

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



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RNA Helicase DHX9 Plays an Important Role in Maintaining Genome Stability

Replication Fork Stress

Microsatellite Instability

Oncogene Amplification/Activation

Defective DNA Damage Repair

Sources of Replication Stress

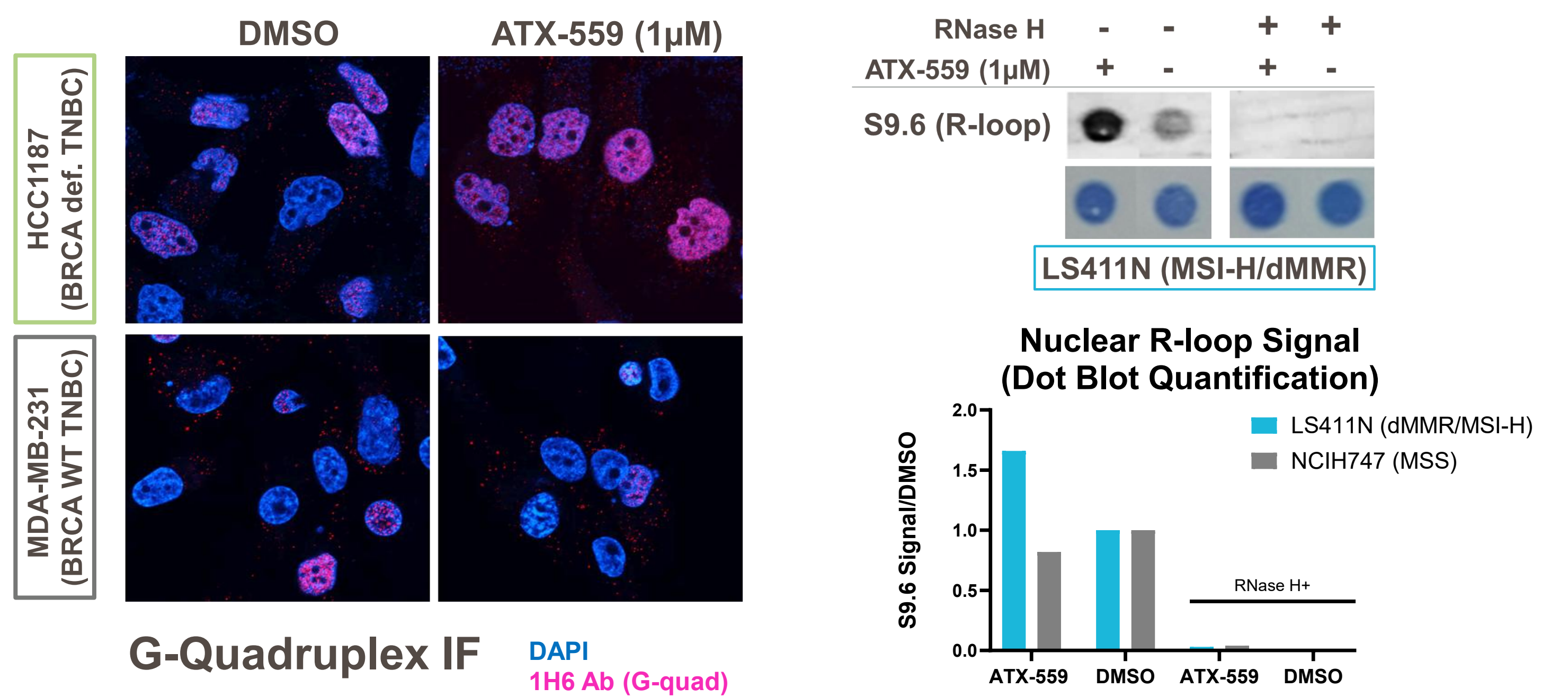
High Replication Stress

Increased Genomic Instability

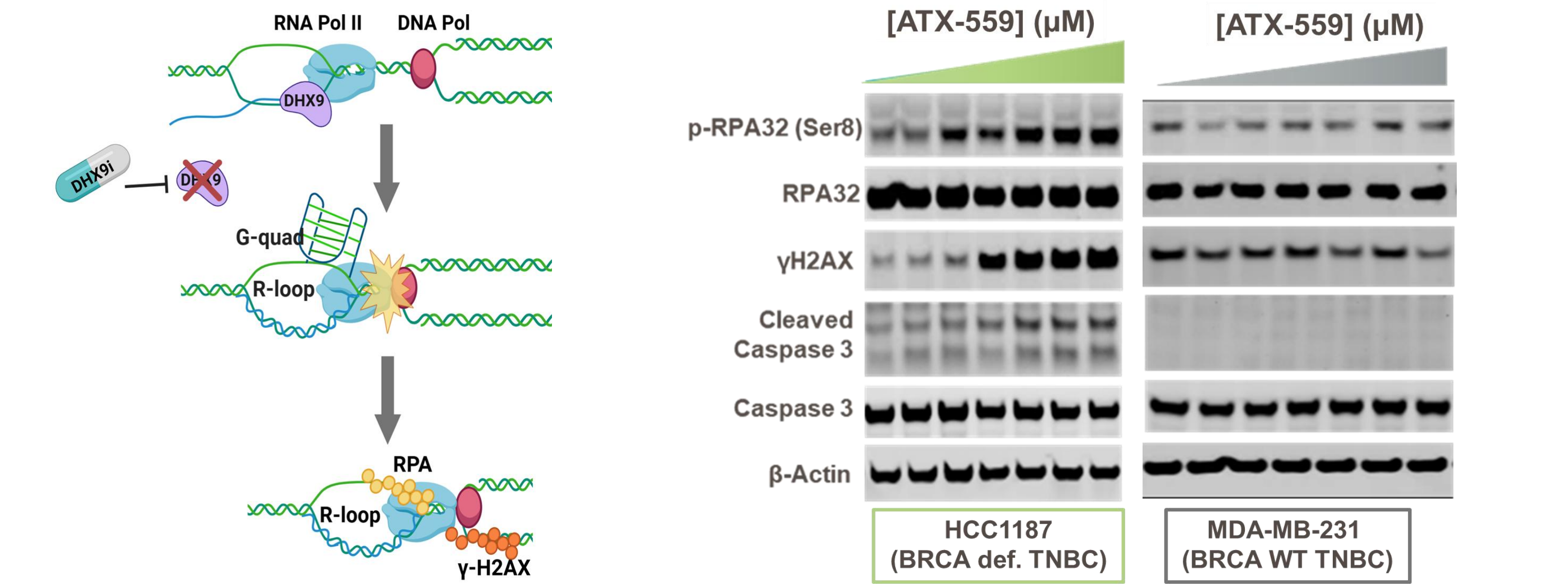
Increased Dependency on DHX9

- 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 dependence 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

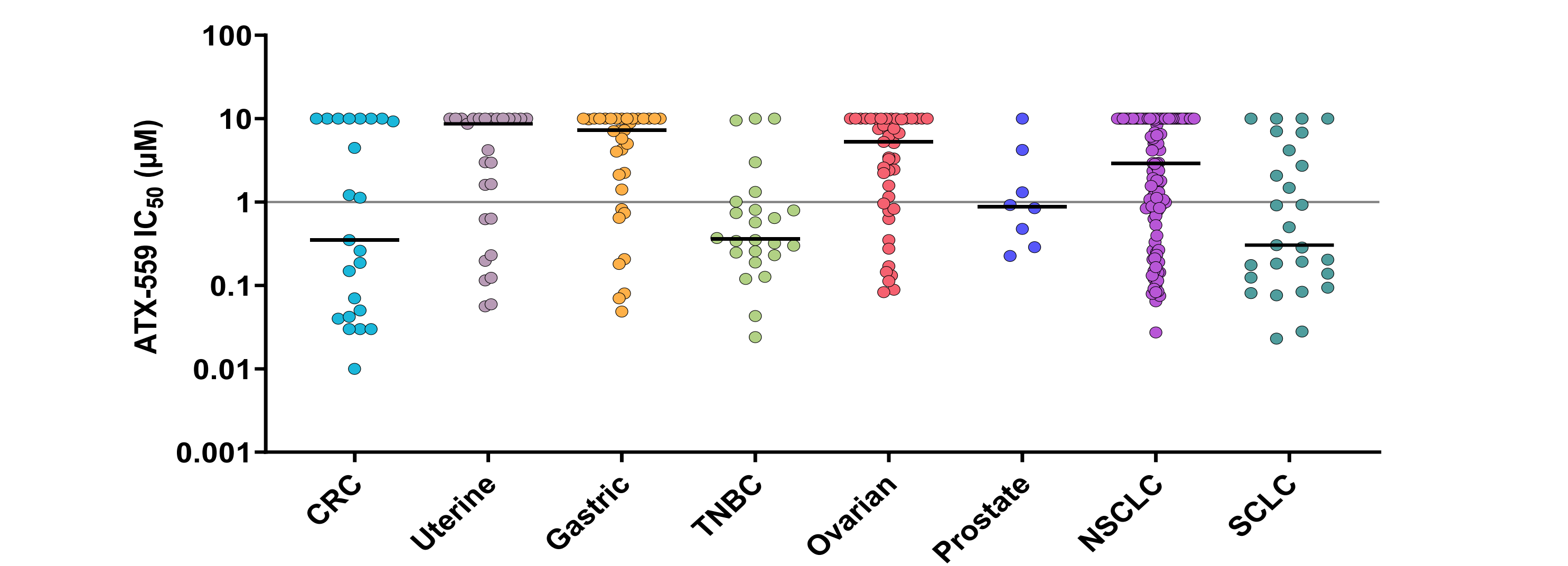
DHX9 Inhibition by ATX-559 Leads to Selective Accumulation of Aberrant Nucleic Acid Secondary Structures



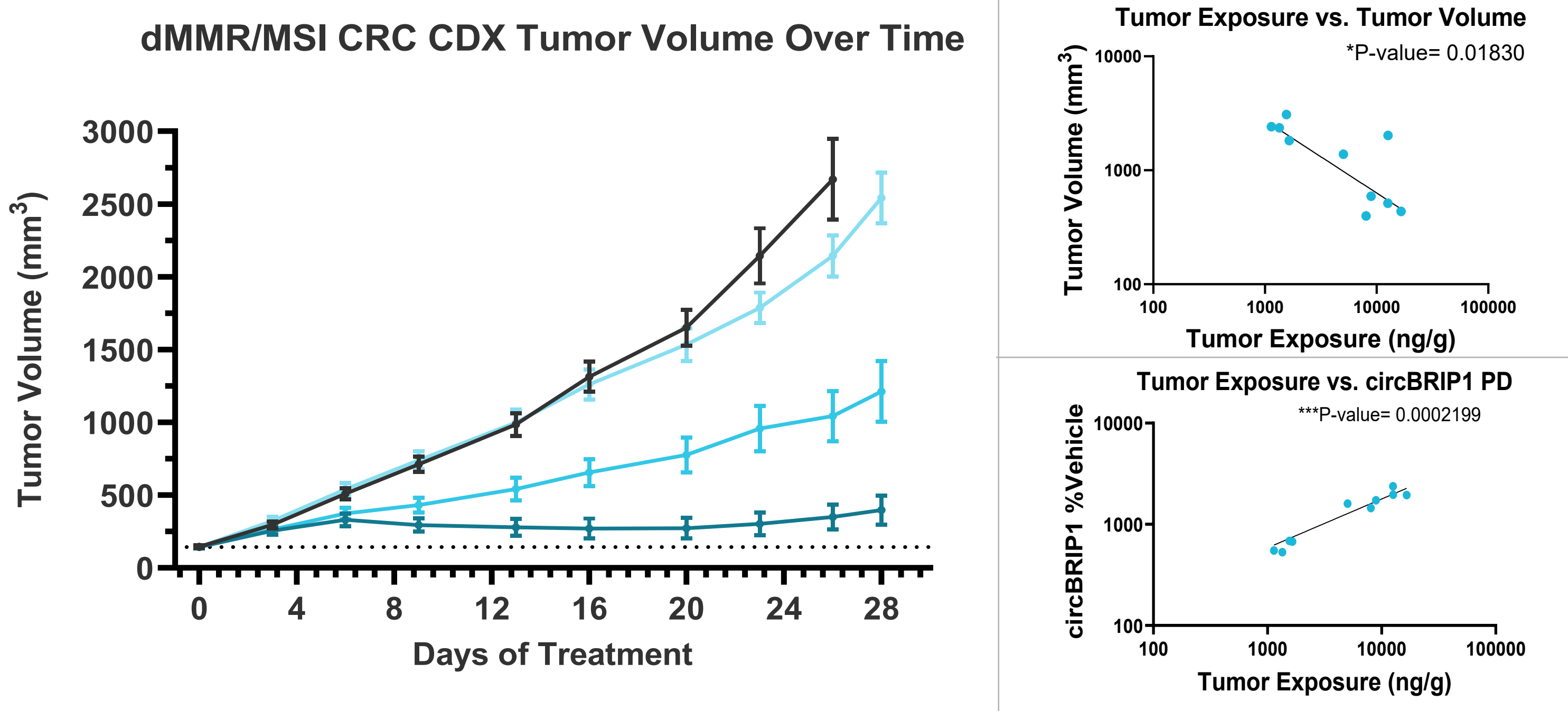
DHX9 Inhibition by ATX-559 Leads to Replication Stress, DNA Damage and Apoptosis



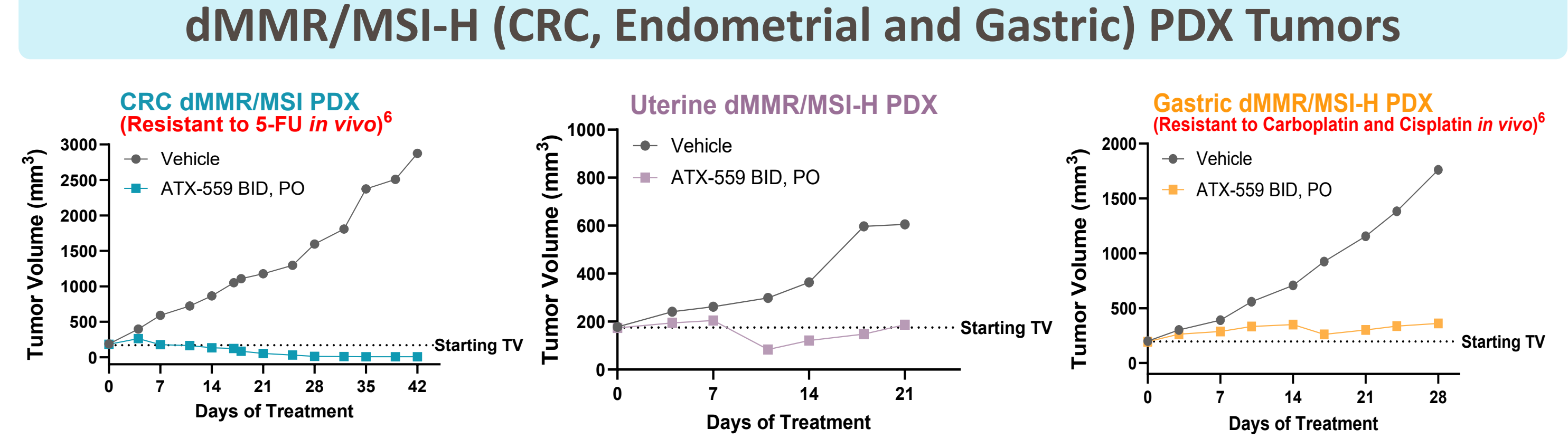
ATX-559 Exhibits Robust Anti-Proliferative Activity in Cancer Cell Lines from Multiple Indications



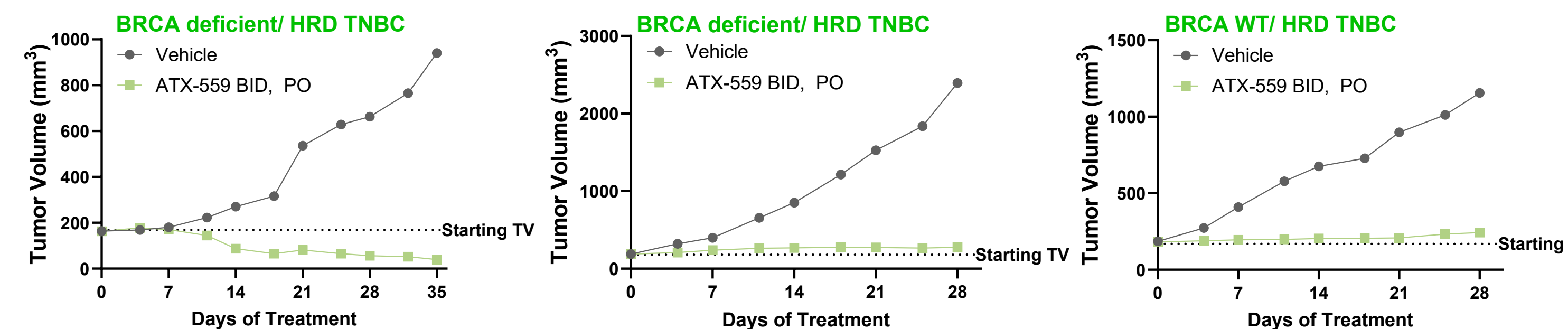
ATX-559 Treatment Shows Dose-Dependent Tumor Growth Inhibition with PK/PD/Efficacy Relationship



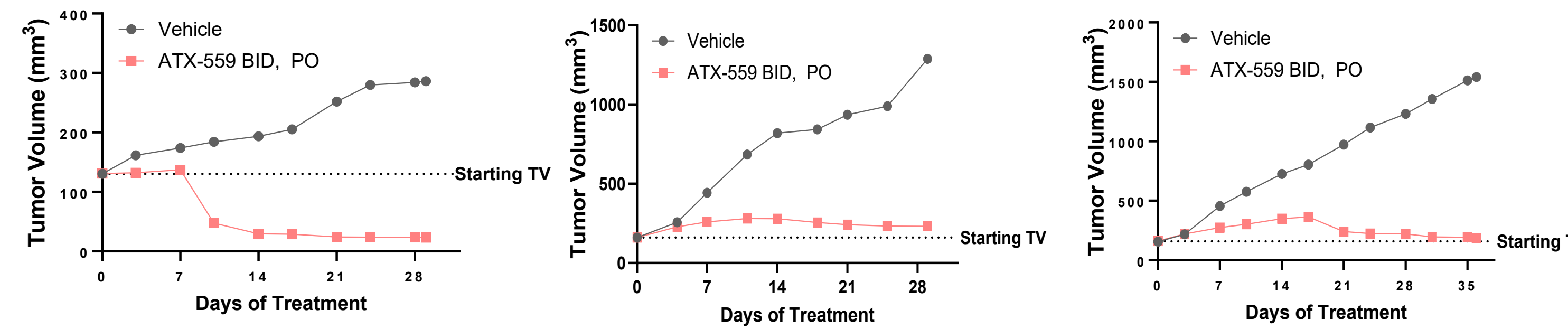
ATX-559 Displays Robust Anti-Tumor Activity in a Panel of Patient-Derived Xenograft (PDX) Models



HR Deficient Breast PDX Tumors



HR Deficient Ovarian PDX Tumors



ATX-559 Phase 1 Clinical Trial Design

