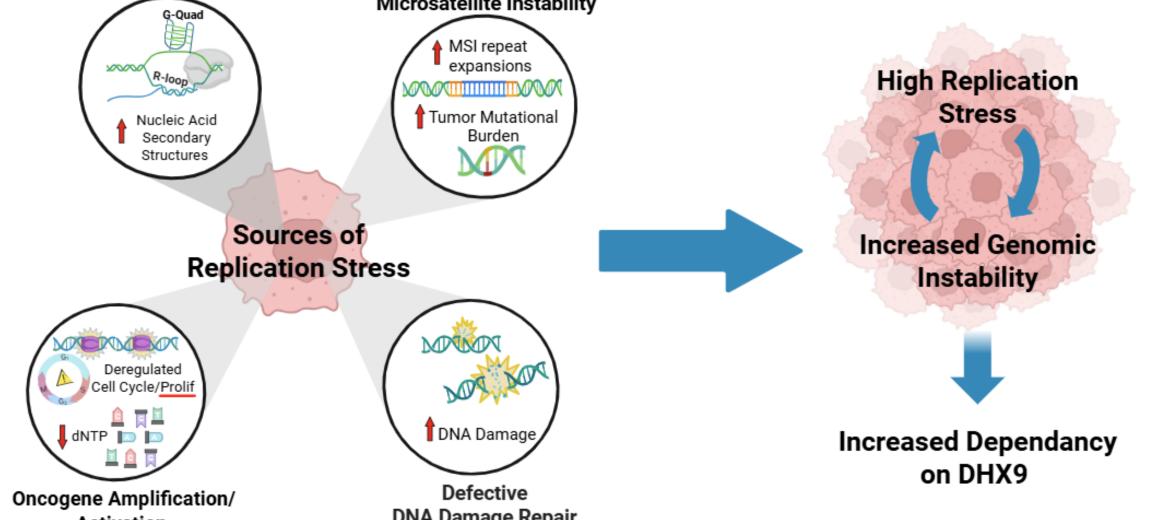
ATX-559, a First-in-Class, Clinical-Stage DHX9 Inhibitor, as a Targeted Therapeutic for Molecularly Defined Tumors with Genomic Instability and Replicative Stress



Sunaina Nayak*, Jennifer Castro*, Monique Laidlaw, Priya Rajaratnam, Maureen Lynes, Stuart Ince, Jason A. Sager & Serena J. Silver

Accent Therapeutics, Lexington, MA / *Presenting Authors

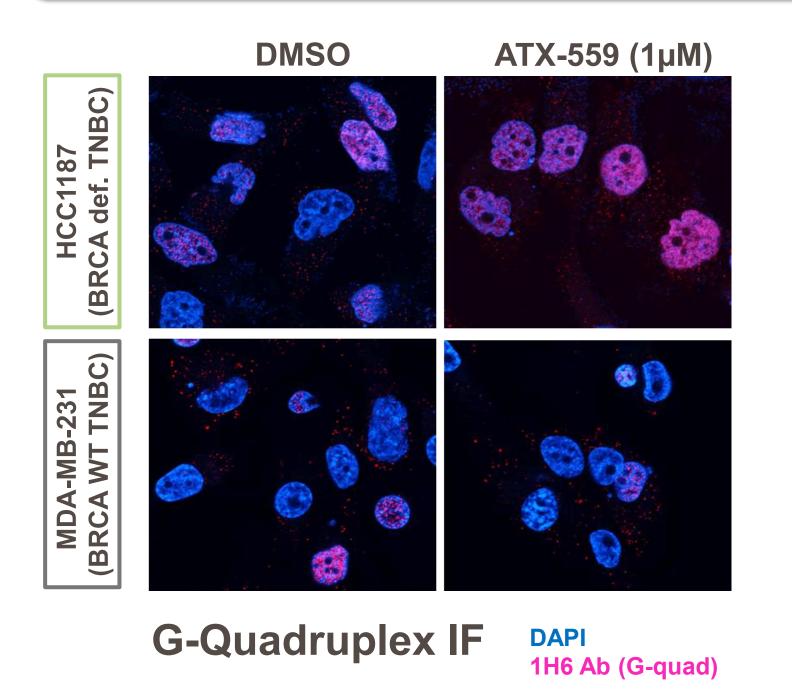
RNA Helicase DHX9 Plays an Important Role in Maintaining Genome Stability

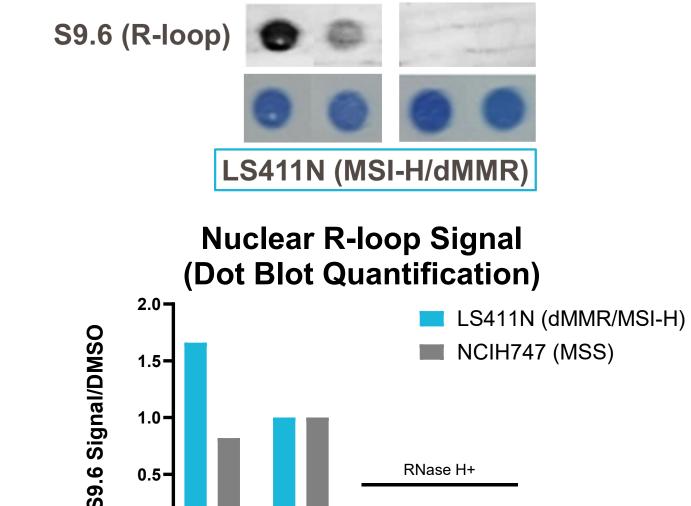


- DHX9 is a multi-functional RNA helicase, and contributes to genome stability by unwinding nucleic acid secondary structures, including DNA/RNA hybrids (R-loops), circular RNA and G-quadruplexes^{1,2,3}
- Selective dependance on DHX9 has been observed in molecularly defined tumors that exhibit genomic instability and elevated replication stress such as through oncogene amplification or defective DNA repair machinery^{4,5}
- We previously demonstrated that DHX9 genetic loss or inhibition by the DHX9 tool compound ATX968 was efficacious in tumors with defective mismatch repair and/or high microsatellite instability (dMMR/MSI-H), alterations in the DDR genes BRCA1 and/or BRCA2 (BRCA) or homologous recombination deficiency (HRD)⁴
- Here we describe ATX-559, a potent, selective, orally bioavailable, small-molecule inhibitor of DHX9 helicase activity currently in clinical development

ATX-559 (1µM)

DHX9 Inhibition by ATX-559 Leads to Selective Accumulation of Aberrant Nucleic Acid Secondary Structures



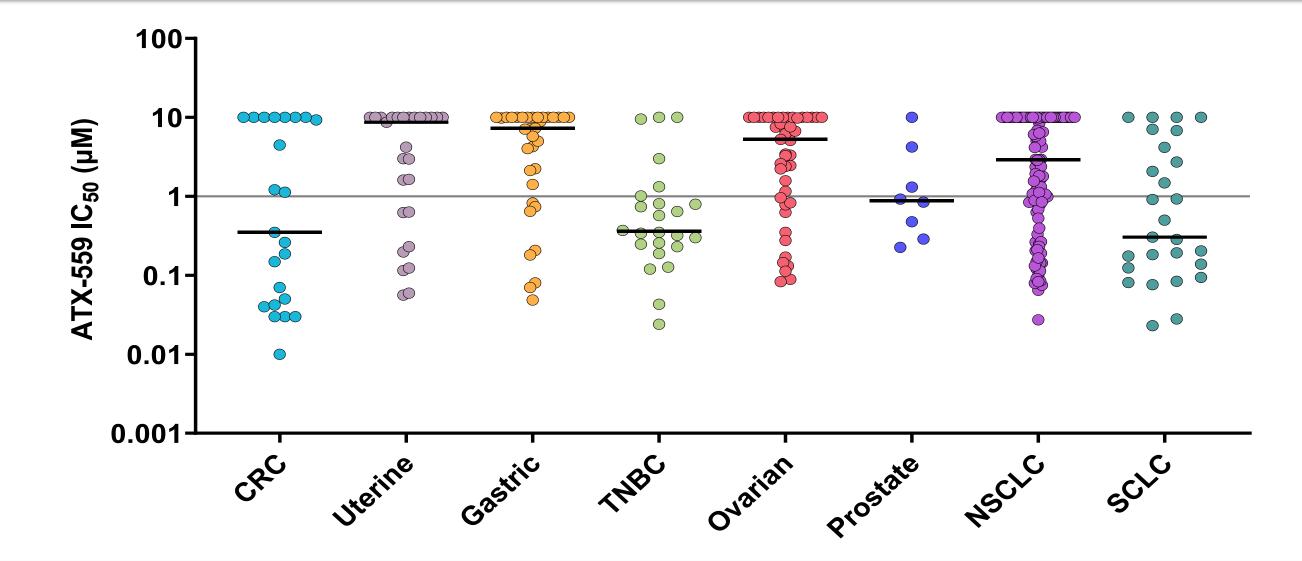


ATX-559 DMSO ATX-559 DMSO

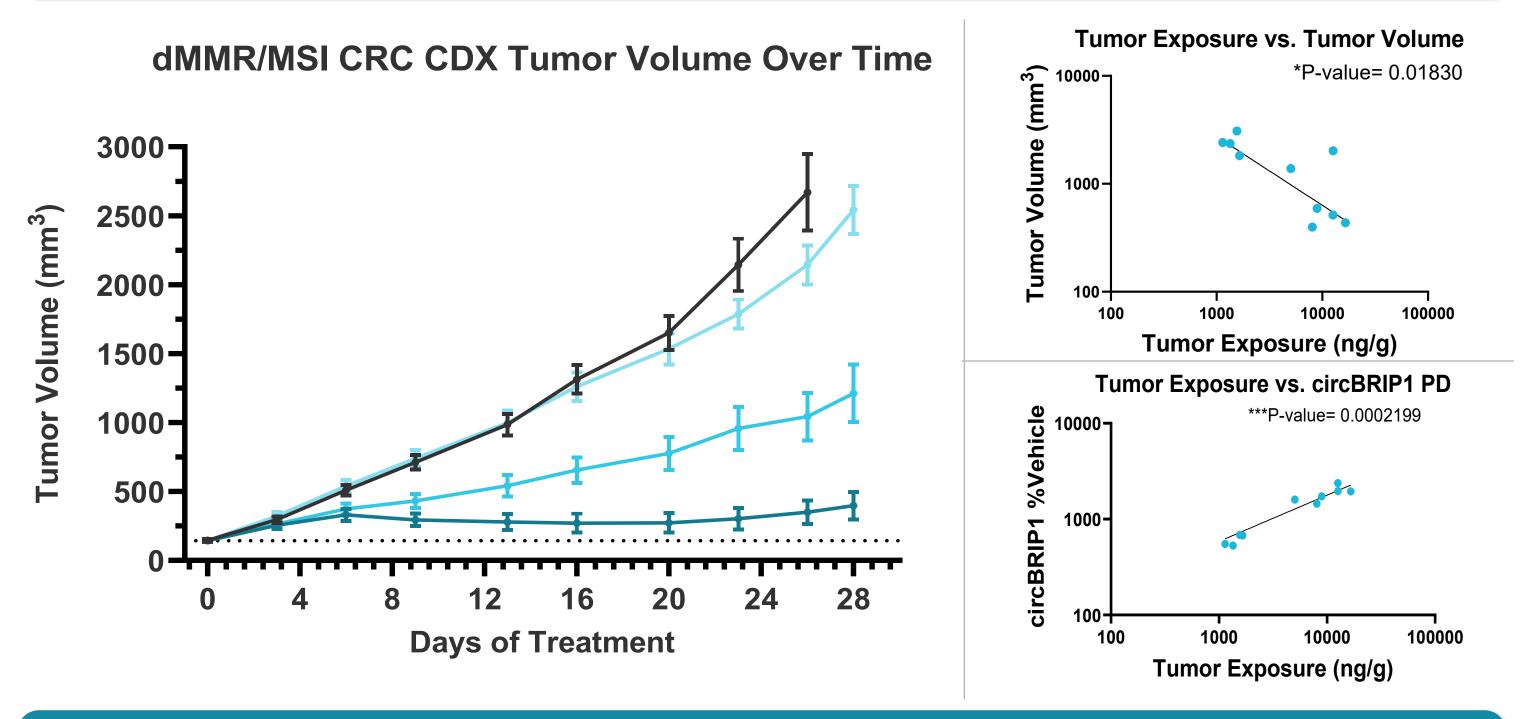
DHX9 Inhibition by ATX-559 Leads to Replication Stress, DNA Damage and Apoptosis



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

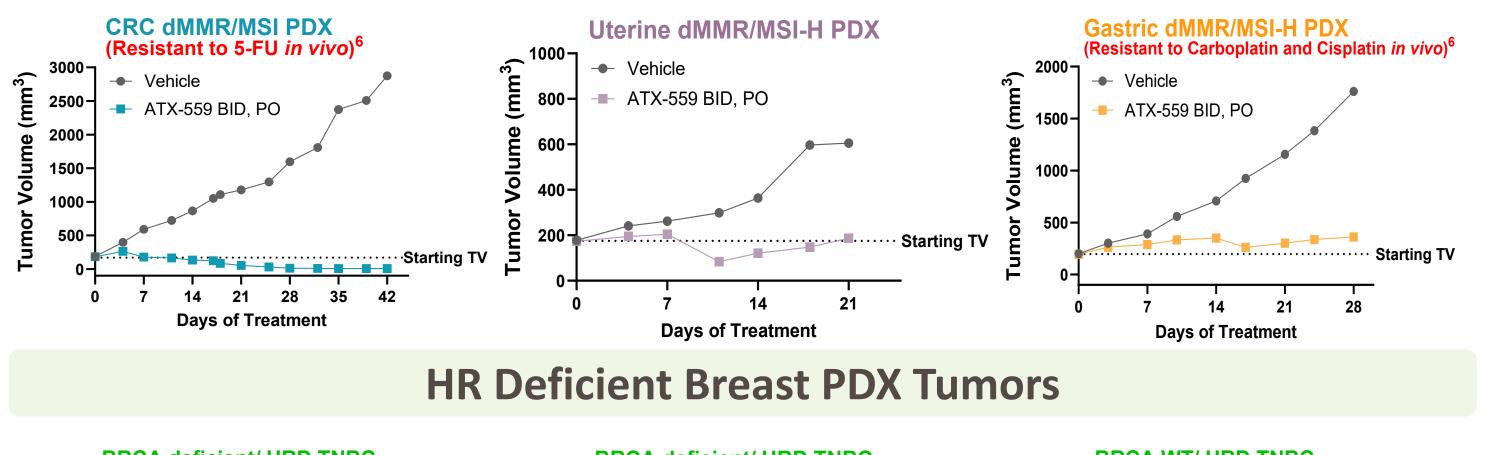


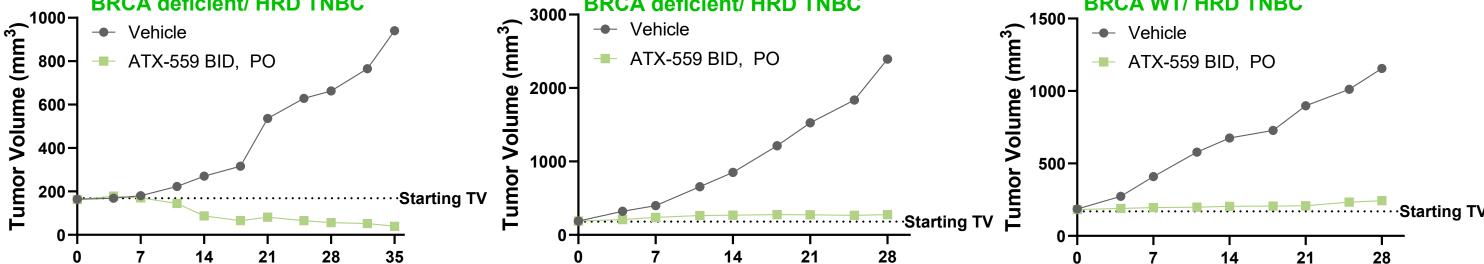
ATX-559 Treatment Shows Dose-Dependent Tumor Growth Inhibition with PK/PD/Efficacy Relationship



ATX-559 Displays Robust Anti-Tumor Activity in a Panel of Patient-Derived Xenograft (PDX) Models

dMMR/MSI-H (CRC, Endometrial and Gastric) PDX Tumors



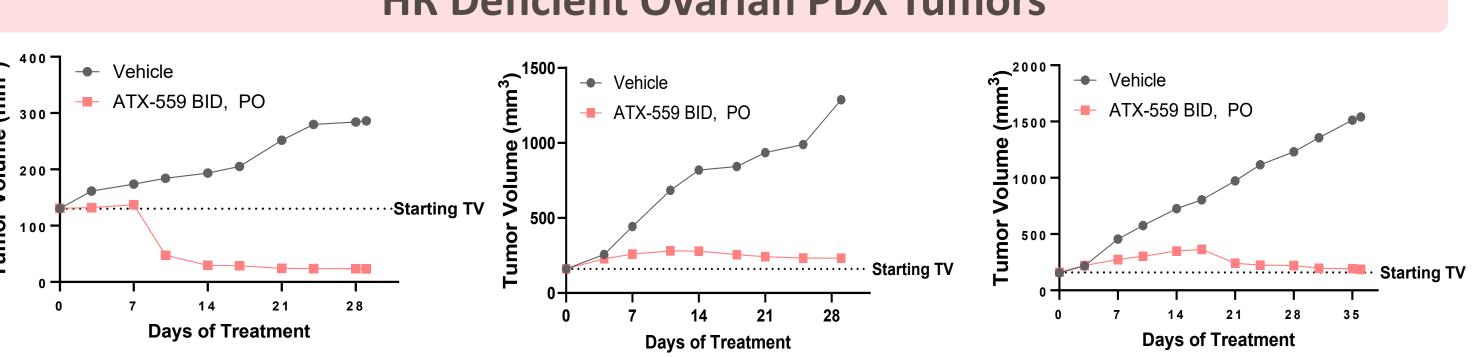


Days of Treatment

Days of Treatment



Days of Treatment



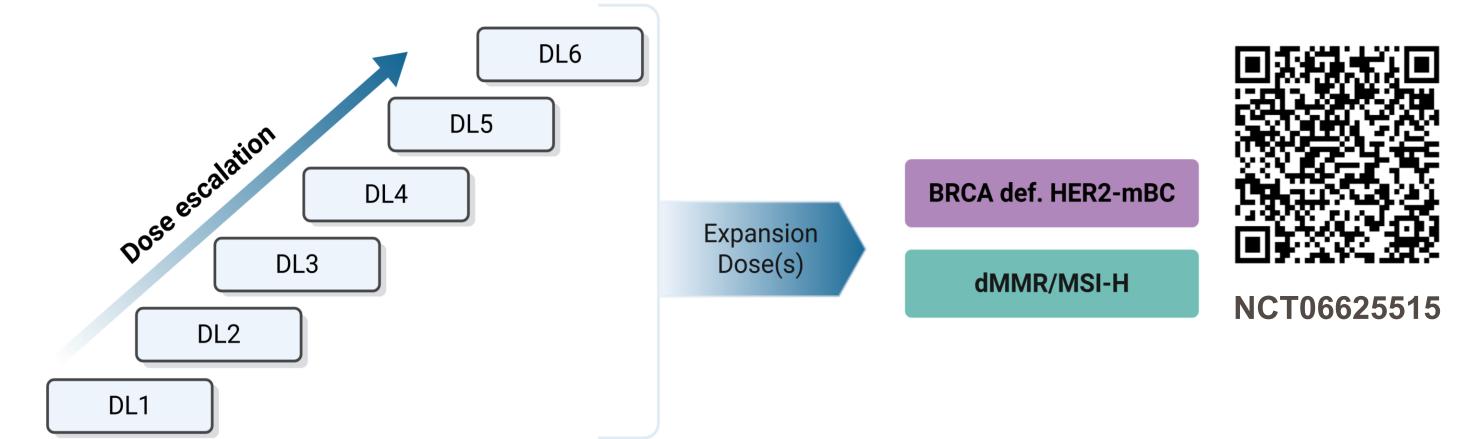
ATX-559 Phase 1 Clinical Trial Design

• 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 instabilityhigh (MSI-H) and/or deficient mismatch repair (dMMR)

Dose Escalation and Dose Finding (mTPI-2)

Simon 2 Stage Dose Optimization

Focus on dMMR/MSI-H or BRCA deficient tumors



- Participant enrollment and continuous safety assessment will be guided by a mTPI-2 design to identify an acceptable dose⁷
- To assess evidence of preliminary antitumor activity, a Simon 2-stage design will be used during dose expansion⁸
- A randomized Project Optimus cohort and Biopsy Sub-study are also included in the protocol design

Summary

ATX-559 treatment leads to robust tumor growth inhibition and regression in dMMR/MSI-H and BRCA deficient/HRD CDX and PDX models

ATX-559 is a first-in-class potent, selective and orally bioavailable inhibitor of DHX9

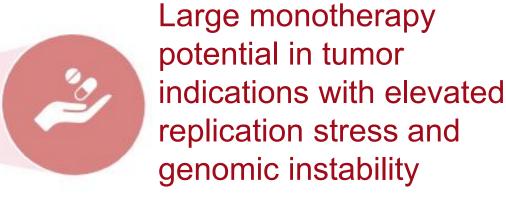


ATX-559 is currently under investigation in a first-in-human, Phase 1/2, open-label, doseescalation and expansion study (NCT06625515)

DHX9 is a novel target critical for maintaining genome stability by unwinding RNA/DNA secondary structures







References

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- ² Chakraborty et al, Nature Comm (2021) ³ Gulliver et al, Future Science (2020)
- ⁴ Castro et al, Cancer Res; 85(4) (2025)
- ⁵ Murayama et al, Cancer Discov (2024)
- ⁶ Crown Bioscience, Inc. HuBase™. Available at: https://hubase.crownbio.com/. Accessed October 3, 2025 ⁷ Guo et al, Contemp Clin Trials (2017)
- ⁸ Simon et al, Control Clin Trials (1989)

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- Figures created in BioRender; https://BioRender.com