TNG348, a selective USP1 inhibitor, shows strong preclinical combination activity with PARP inhibitors and other agents targeting DNA repair

INTRODUCTION

Tumors that are deficient in homologous recombination repair are generally sensitive to agents that target pathways involved in DNA repair, including PARP inhibitors (PARPi) and platinum-based drugs. Despite the clinical benefit of PARPi inhibitors, which are FDA-approved for the treatment of certain BRCA-mutant cancers, many patients achieve incomplete disease control and develop resistance. PARP inhibitors have been shown to synergize with chemotherapy and platinum-based drugs, but such combinations are limited clinically due to overlapping toxicities, highlighting the need for novel combination strategies. We previously reported the identification of USP1 as a target that selectively kills BRCA1/2-mutant cancer cells. TNG348 is an oral, allosteric and selective inhibitor of USP1, demonstrating strong preclinical combination activity with PARPi. In a PDX model of acquired PARPi resistance, TNG348 demonstrates strong combination synergy with PARPi demonstrating the ability of USP1i + PARPi to restore sensitivity to PARPi in the setting of acquired resistance. CRISPR-based drug anchor screens with and without PARPi or USP1i reveal that this synergy is driven by non-overlapping mechanisms of action. While sensitivity to either USP1i or PARPi is associated with HRD status, resistance to PARPi, but not USP1i, occurred with knock out of shld2 and other previously reported mechanisms. In contrast, resistance to USP1i was uniquely gained by knocking out genes involved in PCNA ubiquitination and translesion synthesis. In summary, these data support the clinical development plan to evaluate TNG348 in patients with BRCA1/2 mutant and other HRD tumors as single agent and in combination with PARPi.

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 PARPi inhibitors

TNG348 is selective for BRCA1mut and HRD+ cell lines

TNG348 is a potent and selective inhibitor of USP1

TNG348 synergizes with PARPi in HRD+ cells

TNG348 synergizes with DNA damaging agents

• PARPi resistant model was generated by consecutive passages in mice with constant olaparib exposure
• TNG348 can restore sensitivity to PARPi after acquired resistance to PARPi
• TNG348 is well tolerated, no body weight loss was observed in in vivo studies

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