Starting Tumor Volume

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*defined as final % ΔT/ΔC <50%

Conclusions

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- A large cell panel screen demonstrates the potential for KIF18A inhibition across multiple solid tumor indications with high CIN, including HNSCC, breast, lung, and ovarian cancer

- ATX-295 is a potent and selective KIF18A inhibitor that induces mitotic arrest, cell death, and anti-tumor activity selectively in CIN+ models

- Whole genome doubling, a CIN surrogate, is predictive of ATX-295 sensitivity, as demonstrated in an ovarian cancer PDX screen

ATX-295 Ph 1/2 Study

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First-in-Human Study of ATX-295, an Oral Inhibitor of KIF18A, in Patients With Advanced or Metastatic Solid Tumors, Including Ovarian Cancer

ClinicalTrials.gov ID NCT06799065

Sponsor Accent Therapeutics

Study Overview

Brief Summary

The goal of this study is to identify a safe and tolerated dose of the orally administered KIF18A inhibitor ATX-295. In addition, this study will evaluate the pharmacokinetics, pharmacodynamics and preliminary antitumor activity of ATX-295 in patients with advanced solid tumors and ovarian cancer.

Detailed Description

ATX-295 is an oral drug that inhibits a protein called KIF18A, an adenosine triphosphate (ATP)-dependent, plus end-directed mitotic kinesin. KIF18A facilitates chromosomal alignment and spindle microtubule dynamics during mitosis in certain advanced solid tumors. ATX-295 has been shown preclinically to induce robust anti-tumor activity of a variety of different solid tumors, including high-grade serious ovarian cancer and triple negative breast cancer.

This is a first-in-human, Phase 1, open-label, single-arm, dose-escalation and Simon 2-Stage expansion study to evaluate the safety profile of ATX-295 and determine the recommended phase 2 dose (RP2D). In addition, the study aims to characterize the PK, PD, and preliminary anti-tumor activity of orally administered ATX-295. Exploratory objectives include examination of biomarker responses in relationship to ATX-295 exposure.

Patients with locally advanced or metastatic solid tumors will be enrolled to preliminarily assess the anti-tumor effect, and further examine the safety and PK of ATX-295 at the RP2D.

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