

TNG348 is a potent and selective inhibitor of USP1 for the treatment of BRCA1/2mut and HRD+ cancers

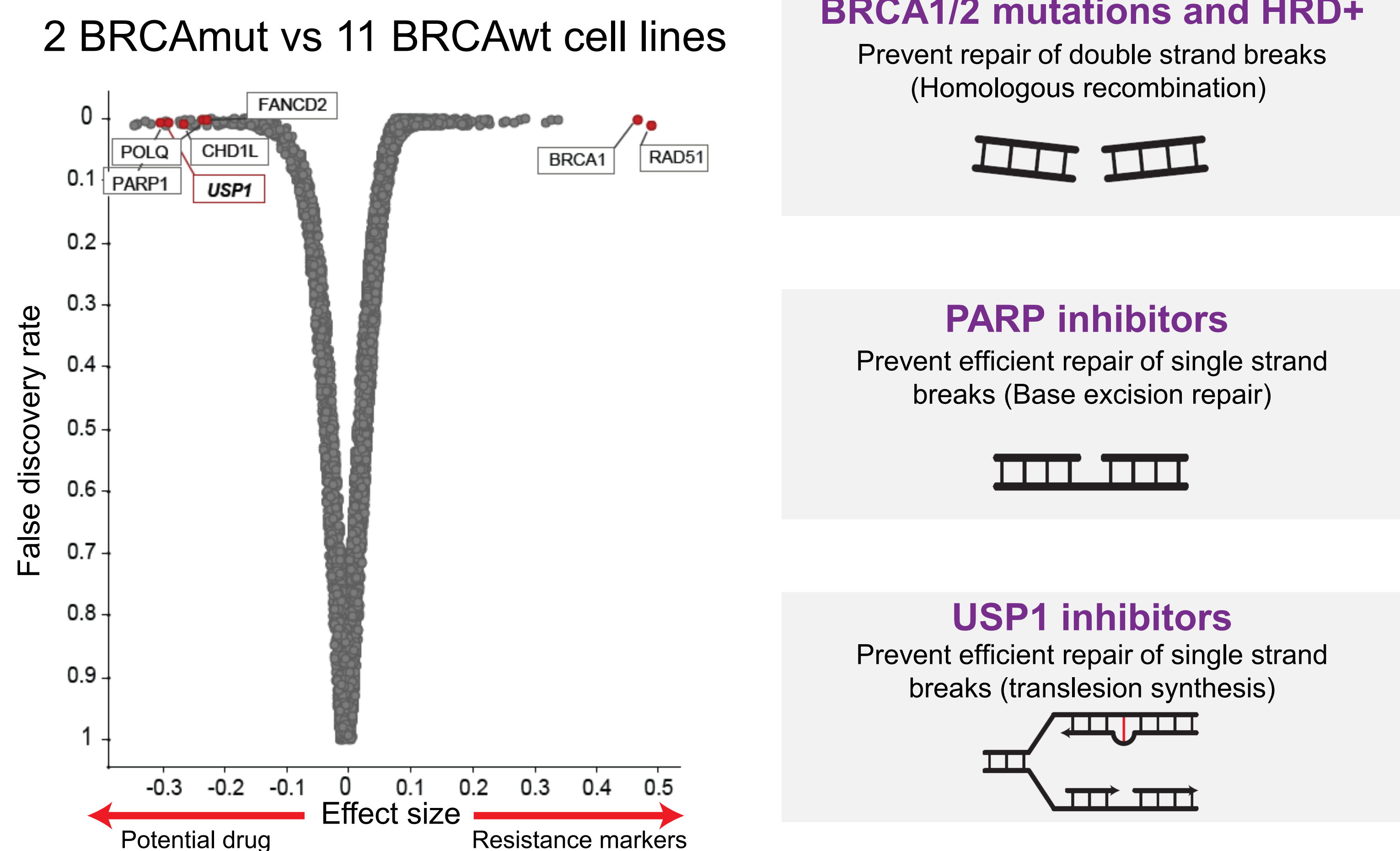
Abstract #4968

Antoine Simoneau, Hsin-Jung Wu, Madhavi Bandi, Katherine Lazarides, Sining Sun, Shangtao Liu, Samuel Meier, Ashley Choi, Hongxiang Zhang, Binzhang Shen, Douglas Whittington, Sirimas Sudsakorn, Wenhai Zhang, Yi Yu, Yong Liu, Colin Liang, Michael Palmieri, Yingnan Chen, Brian Haines, Alice Tsai, Minjie Zhang, Alan Huang, Jannik Andersen, Tianshu Feng, Scott Throner, John Maxwell

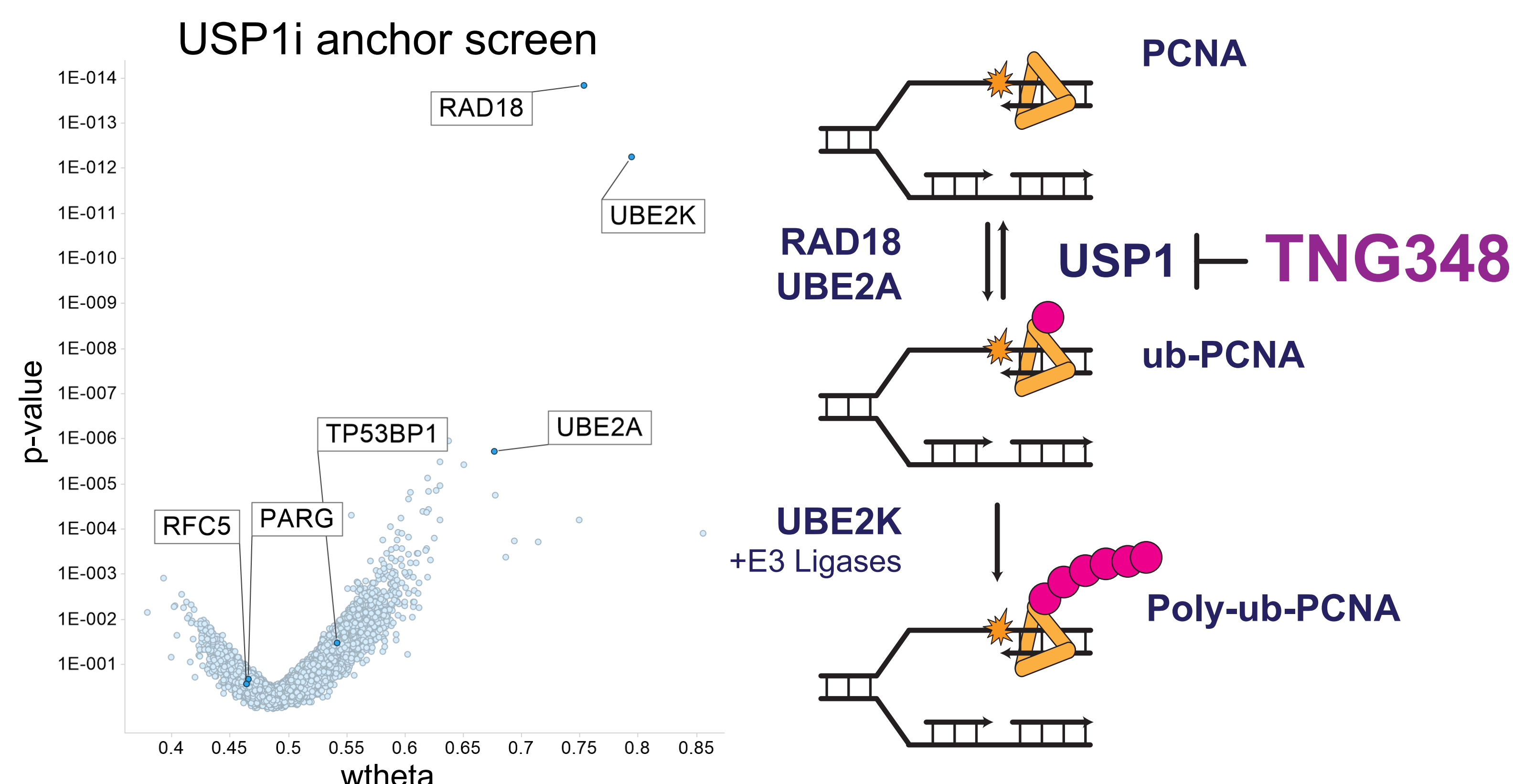
INTRODUCTION

TNG348 is a selective and potent inhibitor of the deubiquitinating enzyme USP1 designed to target BRCA1/2mut vulnerabilities in breast and ovarian tumors. Here we present the biochemical, mechanistic, and in vitro and in vivo characterization of TNG348, an oral, allosteric and highly potent inhibitor of USP1. Upon treatment, TNG348 causes loss of viability in breast and ovarian cell lines with BRCA1/2 mutations. Cell line panel analysis shows TNG348 activity extends beyond BRCA1/2mut models with homologous recombination deficiency (HRD) as an additional feature correlating with USP1 inhibition sensitivity. We show that TNG348 induces cell death through a pathway that is distinct from PARPi and TNG348 demonstrates robust synergy when combined with first- or second-generation PARPi. Moreover, TNG348 exhibits strong tumor growth inhibition in combination with PARPi in BRCA1/2mut and HRD+ xenograft models as well as models of acquired PARPi resistance. We plan to evaluate TNG348 as single agent and in combination with PARPi in patients with BRCA1/2 mutant or HRD+ tumors that are naïve to PARPi and with prior PARPi treatment history.

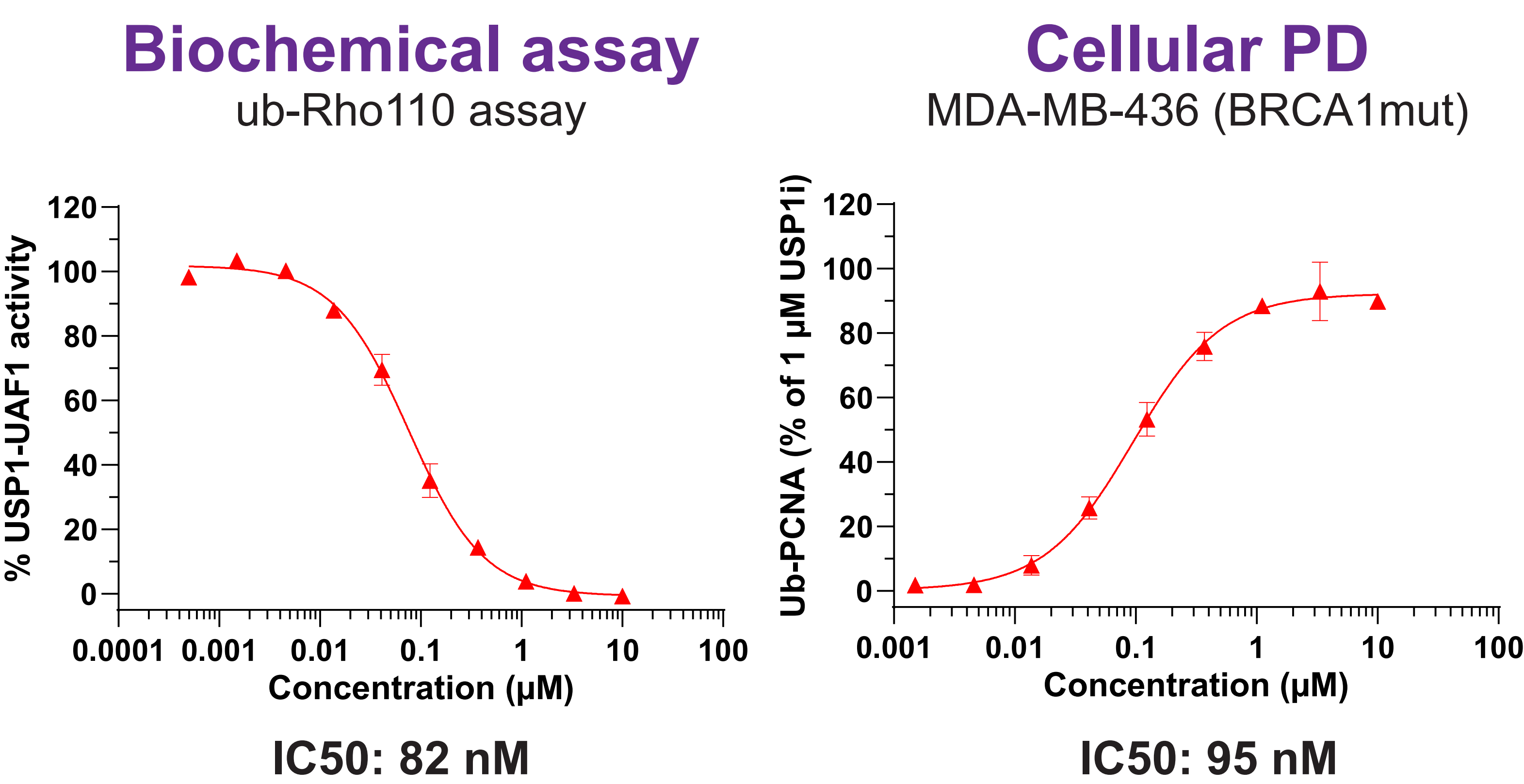
USP1 was identified as a synthetic lethal target in BRCA1/2 mutant cell lines



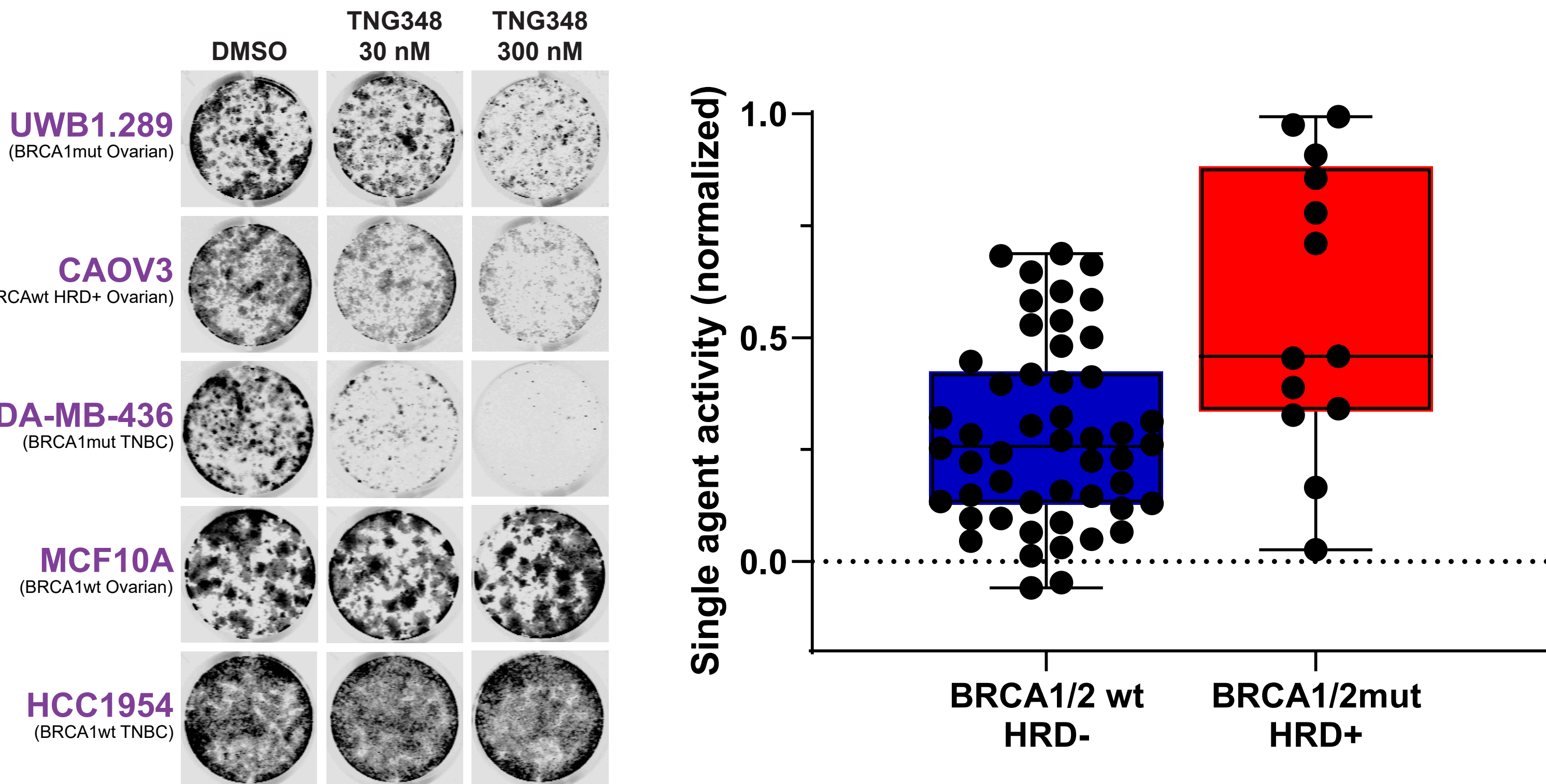
TNG348 acts through a ub-PCNA-dependent pathway that is distinct from PARP inhibitors



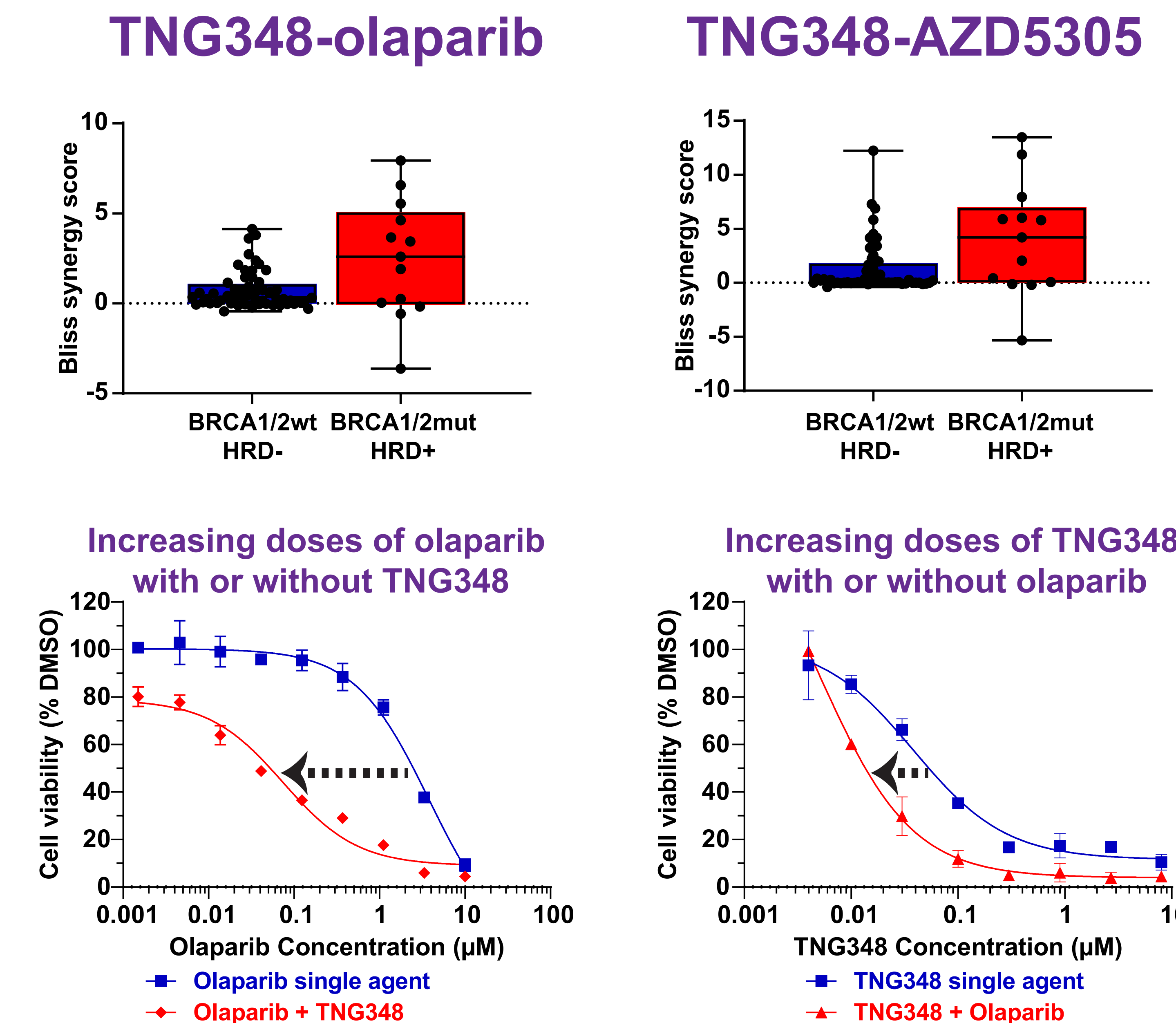
TNG348 is a potent inhibitor of USP1



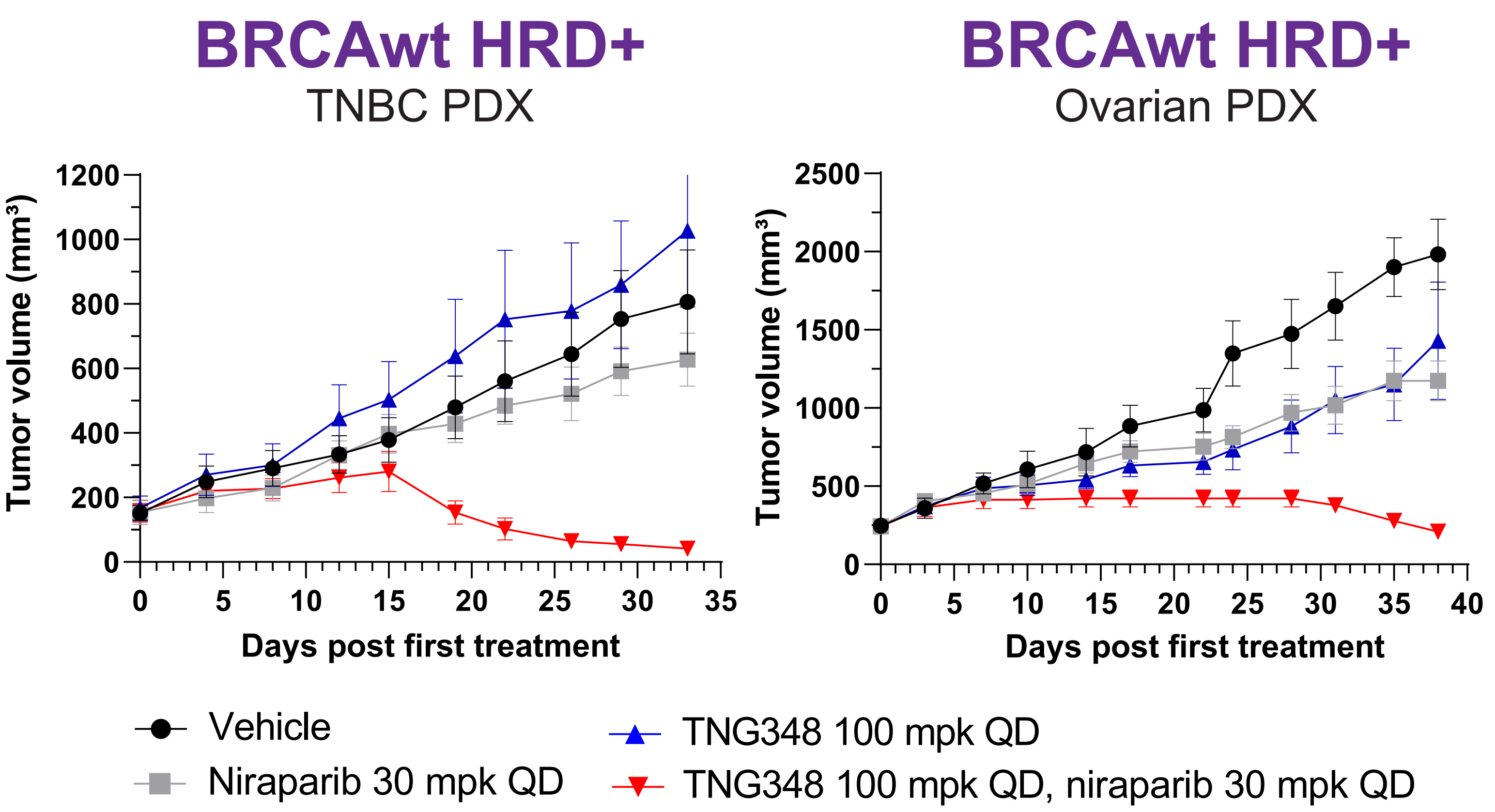
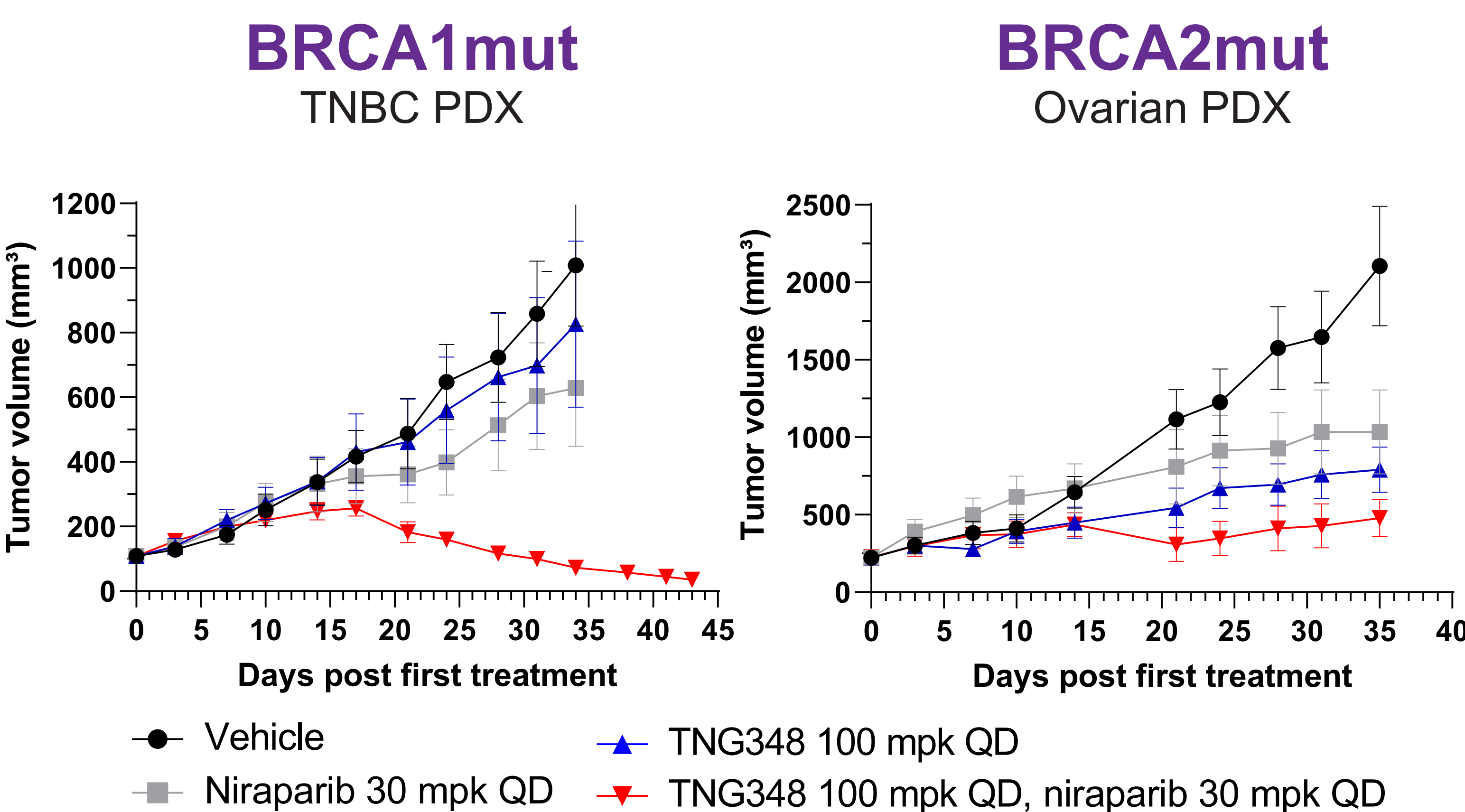
TNG348 is selective for BRCA1/2mut and HRD+



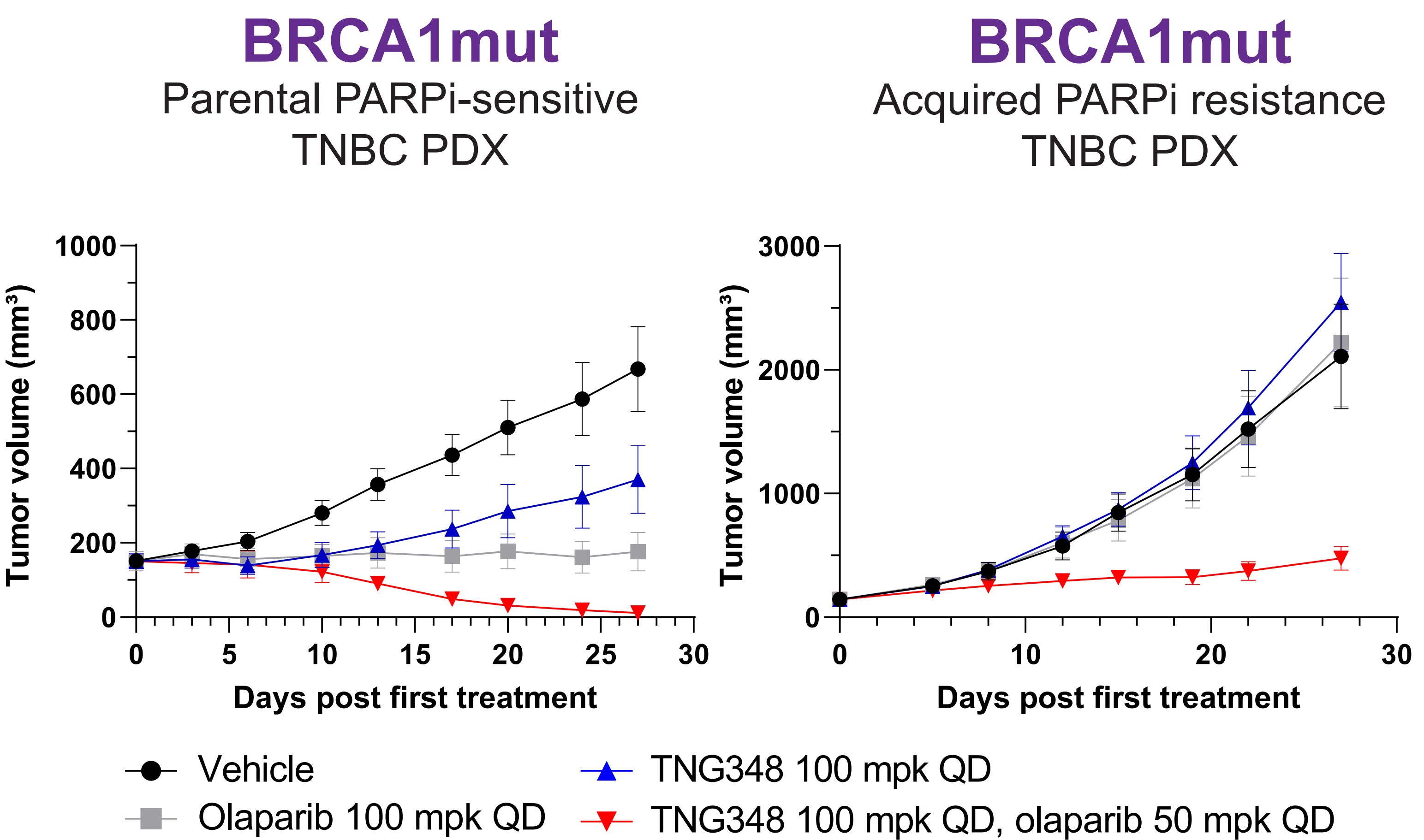
TNG348 synergizes with PARP inhibitors in vitro



TNG348 synergizes in vivo with PARPi



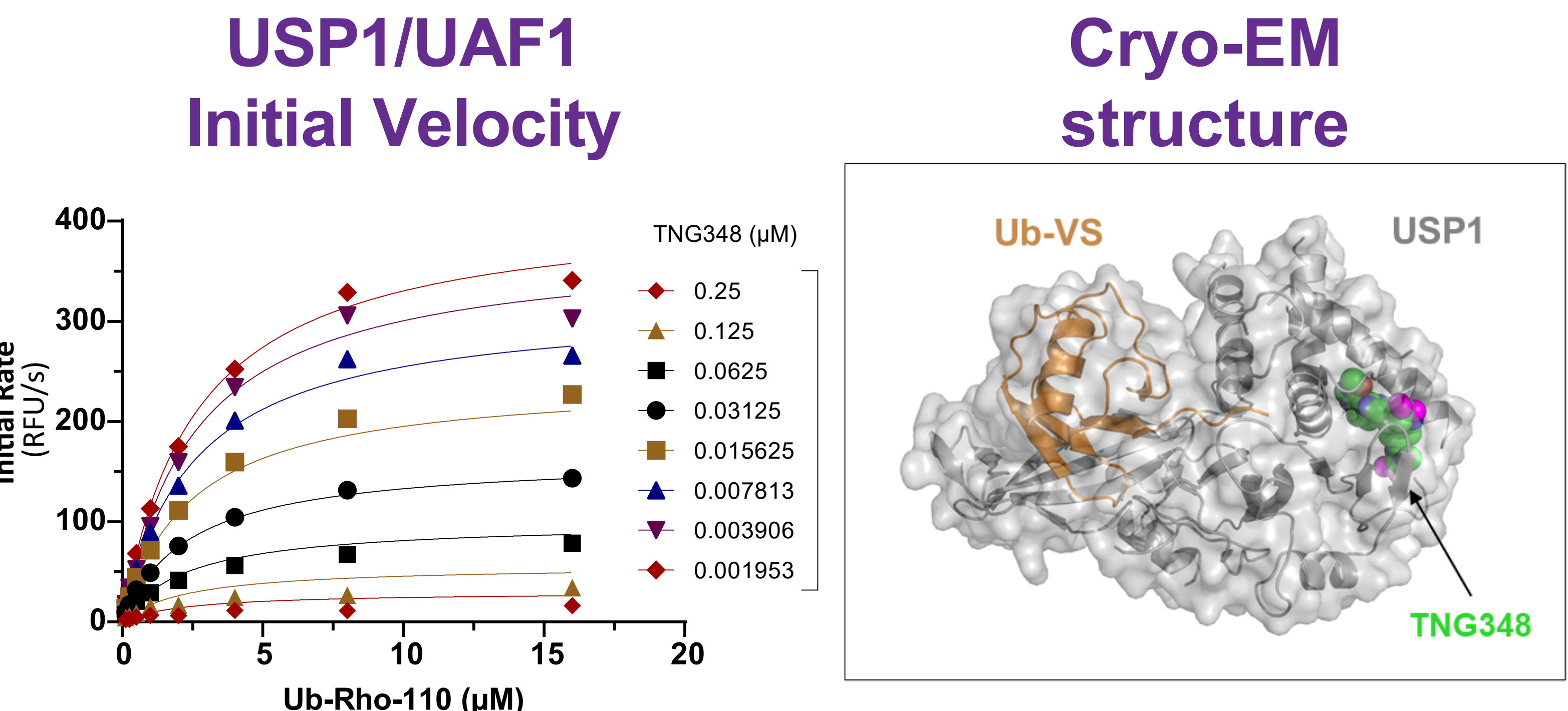
TNG348 can overcome acquired PARPi resistance



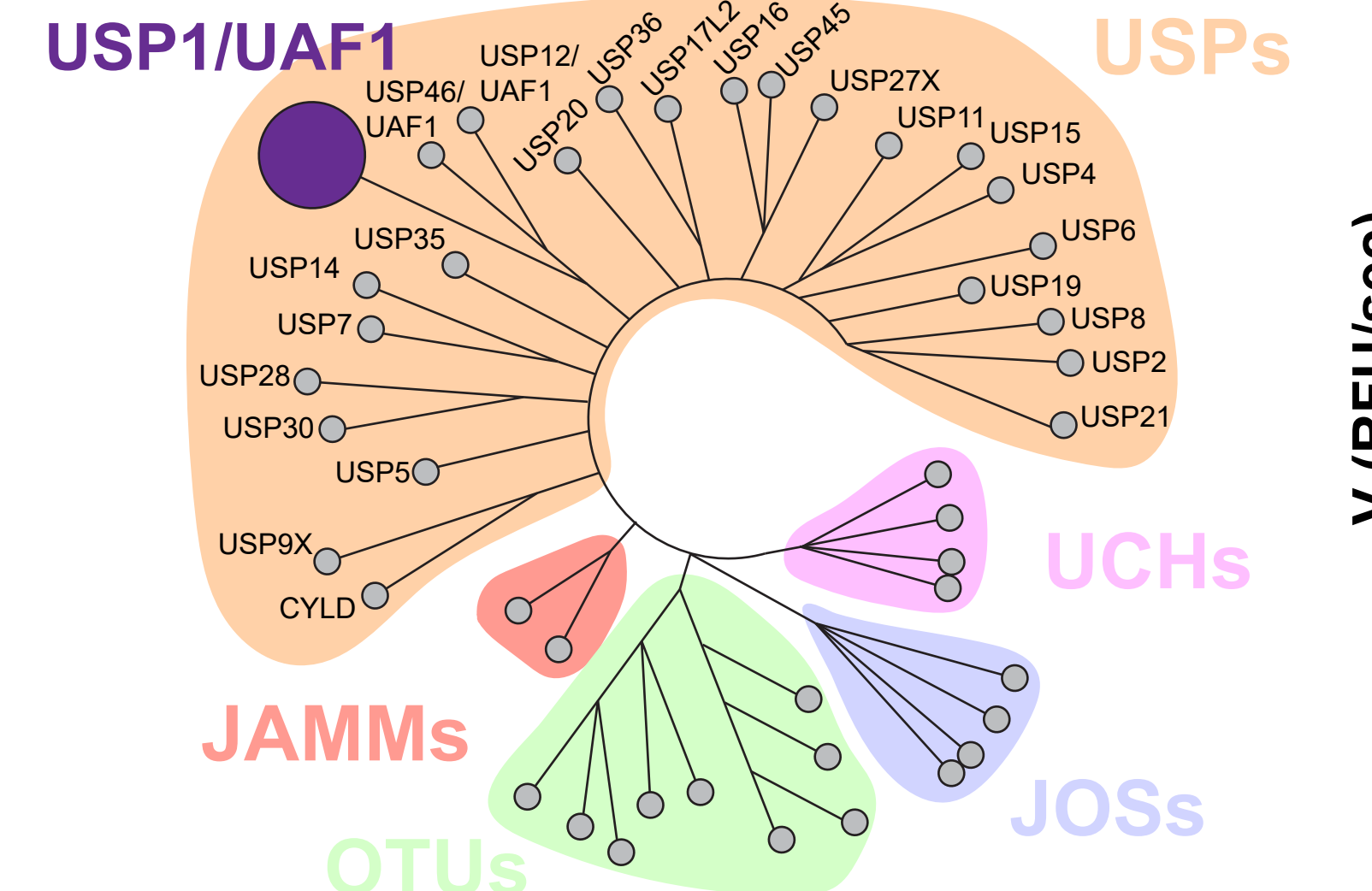
• PARPi resistant model was generated by consecutive passages in mice with constant olaparib exposure

• TNG348 is well tolerated, no body weight loss was observed in in vivo studies

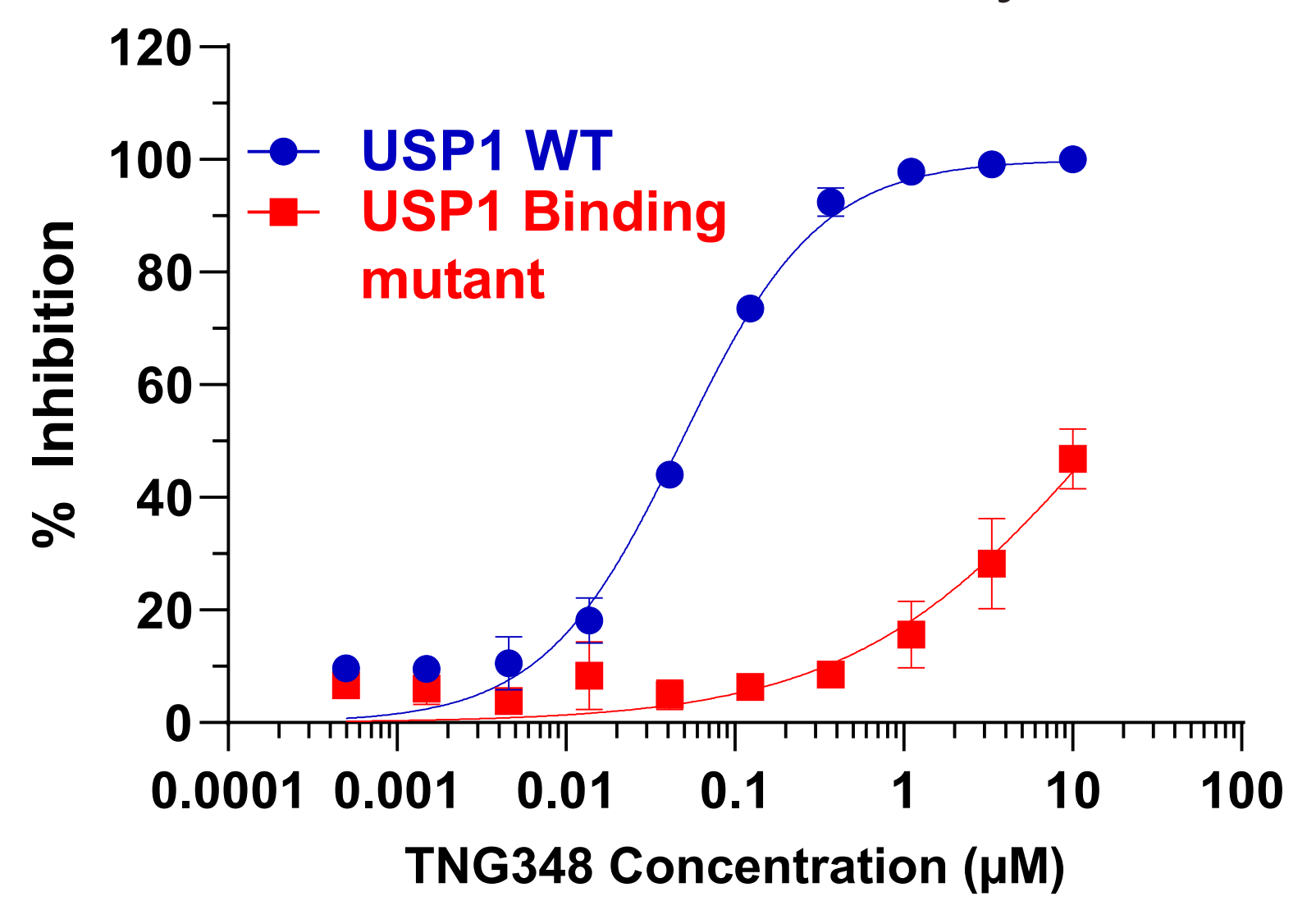
TNG348 is a selective allosteric inhibitor of USP1



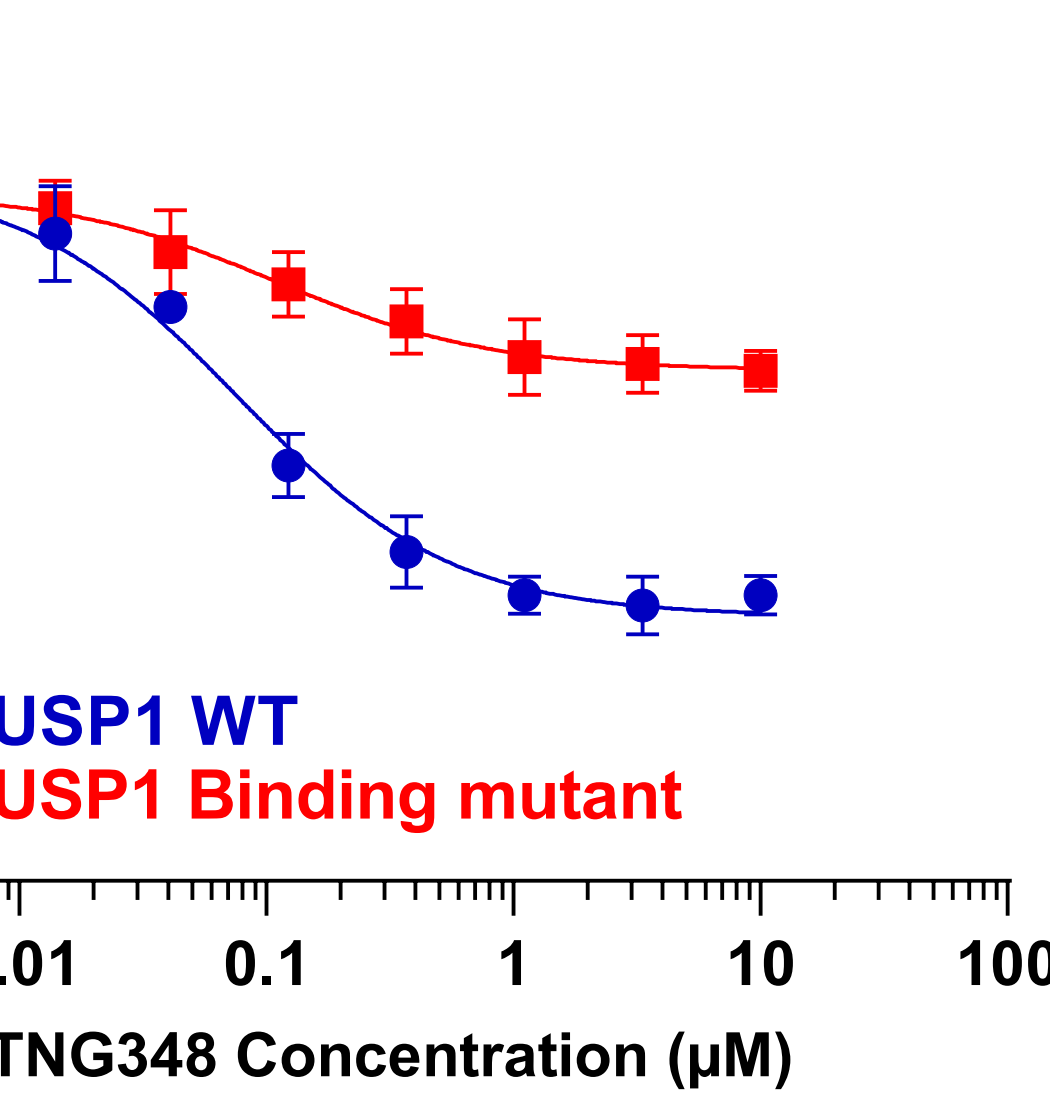
Selectivity across DUBs



TNG348 potency



Cell viability



SUMMARY

- USP1 inhibition is synthetic lethal with BRCA1/2 mutations through a distinct mechanism of action from PARPi
- Highly selective for USP1 in a panel of DUBs, consistent with its allosteric binding mode
- Single agent activity and strong PARPi synergy in breast and ovarian models with BRCA1/2 mutation or that are BRCA1/2wt but HRD+
- HRD+ cancers, including BRCA1/2 mutations, represent up to 50% of ovarian cancers, 25% of breast cancers, 10% of prostate cancers and 5% of pancreatic cancers
- Synergy in both PARPi-sensitive and -resistant models provides a clinical path in a large patient population
- TNG348 is clinical development candidate and we plan to file an IND in mid-2023

ACKNOWLEDGEMENTS

Chempartner, WuXi AppTec, Pharmaron, Xentech, XenoStart, Birtus Champions Oncology, Crown Bioscience, Enamine