A NOVEL ATR INHIBITOR WITH HIGH SELECTIVITY AND SUPERIOR POTENCY ACROSS MULTIPLE TUMOR TYPES HAVING NO SIDE-EFFECTS ON RETICULOENDOTHELIAL OR HEMATOPOIETIC SYSTEM

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Ataxia Telangiectasia and Rad3-related (ATR) and Checkpoint Kinase 1 (CHK1) stabilize stalled replication forks and prevent their collapse into DNA double strand breaks (DSBs). Targeting ATR increases sensitivity to treatment with DNA-damaging agents and clinically approved PARP inhibitors making this approach particularly attractive for development of novel combinatorial therapies. Atrin Pharmaceuticals has designed a novel series of macrocyclic ATR inhibitors that are highly specific for inhibiting ATR over other closely-related PIK kinases. The specificity and potency of our lead compound ATRN-119 is superior to other ATR inhibitors with an *in vitro* kinase IC_{50} of 20 nM and cellular IC_{50} of 5nm measured as inhibition of phosphorylated CHK1 (pS345). Following broad spectrum of in-vivo efficacy, oral dosing of ATRN-119 showed significant antitumor effects as a monotherapy in human ovarian, pancreatic and colon cancer xenografts. Exploratory toxicity studies in rats and dogs indicate significantly higher tolerability for ATRN-119, including remarkably less anemia and neutropenia in dogs when compared to other known ATR inhibitors. Notably, results from IND-enabling toxicology studies in rats treated with daily oral dosing of ATRN-119 at human equivalent dose (HED) of 1 gram/day per day demonstrated negligible hematological adverse effects (no thrombocytopenia, anemia or neutropenia) up to 4 weeks of treatment. Dogs tolerated ATRN-119 at HED of up to 830 mg/day and showed rapid recovery from MTD of 1.7 gram/day. Combinatorial studies demonstrate remarkable synergy of ATRN-119 with PARP inhibitor in three-dimensional prostate organoid cultures as well as in patient derived ovarian xenografts highlighting the substantial clinical benefit of ATRN-119. Furthermore, ATRN-119 treatment resensitized PARP inhibitor resistant pancreatic and ovarian cancer cell lines. Together, these findings indicate that ATRN-119 has a superior safety and potential broad therapeutic profile which demonstrates synthetic lethality with PARP inhibitors and introduces a new pharmacotherapy opportunity in the DDR anticancer drugs domain.