USP1 inhibitors show robust combination activity and a distinct resistance profile from PARP inhibitors

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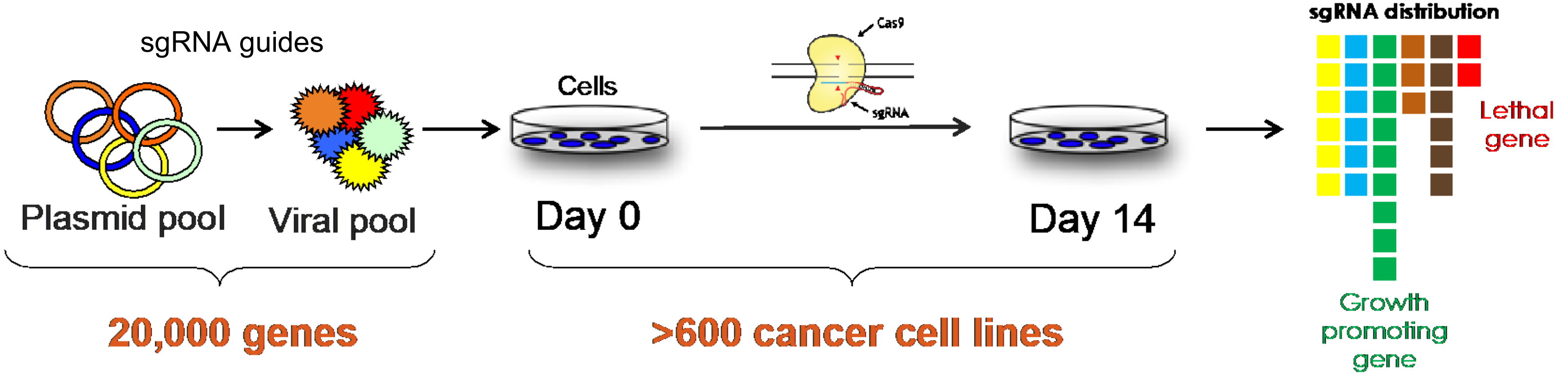
KSQ Therapeutics

Disclosure statement

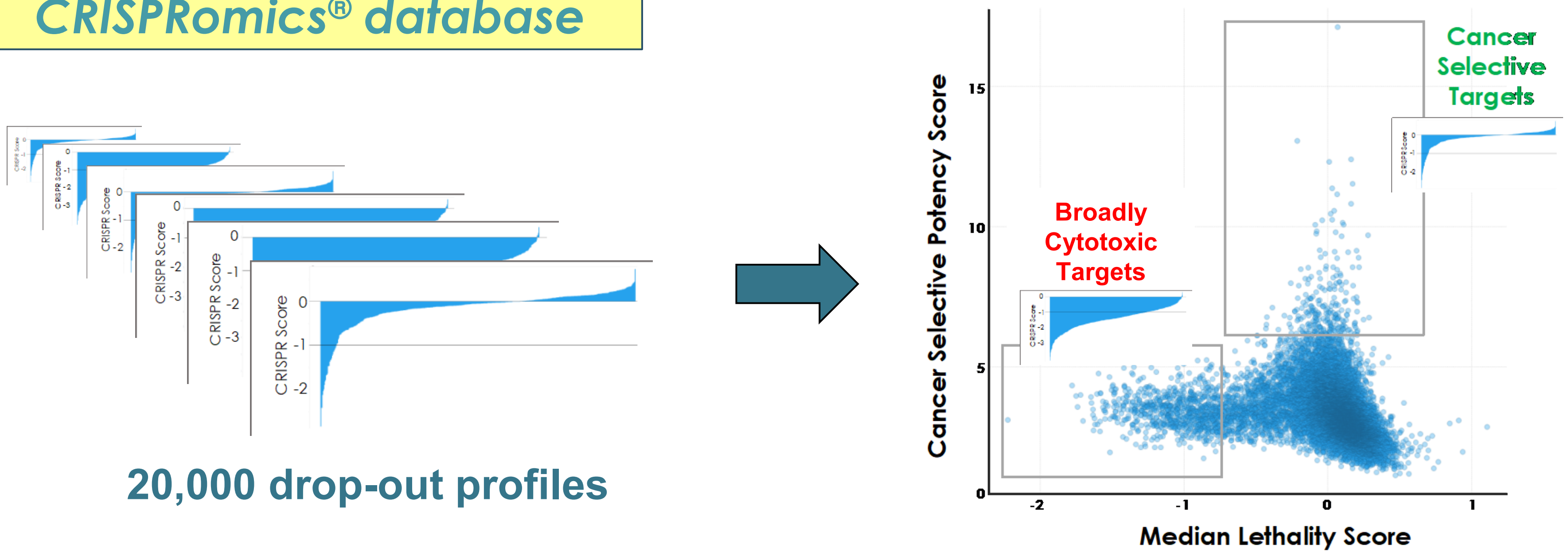
ENA 2020
EORTC NCI AACR
32nd Symposium

- I am an employee of KSQ Therapeutics

KSQ PrecisionOne CRISPR Platform

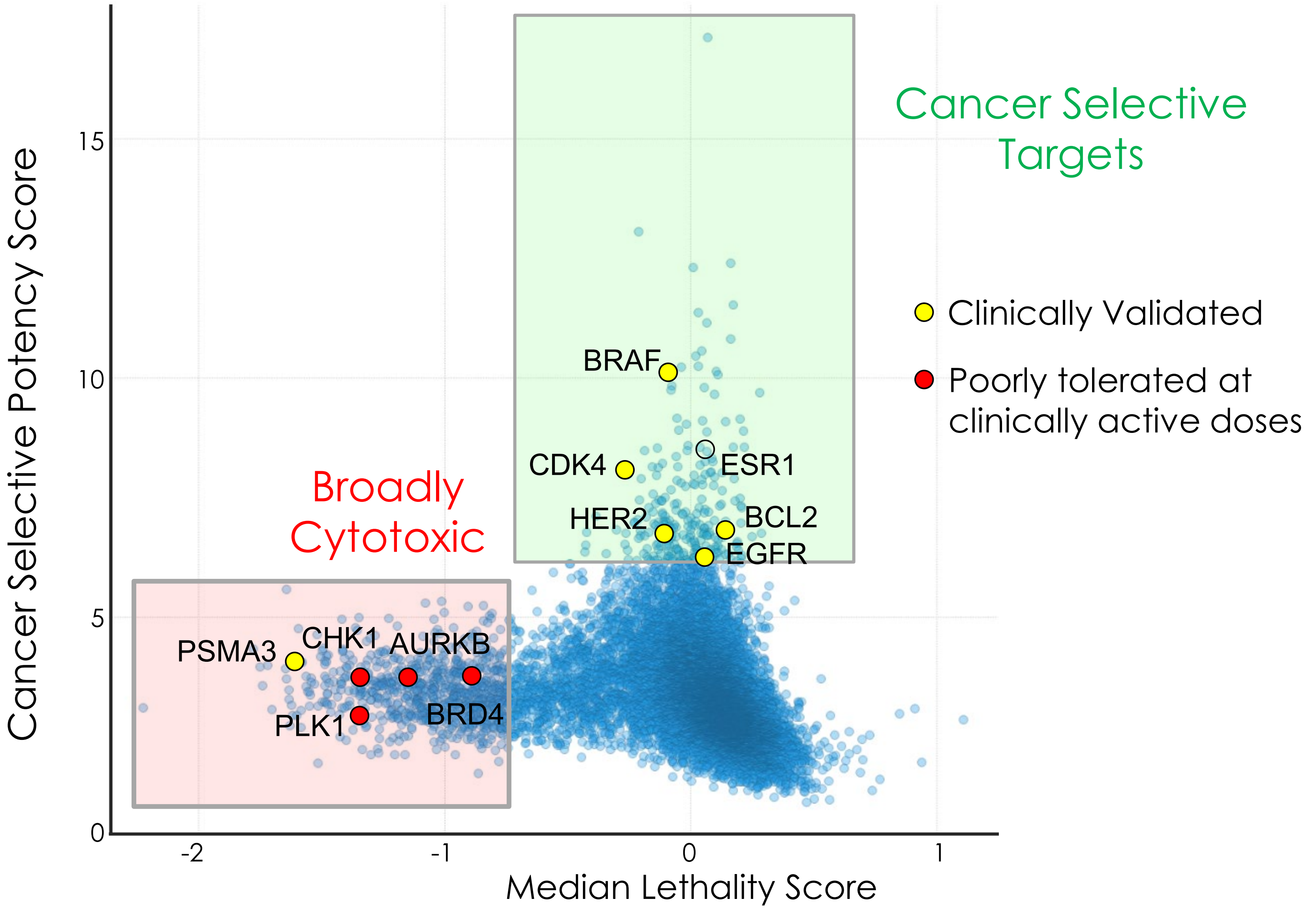


CRISPRomics® database

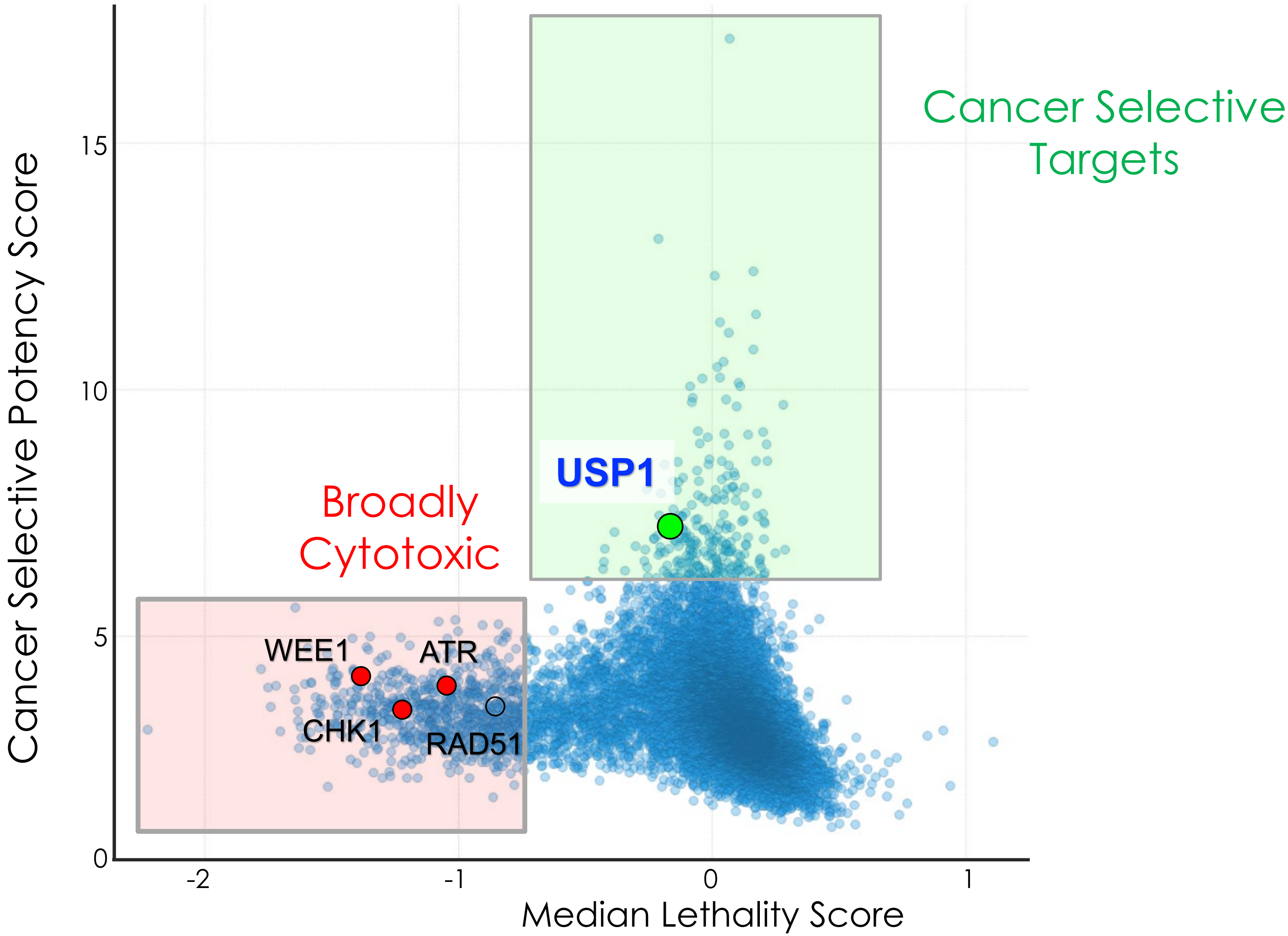


KSQ Knowledgebase: Identification of Cancer-Selective Targets

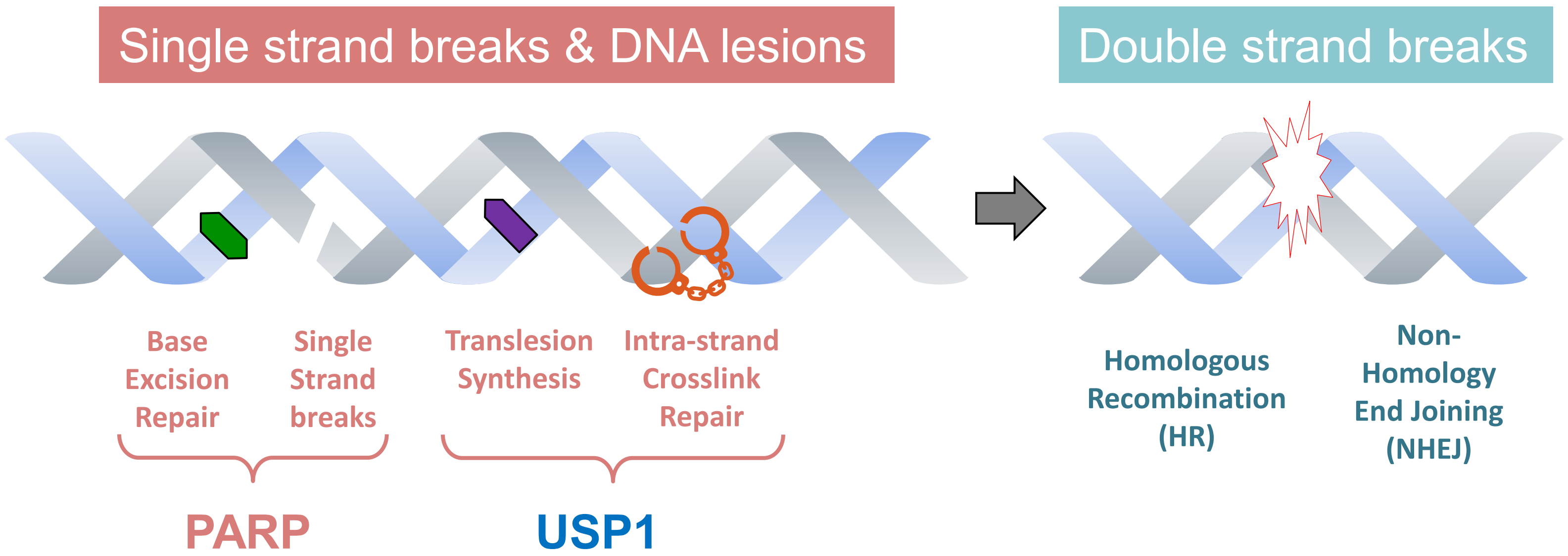
Database Predicts Past Successes and Failures

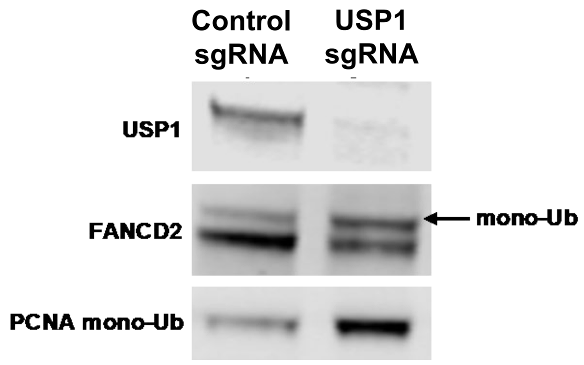


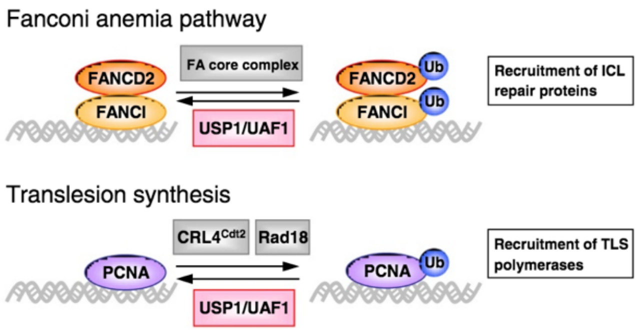
KSQ Knowledgebase Indicates that USP1 is a Cancer Selective Target



USP1 is involved in a distinct set of DNA Damage Response Pathways from PARP inhibitors

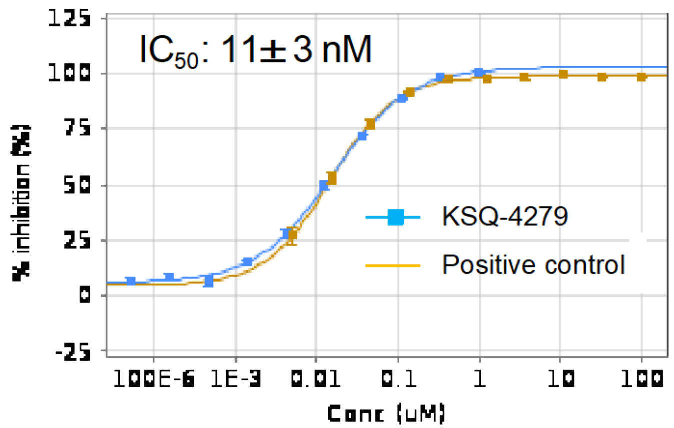




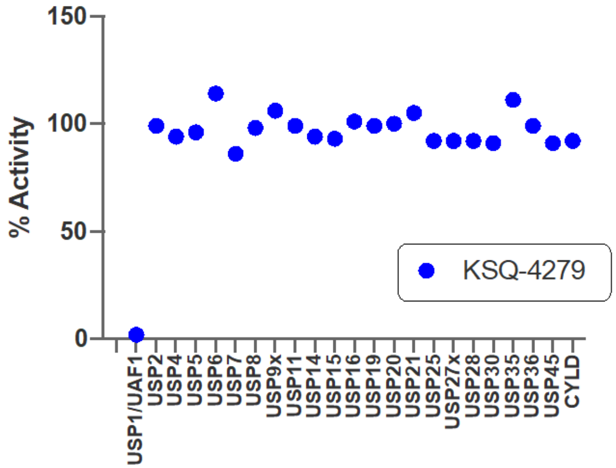


KSQ-4279, a Potent and Selective USP1 Inhibitor, Shows Anti-Proliferative Effects in BRCA1 Mutant Cells

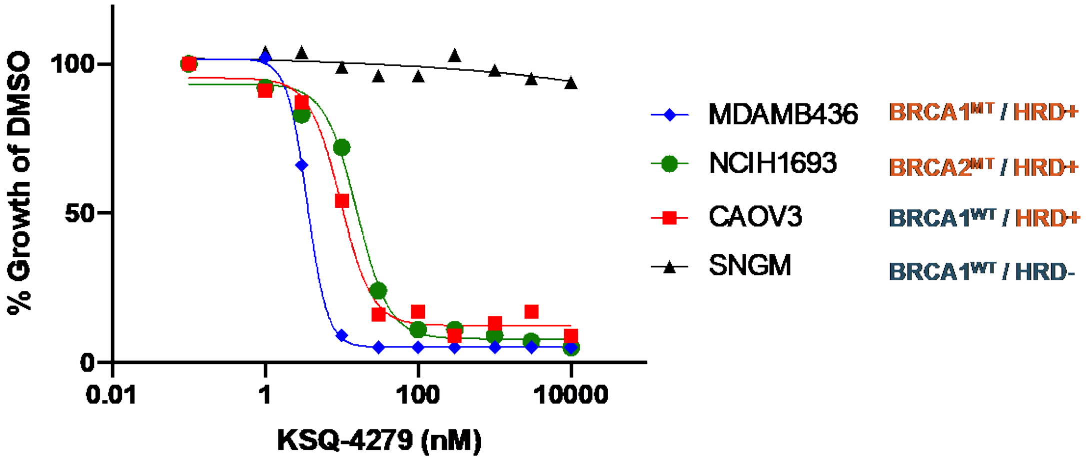
Biochemical assay



DUB Selectivity Panel @ 1uM



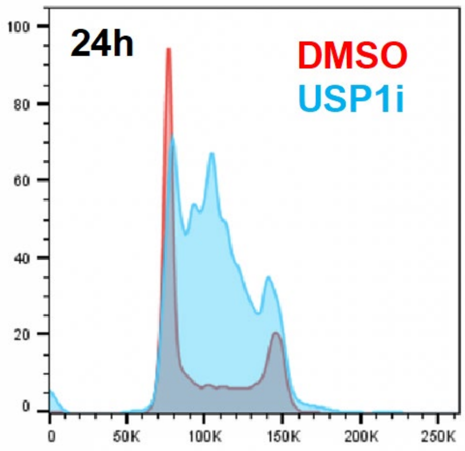
Clonogenic assays reveal activity in BRCA^{MT}/HRD cells



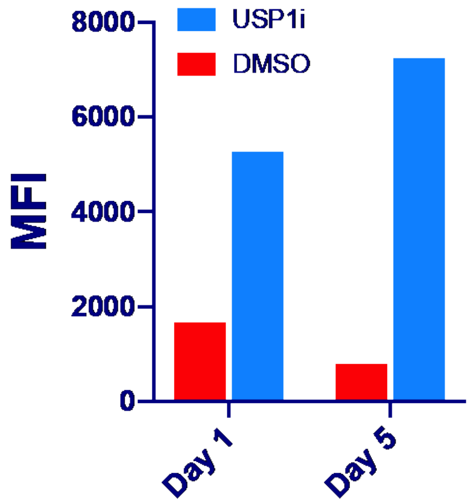
KSQ-4279 Induces S-Phase Arrest and DNA Damage Leading to Apoptosis and Cell Death in BRCA1 Mutant Cells

MDA-MB-436 cells (BRCA1^{MT}, p53^{MT})

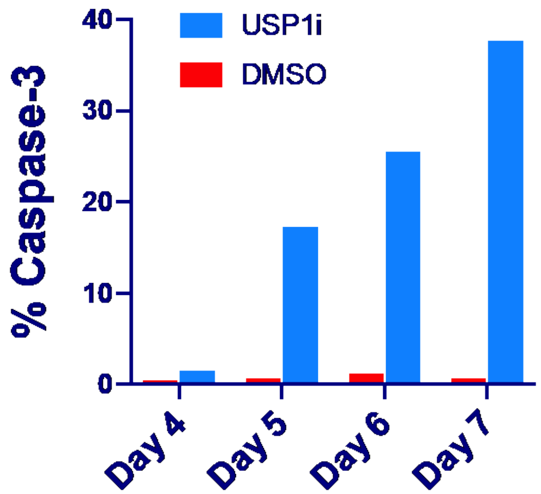
Cell Cycle



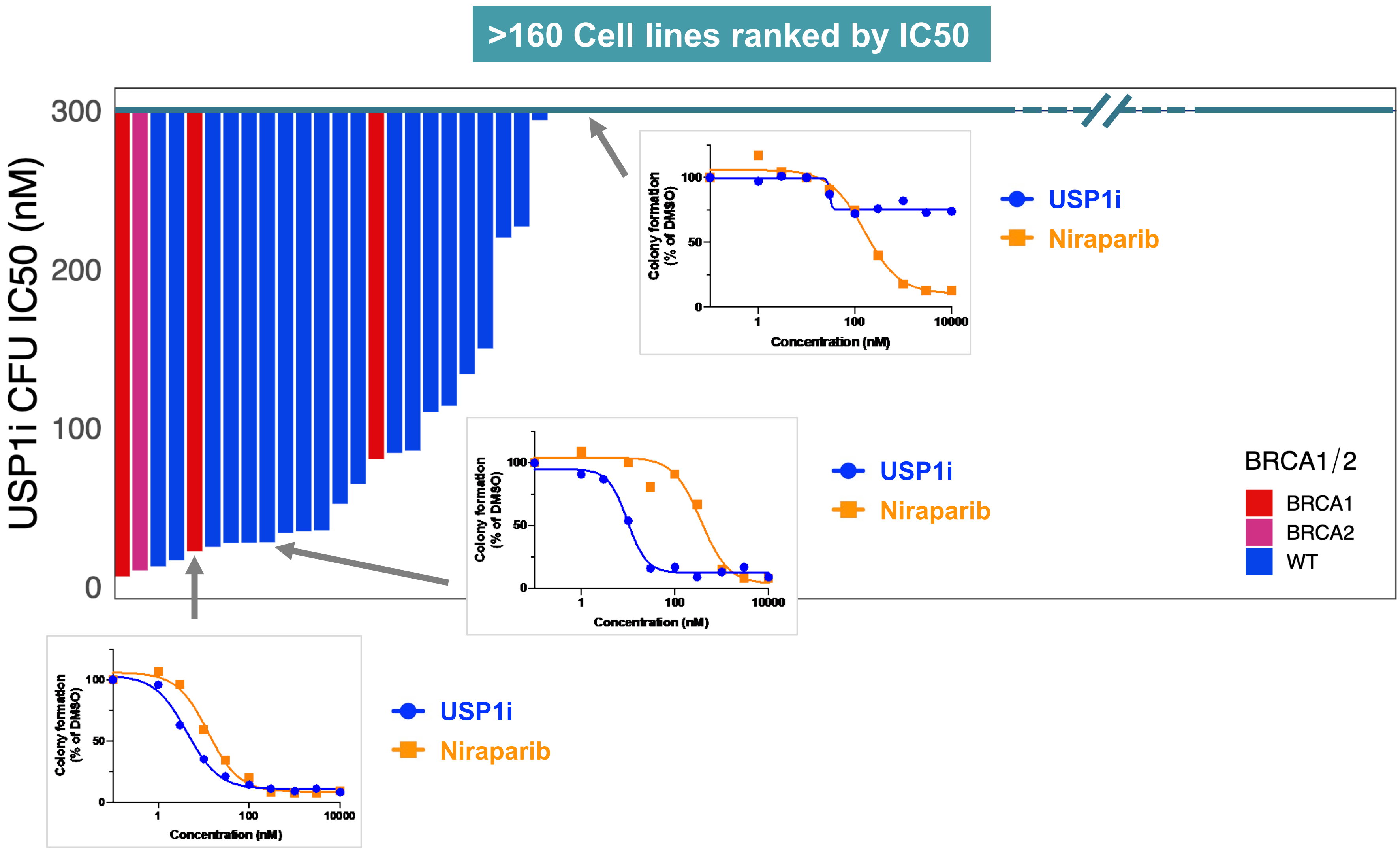
γH2AX



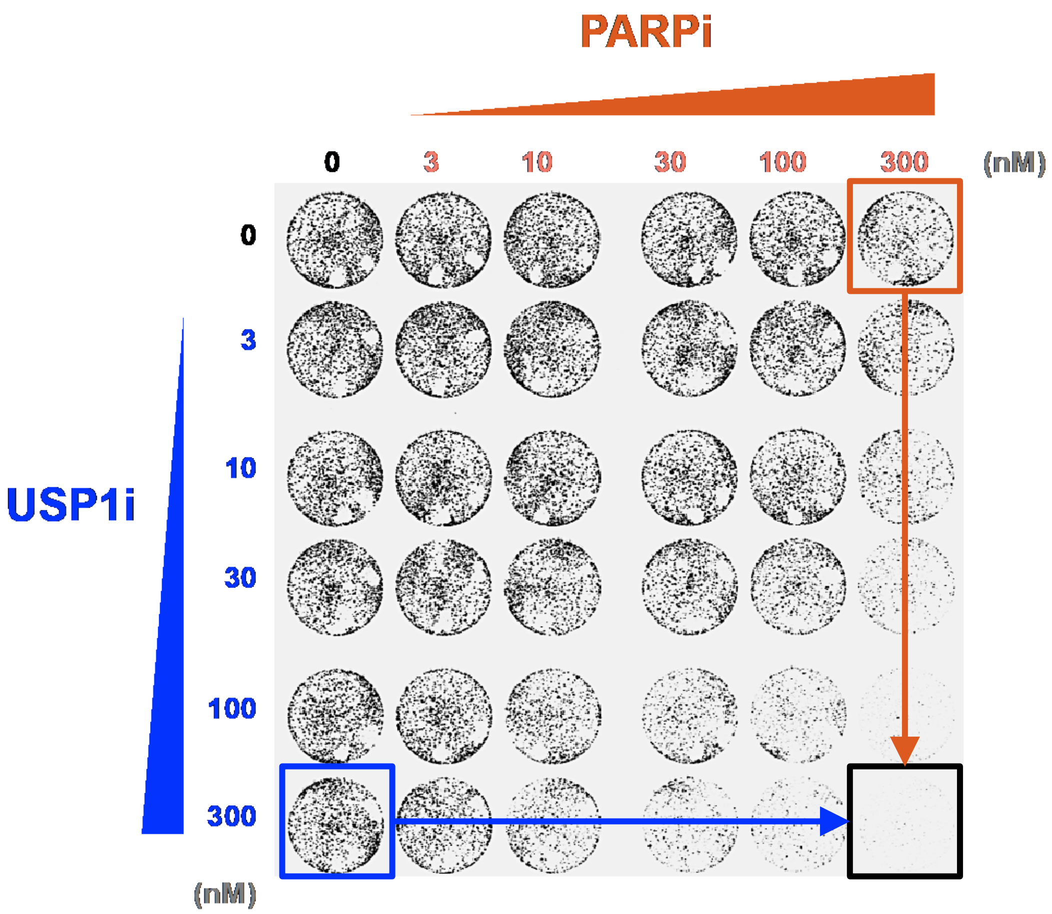
Caspase-3



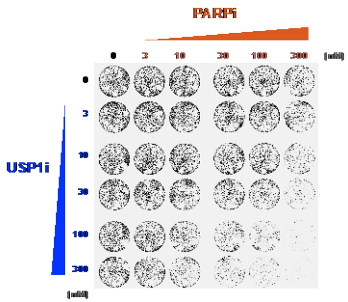
Clonogenic Assay Profiling Confirms USP1 Inhibitors are Active in a Distinct Subset of Cell Lines



USP1i and PARPi Have Synergistic Activity in Clonogenic Assays

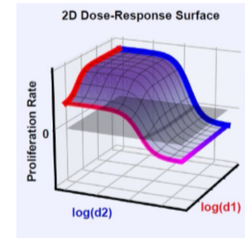


USP1i and PARPi Have Synergistic Activity in Clonogenic Assays

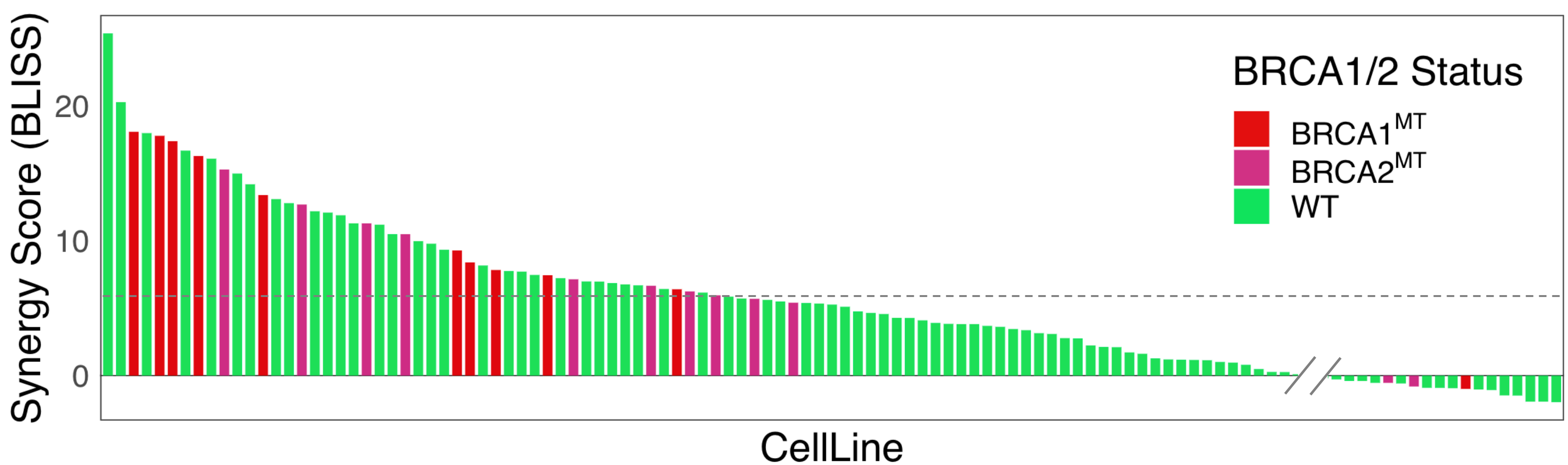


CFU assay quantification
(% of DMSO)

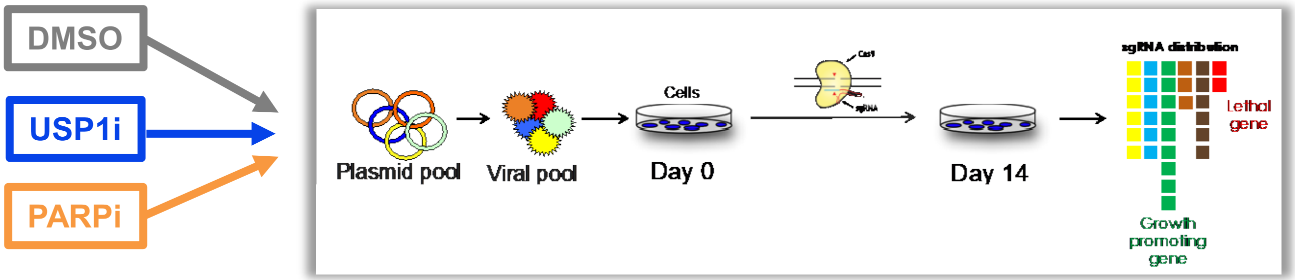
			Niraparib				
		DMSO	3nM	10nM	30nM	100nM	300nM
	DMSO	100	93	85	74	49	18
KSQ-2584	3nM	83	94	75	72	50	14
	10nM	88	87	76	57	34	13
	30nM	75	73	60	32	17	9
	100nM	69	53	34	19	11	8
	300nM	52	42	24	15	9	7

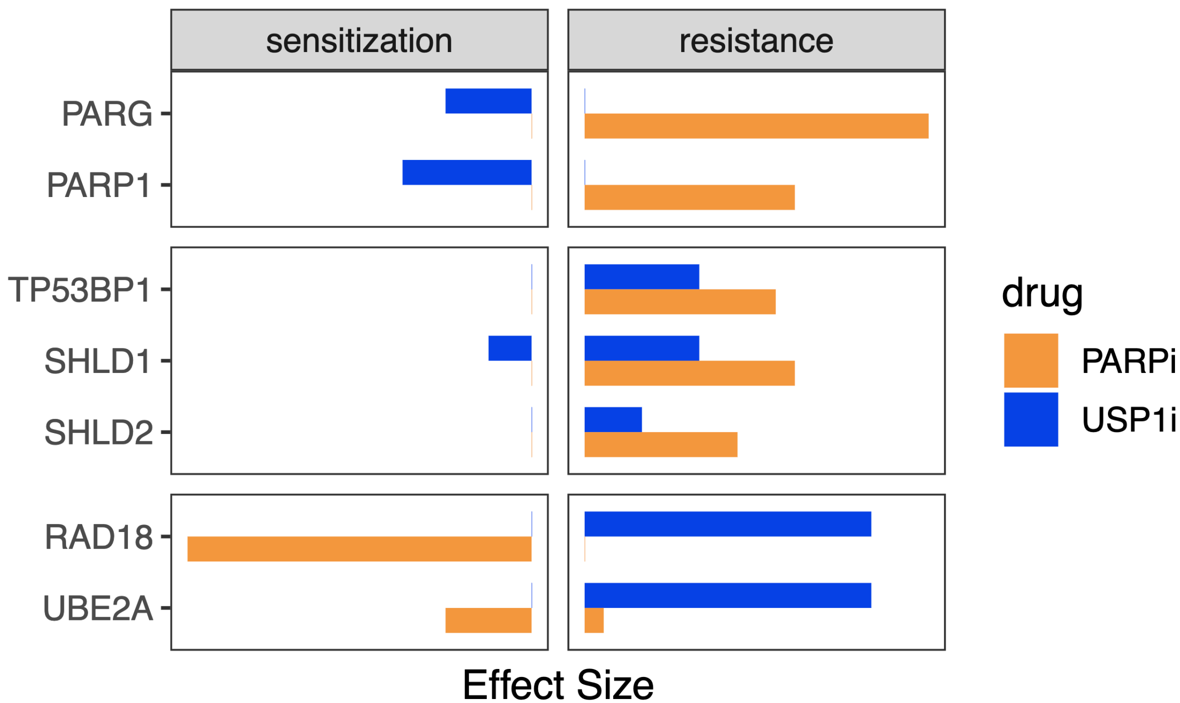


USP1i / PARPi combination synergy ranking across >160 cell lines

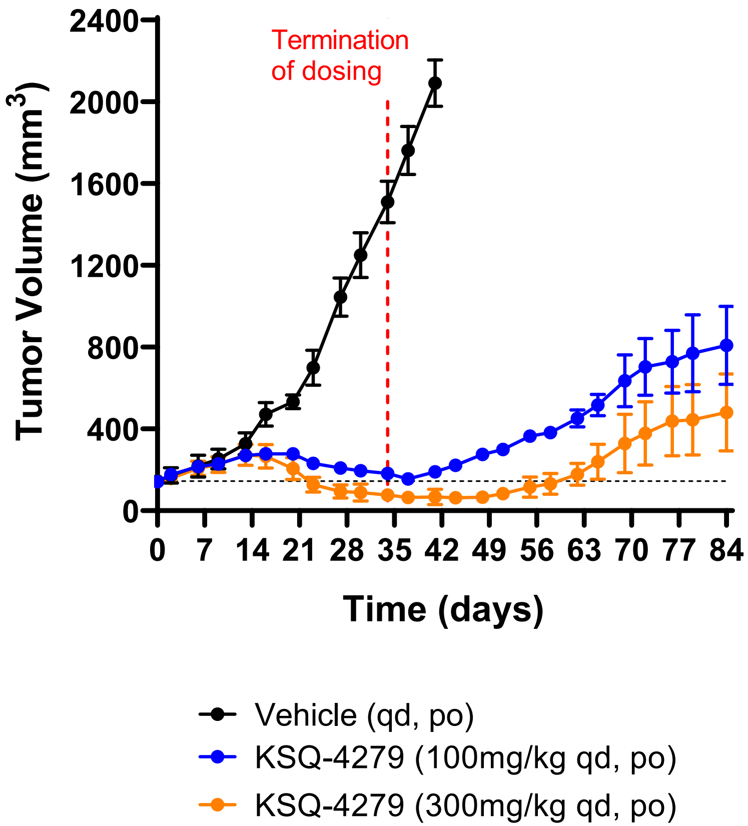


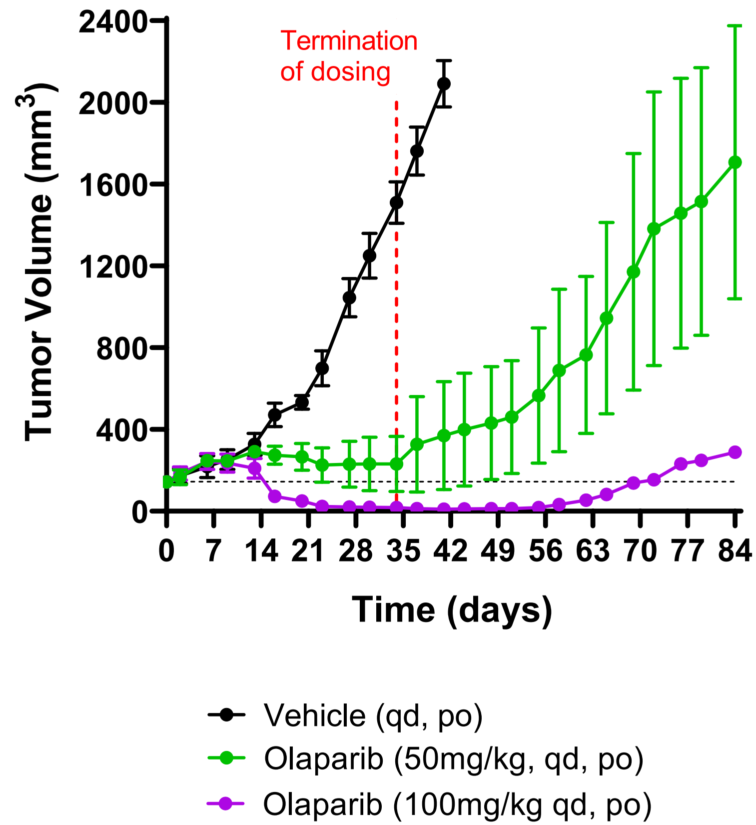
CRISPR Screens Indicate that the Top Scoring Resistance Genes Differ between USP1i and PARPi



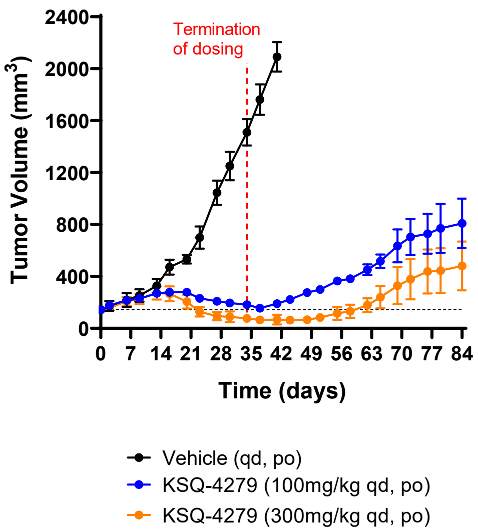


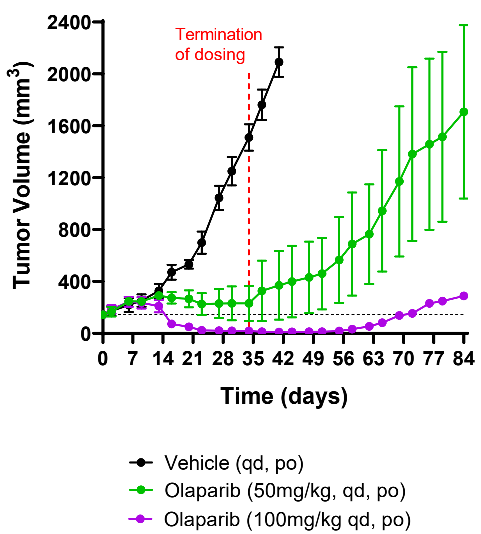
KSQ-4279 is Active as a Monotherapy in Ovarian PDX Model ($BRCA1^{MT}/p53^{MT}$)

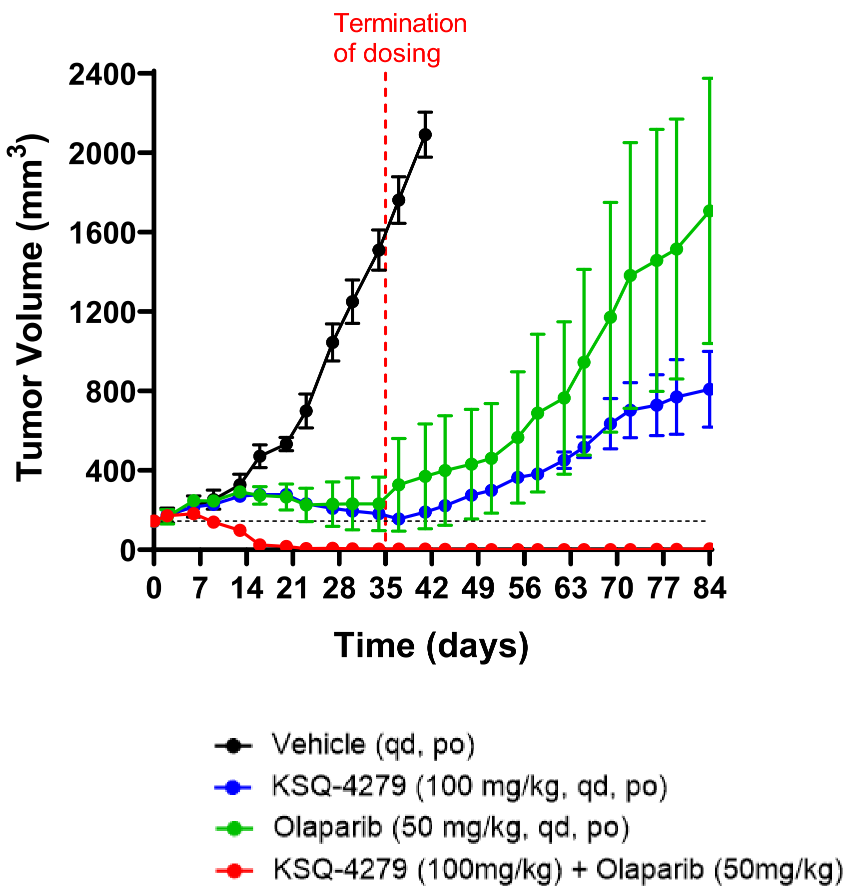




KSQ-4279 is Active as a Monotherapy in Ovarian PDX Model ($BRCA1^{MT}/p53^{MT}$) and in Combination With Olaparib

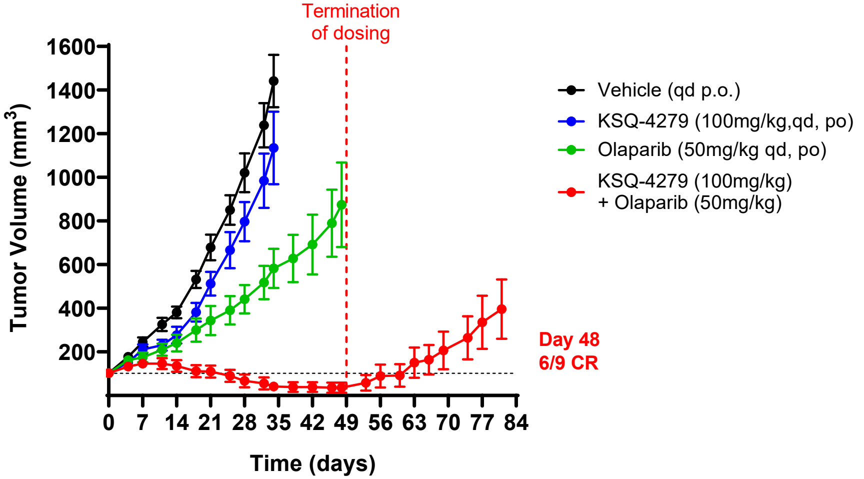




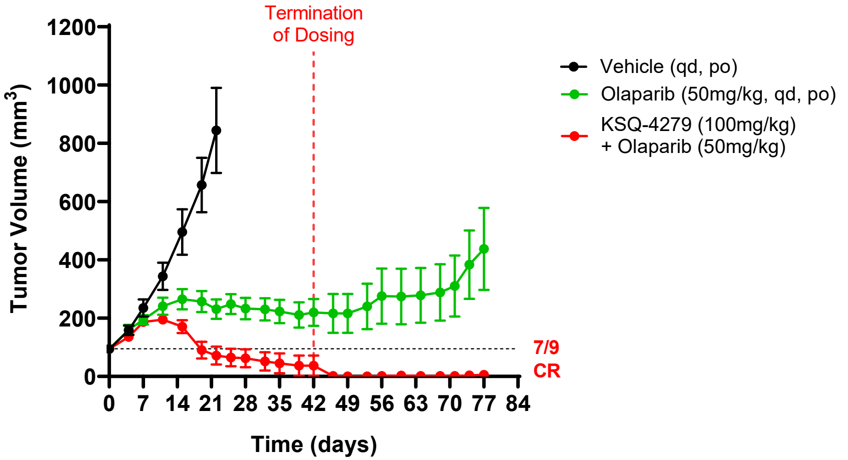


KSQ-4279 in Combination with Olaparib Leads to Tumor Regressions in Multiple TNBC & Ovarian PDX Models

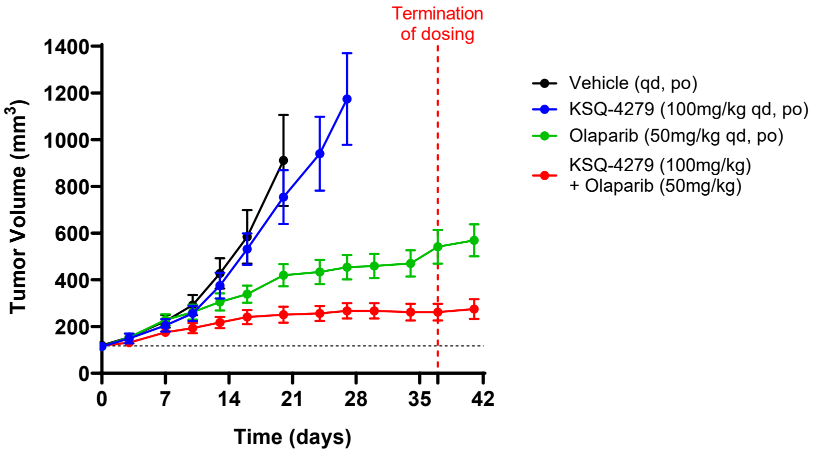
TNBC PDX #1
BRCA1^{MT} & p53^{MT}, HRD High



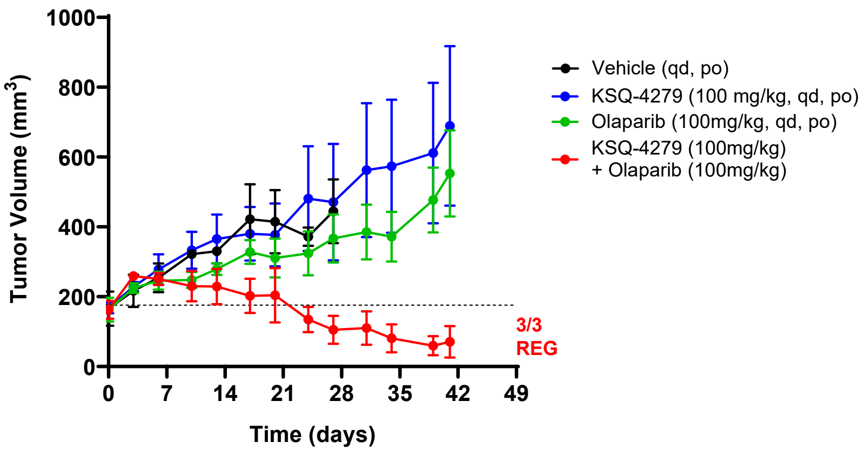
TNBC PDX #2
p53^{MT}, HRD High



TNBC PDX #3
(BRCA1 WT, p53 WT)



Ovarian PDX #1
BRCA1^{MT} & p53^{MT}



KSQ-4279 – A Potential First-in-Class USP1 Inhibitor for the Treatment of Ovarian and TNBC Patients

- **KSQ CRISPRomics® platform identified USP1 as an attractive cancer target**
  - BRCA/HRD deficient cancers show enriched response to USP1 inhibition
  - USP1 regulates DNA damage repair pathways distinct from PARP inhibitors
- **Discovered KSQ-4279, a potent and selective USP1 inhibitor**
- **CRISPRomics® resistance screens indicate that KSQ-4279 has a complimentary resistance profile to PARP inhibitors**
- **KSQ-4279 is active as a single agent in ovarian xenograft model and shows robust combination activity across multiple BRCA/HRD xenograft models**
- **KSQ-4279 is advancing towards IND filing in 2021**

Acknowledgements