VRN19, a Novel USP1 Inhibitor with Anti-Tumor Efficacy and Favorable Safety Profiles

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Abstract
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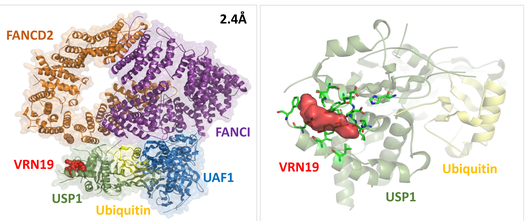
Introduction

- Tumors with BRCA1/2 mutations demonstrate HR repair deficiencies, leading to genomic instability.
- PARP inhibitors have shown representative therapeutic options, but incomplete disease control and the emergence of resistance remain challenges for many patients.
- USP1 (Ubiquitin-specific protease1) plays a critical role in regulating DNA damage repair and has been considered as a synthetic lethal target with BRCA1/2-deficient and PARPi resistant tumors.
- Many investigational USP1 inhibitors have been discovered and developed, but key leading programs showed limited safety or efficacy.
- The phase 1/2 clinical trial of TNG348 was terminated due to liver toxicity in the initial study cohorts[1)] and KSQ-4279 showed limited efficacy and hematologic toxicity such as anemia in its early clinical study[2)].
- Based on these findings, developing a drug with enhanced efficacy and tolerability against heme and hepatoxicity need to be improved.

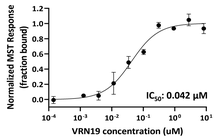
1) TANGO therapeutics announce, 2) 2024 ASCO annual meeting

Selective Allosteric USP1 Inhibitor

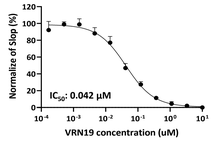
Cryo-EM structure



MST



Deubiquitinase activity



Selective across DUBs

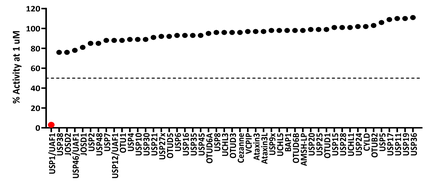
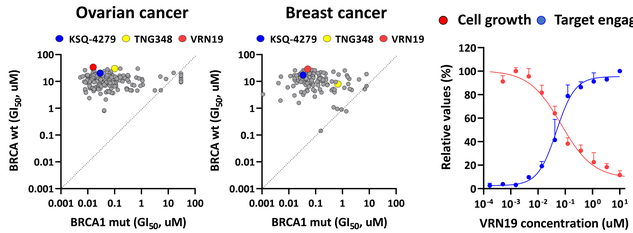


Figure 1. VRN19 inhibits the catalytic activity of the USP1-UAF1 complex by directly binding to USP1, confirmed by Cryo EM and MST. Selectivity was assessed on a DUB panel using DUBprofiler™ assay (Ubiquigent, UK) at 1 uM.

High Potency and Selectivity in BRCA1 Mutant Cancer



	Cancer cell		KSQ-4279	VRN19
Proliferation	Breast	GI_{50} (μM)	0.040	0.051
	Ovarian		0.028	0.016
Target engagement	Breast	EC_{50} (μM)	0.033	0.047
Selectivity (BRCA wt/mut)	Breast	ratio	474	563
	Ovarian		658	2,122

Figure 2. VRN19 was selected from 300 lead candidates for its potent activity in BRCA1-mutant ovarian and breast cancers while sparing BRCA wt cells. It exhibited double-digit nM GI50 in BRCA1-mutant cancer cells and over 500-fold selectivity against BRCA wt cells. VRN19 demonstrated a strong correlation between cell growth inhibition and target engagement (ubi-PCNA).

Superior Solubility

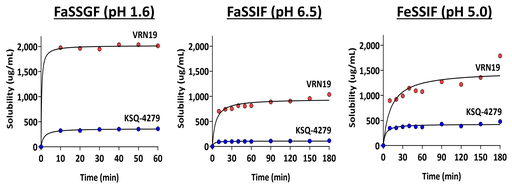


Figure 3. *In vitro* thermodynamic solubility assay demonstrated that VRN19 dissolves more effectively than KSQ-4279 in FaSSGF (Fasted State Simulated Gastric Fluid), FaSSIF (Fasted State Simulated Intestinal Fluid), and FeSSIF (Fed State Simulated Intestinal Fluid).

Excellent PK/PD Correlation

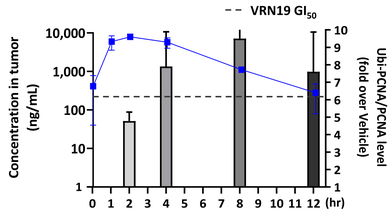
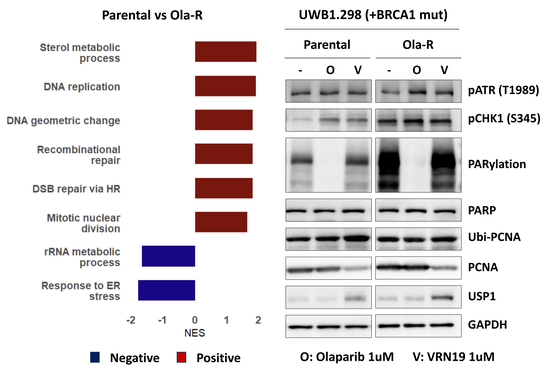
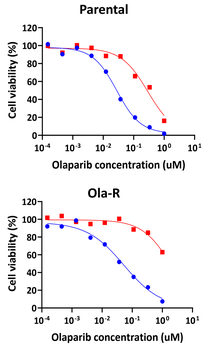


Figure 4. VRN19 was administered orally at 30 mg/kg, BID for 7 days in the MDA-MB-436 tumor bearing mice. Tumor samples from 3 mice were taken at indicated time points after last dosing and VRN19 concentration and ubi-PCNA levels were measured.

Overcoming Acquired PARP Inhibitor Resistance





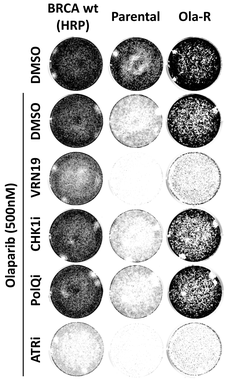
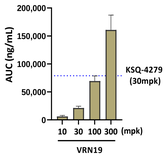


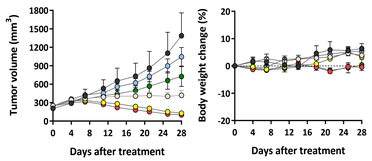
Figure 5. Acquired Olaparib-resistant cells (Ola-R) were generated based on UWB1.289. Expression levels and activity changes in HRD or DDR-related genes were analyzed using bioinformatics and biochemical approaches, confirming a shift from HRD to HRP-like characteristics. Combination treatment of VRN19 with Olaparib in Ola-R cells overcame Olaparib resistance. Among DDR-targeting inhibitors, USP1 inhibition was identified as the most effective combi partner for overcoming Olaparib resistance, as demonstrated by CFA analysis.

Synergistic Effects with PARP Inhibitor or Carboplatin in CDX and PDX Models

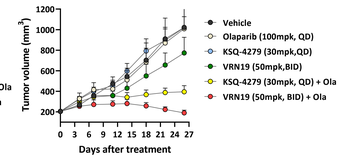
VRN19 PK



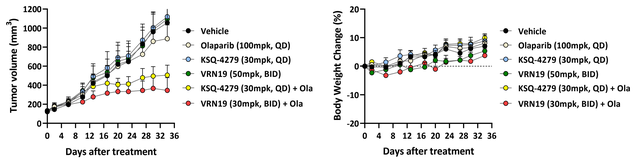
MDA-MB-436 (BRCA1 mut / HRD) SC xenograft model



OVCAR3 (BRCA wt / HRD) SC xenograft model



Olaparib resistance TNBC PDX model



OVCAR3 (BRCA wt / HRD) SC xenograft model

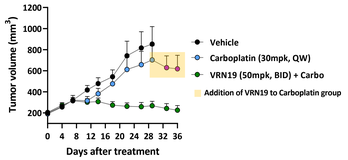
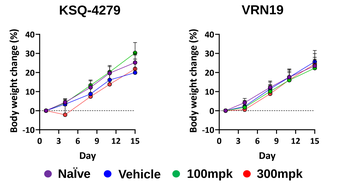


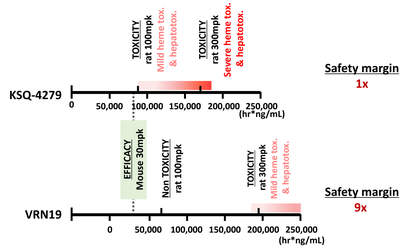
Figure 6. VRN19 demonstrated a synergistic effect with Olaparib (Ola) in a BRCA1-mutated breast cancer CDX model (MDA-MB-436). In Olaparib-resistant PDX model, VRN19 overcame resistance when administered in combination. In an ovarian cancer with BRCA wt CDX model, VRN19 exhibited synergy not only with Olaparib but also with Carboplatin (Carbo). Furthermore, the synergistic efficacy of VRN19 was observed even in tumors previously exposed to Carboplatin.

Favorable Safety Profiles

Body weight change



Safety margin



CBC & Biochemistry analysis

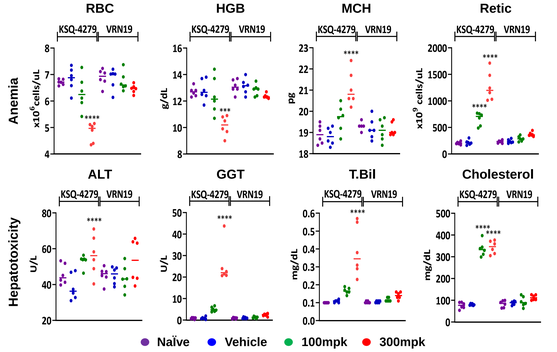


Figure 7. Unlike VRN19, administration of KSQ-4279 to rats for 2 weeks resulted in anemia, hepatotoxicity, and hematotoxicity. These toxic effects are similar to the adverse events(AEs) observed in KSQ-4279 clinical trials. VRN19 exhibits a superior safety margin compared to KSQ-4279.
Values are in mean ± standard error of the mean; One-way ANOVA analysis test
(* : P ≤ 0.05; ** : P ≤ 0.01; *** : P ≤ 0.001; **** : P ≤ 0.0001)

Conclusion

- VRN19 is highly potent and selective allosteric inhibitor and synergized with PARP inhibitor in CDX or PDX models.
- VRN19 can overcome acquired PARP inhibitor resistance.
- VRN19 is a promising novel USP1 inhibitor with favorable safety and improved therapeutic outcomes.
- VRN19 is advancing under IND enabling

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