Potent and Durable Anti-Tumor Activity of the Novel KIF18A Inhibitor, ATX-295, in Preclinical Models of Chromosomally Instable Tumors

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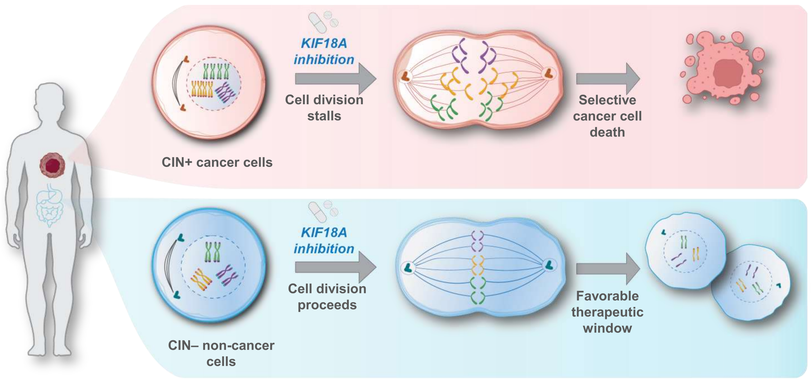
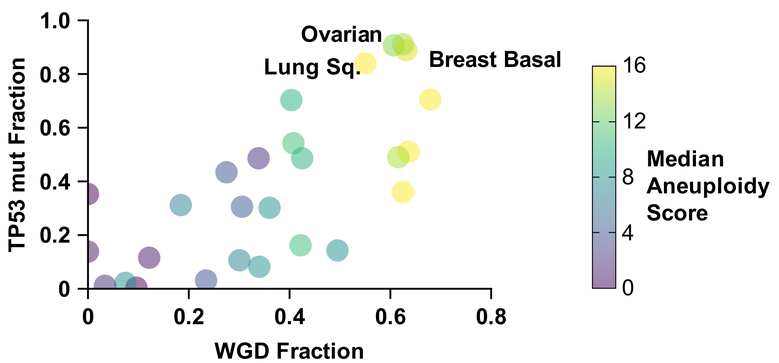
Mitotic Kinesin KIF18A is a Selective Vulnerability in Chromosomally Instable (CIN) Tumors

- KIF18A is a plus-end directed kinesin that facilitates chromosome alignment and spindle microtubule dynamics during mitosis[1]
- 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[2,3,4,5,6]
- A landscape analysis of genetic and genomic CIN correlates across 27 different cancer types from The Cancer Genome Atlas (TCGA) shows high proportion CIN correlates in indications such as ovarian, lung cancer and breast
- ATX-295, a proprietary Accent Therapeutics KIF18A inhibitor currently undergoing clinical testing, potently inhibited proliferation in a panel of high grade serous ovarian (HGSOC), squamous non-small cell lung cancer (sqNSCLC) and triple negative breast cancer (TNBC) cell lines; sensitivity is enriched in cells positive for whole genome doubling, a correlate of CIN
- Mechanistically, ATX-295 induced mitotic arrest, G2/M accumulation, and apoptosis selectively in CIN high ovarian, lung squamous cell carcinoma and triple negative breast cancer cell lines
- ATX-295 treatment induced durable tumor growth inhibition in WGD+ ovarian cancer, sqNSCLC and TNBC PDX models
- These data identify WGD, a CIN surrogate, as a potential biomarker of ATX-295 sensitivity in ovarian cancer models, and further validate KIF18A as a synthetic lethal vulnerability in CIN high tumors



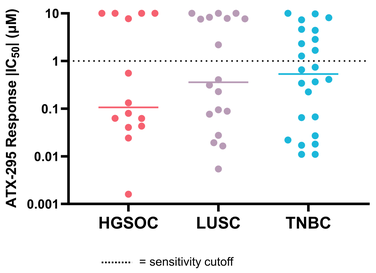
CIN+ Cancers: Large Patient Opportunity Across Multiple Solid Tumor Indications

CIN correlates are Enriched in Ovarian, Lung Squamous and Breast basal-like Cancers (TCGA)



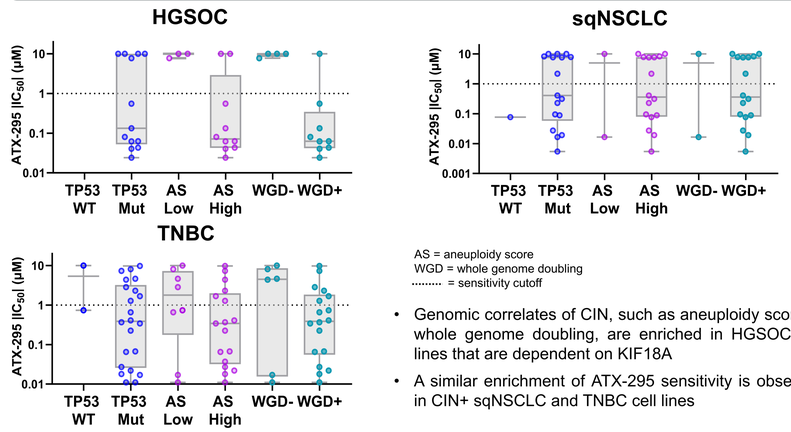
- As both genetic and genomic alterations can contribute to the CIN+ status, we ran a landscape analysis of different CIN correlates across 27 different cancer types from The Cancer Genome Atlas (TCGA)
- Correlates of CIN, such as TP53 mutation, WGD, and aneuploidy score, are highly enriched in several solid tumor indications, such as Ovarian, Lung Squamous Cell Carcinoma, and Breast (basal type)

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



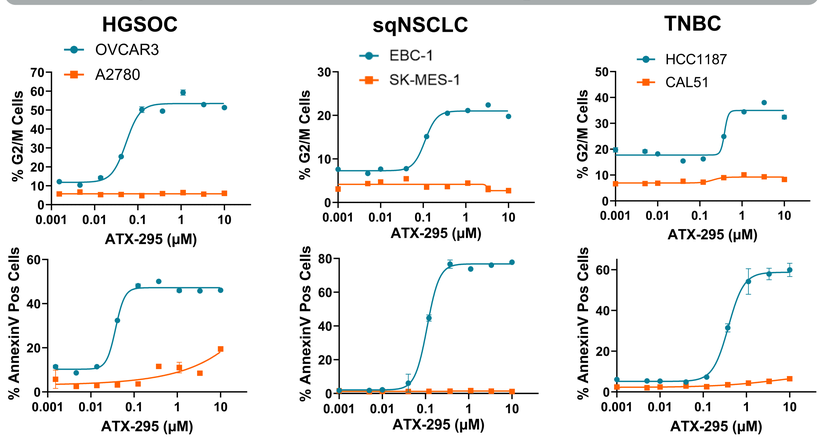
- ATX-295 is a potent and selective proprietary Accent Therapeutics clinical candidate, and inhibits KIF18A biochemical activity with an IC_{50} of 16 nM
- ATX-295 shows robust *in vitro* anti-proliferative activity in multiple indications:
  - 64% (9 out of 14) of HGSOC cell lines are sensitive to ATX-295
  - 56% (10 out of 18) of sqNSCLC cell lines are sensitive to ATX-295
  - 56% (14 out of 25) of TNBC cell lines are sensitive to ATX-295
- These results are consistent with the elevated chromosomal instability observed in HGSOC and TNBC tumors[3]

Correlates of CIN Enrich for KIF18A Dependence in Ovarian, sqNSCLC and TNBC Cell Lines



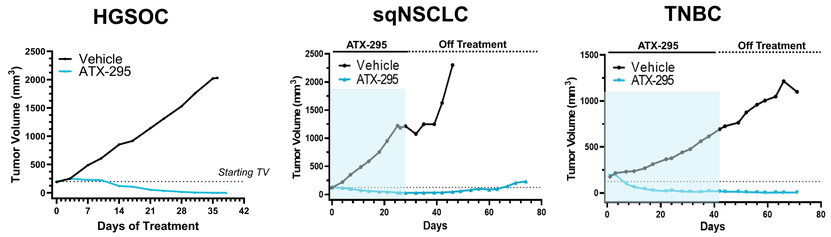
- Genomic correlates of CIN, such as aneuploidy score or whole genome doubling, are enriched in HGSOC cell lines that are dependent on KIF18A
- A similar enrichment of ATX-295 sensitivity is observed in CIN+ sqNSCLC and TNBC cell lines

ATX-295 Alters Microtubule Dynamics Leading to Mitotic Catastrophe and Cell Death in CIN High Cancer Cell Lines



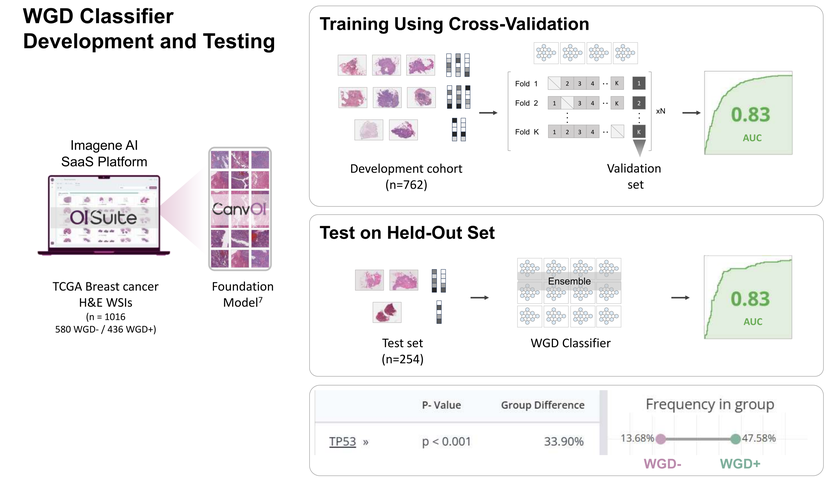
- ATX-295 disrupts mitotic spindle dynamics, leading to dose-dependent cell cycle arrest in mitosis in CIN high OVCAR3, EBC-1 or HCC1187 cancer cells due to dependency on KIF18A for M phase progression
- Cell death by apoptosis is also induced in a dose-dependent manner by ATX-295 treatment of CIN high cancer cells
- A2780, SK-MES-1 or CAL51 cells, which are not dependent on KIF18A, do not exhibit mitotic arrest or apoptosis induction consistent with the lack of dependence on KIF18A in this cell line

ATX-295 Induces Robust Tumor Growth Inhibition in WGD+ PDX Models



- Oral dosing of ATX-295 leads to durable tumor regression in the WGD+ Ovarian, sqNSCLC and TNBC PDX models
- ATX-295 was well tolerated with no significant changes in body weight

Combination of Molecular Pathology and Artificial Intelligence Reveals Opportunities for WGD Detection in Clinical Samples



- The WGD classifier was independently developed and validated within minutes on the OI Suite platform, using a fully no-code workflow, achieving an AUC of 0.83 on a held-out test set
- TP53 mutations were enriched in WGD+ predicted samples, consistent with known biology[3]
- Cross-indication robustness was confirmed by a WGD classifier trained on multi-indication TCGA cohorts, which achieved an AUC of 0.96 on a held-out TCGA ovarian cancer cohort
- These results demonstrate proof-of-concept for AI-based WGD detection in clinical samples

Conclusions

- ATX-295 is a potent and selective KIF18A inhibitor that leads to mitotic arrest and apoptosis due to DNA damage and malformed mitotic spindles in CIN+ cells
- Whole genome doubling, a CIN surrogate, is associated with ATX-295 sensitivity, *in vitro* and *in vivo* as demonstrated in an ovarian cancer, sqNSCLC and TNBC cell line panel and in PDX models
- AI-based detection of WGD from patient H&E-stained tissue slides[8] demonstrates promise as a tool for identifying patients most likely to respond to ATX-295 therapy
- For more info on our current clinical trial, please visit *ClinicalTrials.gov* ID: NCT06799065

Acknowledgements & References

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