**P052  First-in-human biomarker-driven phase I TRESR trial of ataxia telangiectasia and Rad3-related inhibitor (ATRi) RP-3500 in patients (pts) with advanced solid tumors harboring synthetic lethal (SL) genomic alterations.** Timothy Yap1, Elizabeth Lee2, David Spigel3, Elisa Fontana4, Martin Højgaard5, Stephanie Lheureux6, Niharika B. Mettu7, Louise Carter8, Ruth Plummer9, Danielle Ulanet10, Peter Manley11, Ying Jiang10, Ezra Rosen12.  
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**Background:** RP-3500 is a novel potent and selective ATRi. A genome-wide CRISPR/Cas9-based screening platform (SNIPRx) was utilized to identify and validate synthetic lethal (SL) genomic alterations that predict sensitivity to RP-3500. This is the first presentation of data from the ongoing Phase I TRESR (Treatment Enabled by SNIPRx) study. **METHODS:** Pts with advanced solid tumors harboring RP-3500 sensitizing alterations were recruited. Pts received oral RP-3500 in 21-day cycles on different doses and schedules using a BOIN design. Pharmacokinetic (PK) and pharmacodynamic (PD) studies were conducted in serial tumor and/or blood samples. Biomarker tests included somatic and germline NGS, including zygosity studies, ATM and γH2AX IHC, and circulating tumor DNA (ctDNA). **RESULTS:** 62 pts (mean age 62 y, 42% males, 43% ≥5 prior lines of therapy) received RP-3500 (range: 1–8+ cycles). 44 pts remained on RP-3500 at the June 4, 2021, data cut-off. Tumors with ATM (n=26), BRCA1/2 (n=16), CDK12 (n=5) and other (n=20) molecular alterations were included. Germline (22 germline and 15 somatic, 25 pending) and zygosity status (10 bi-allelic and 5 mono-allelic, 46 pending) will be presented. Treatment-related adverse events (TRAEs) were mostly Grade (G)1 and transient. TRAEs occurring in >10% of pts were limited to anemia (all grades 37%, G3 26%, G4–5 0%) and fatigue (all grades 13%, G3 2%). Other ≥G3 TRAEs occurred in <5% of pts and included thrombocytopenia (4.8%) and neutropenia (1.6%). No pts discontinued RP-3500 due to TRAEs, 17/62 discontinued due to progressive disease or clinical progression and 1/62 due to withdrawal of consent. RP-3500 plasma exposures showed a dose-dependent increase with T1/2 of 6 hrs. Once-daily dosing was sufficient to meet RP-3500 exposure requirements set from pre-clinical studies. Tumor γH2AX induction (median increase =140%; p-value =0.02) was seen across doses and genotypes confirming target modulation. Declines in variant allele frequencies (>50%) in ctDNA were observed in 8/14 evaluable pts and correlated with antitumor activity (Pearson correlation coefficient =0.65; p-value =0.015). Of 31 pts evaluable for response, 14 (45%) had tumor regression on at least 1 radiologic evaluation. Objective responses were seen in 6 pts: 4 RECISTv1.1 partial responses in tumors with CDK12 and BRCA1 alterations (2 confirmed; 2 unconfirmed), and 2 PCWG3 in tumors with ATM loss. Six pts had stable disease ≥4 cycles. **CONCLUSIONS:** The TRESR study represents the largest biomarker-driven FIH trial for a single agent ATRi and validates prospective pt selection based on the presence of SL genomic alterations. RP-3500 shows a robust PK/PD profile, preliminary anti-tumor activity, and predictable and manageable on-target anemia (<30% G3, no G4/5) with low potential for off-
target toxicity. Enrollment continues, including combinations with PARPi and other therapies. Clinical trial information: NCT04497116.