Abstract

Background: Drugs targeting poly (ADP-ribose) polymerase (PARP) have provided significant clinical benefit for cancer patients with tumors harboring mutations in BRCA1/2 or other homologous recombination deficiencies (HRD). Despite their success, not all patients respond to PARP inhibitors, and those who do benefit often develop resistance. To address these challenges, we applied our proprietary CRISPRomics™ technology to over 600 cancer cell lines, a subset of which contained mutations in either BRCA1/2 or other genes involved in DNA repair. The genomic dependencies that were selective for this subset of cell lines were then ranked for their suitability for therapeutic targeting.

Results: One of the top-ranked targets was the deubiquilating enzyme USP1. USP1 has established roles in DNA damage repair processes, including Translesion synthesis and the Fanconi anemia pathway. We developed a series of small molecule inhibitors that are potent and highly selective for USP1 relative to other family members. These inhibitors were active in cells, leading to the accumulation of mono-ubiquitinated substrates of USP1 and demonstrating selective antiproliferative activity in cell lines with all 16 or other genetic or other HRD alterations. Evaluation of our lead compound, KSQ-4279, in both ovarian-derived and triple-negative breast cancer (TNBC) derived tumor xenograft models, demonstrated dose-dependent tumor growth inhibition. In xenograft models with only partial sensitivity to PARP inhibitors, the combination of KSQ-4279 with a PARP inhibitor led to significantly greater and more durable tumor regressions than either agent alone. KSQ-4279 has favorable in vitro ADME properties and pharmacokinetic profile across multiple non-clinical species. Preliminary safety data indicates that KSQ-4279 is well tolerated as a single agent and in combination with PARP inhibitors, with no evidence of dose limiting heme-related toxicities.

Conclusions: Our data supports the clinical evaluation of KSQ-4279 as a potential first-in-class USP1 inhibitor in patients with tumors harboring BRCA1/2 or other HRD mutations, both as a single agent and in combination with PARP inhibitors.

Figure 1: CRISPRomics™ Target Discovery Platform Identifies USP1 as Attractive Target

Figure 2: USP1 is a Key Regulator of DNA Damage Repair Pathways Distinct from PARP Inhibitors

Figure 3: KSQ-4279 is a Potent and Selective USP1 Inhibitor

Figure 4: KSQ-4279 Demonstrates Monotherapy Activity in Human PDX Model

Figure 5: KSQ-4279 Enhances Olaparib Activity Leading to Significant and Durable Anti-tumor Response in BRCA1T-high HRD PDX Models

Figure 6: KSQ-4279 is Well Tolerated in Combination with Olaparib at Multiple Dose Levels

Figure 7: KSQ-4279 Has Favorable Pharmacokinetic Profile Across Non-clinical Species