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

Abstract #B054

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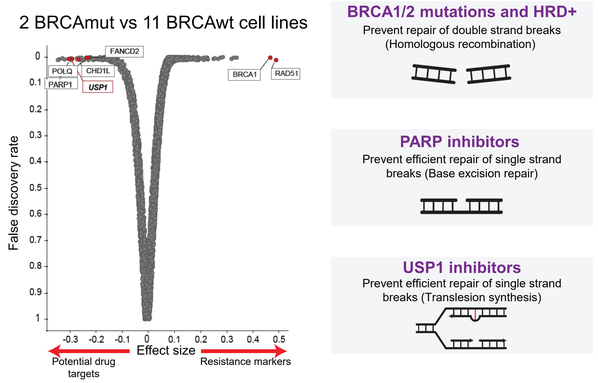
INTRODUCTION

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 PARP1/2 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 potent inhibitor of USP1 (USP1i). Here we present the mechanism of action and preclinical efficacy of TNG348 across multiple BRCA1/2 mutant and other homologous recombination deficient (HRD) tumor models, demonstrating its therapeutic potential. In preclinical models, TNG348 activity is further enhanced when combined with agents targeting DNA repair pathways, including PARP inhibitors. In a PDX model of acquired PARPi resistance, TNG348 demonstrates strong combination activity 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 shieldin components 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 PARP1i.

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

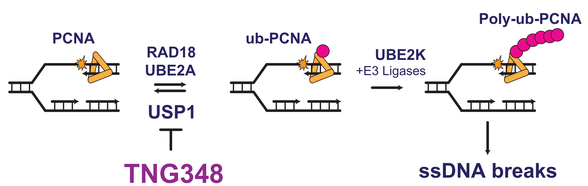


BRCA1/2 mutations and HRD+
Prevent repair of double strand breaks (Homologous recombination)

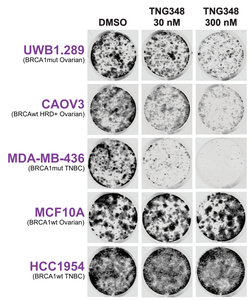
PARP inhibitors
Prevent efficient repair of single strand breaks (Base excision repair)

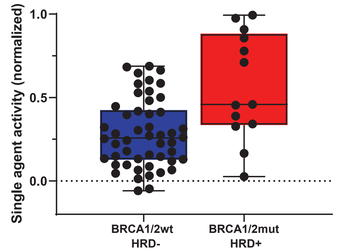
USP1 inhibitors
Prevent efficient repair of single strand breaks (Translesion synthesis)

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



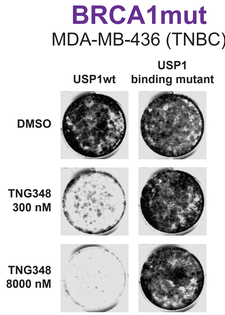
TNG348 is selective for BRCA1/2mut and HRD+ cells



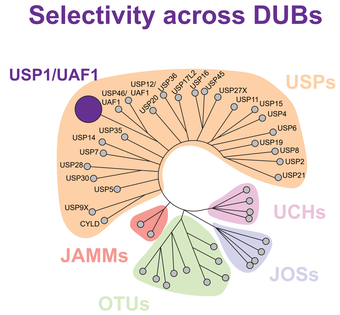


TNG348 is a potent and selective inhibitor of USP1

BRCA1mut
MDA-MB-436 (TNBC)



Selectivity across DUBs



Loss of DNA repair pathways sensitize to USP1i

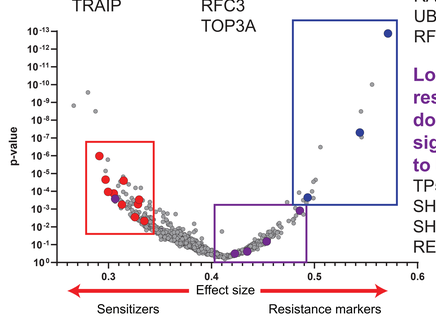
USP1i CRISPRn anchor screen
UWB1.289 (BRCA1mut)

DNA repair
PARP1
XRCC1
APEX2
TRAIP

DNA replication
PCNA
POLD2
POLD3
RFC3
TOP3A

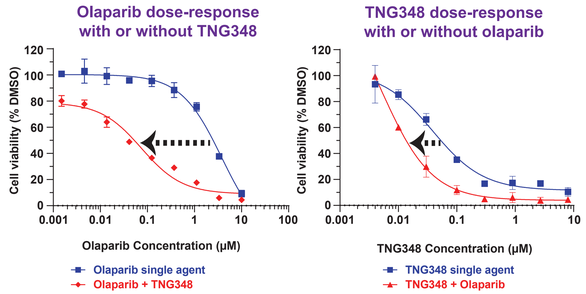
Loss of ub-PCNA pathway causes resistance to USP1i
RAD18
UBE2K
RFWD3

Loss of known PARPi resistance genes do not cause significant resistance to USP1i
TP53BP1
SHLD1
SHLD2
REV7

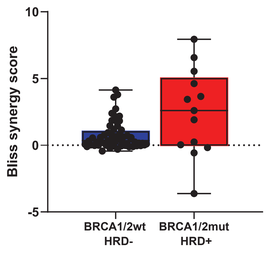


TNG348 synergizes with PARPi in HRD+ cells

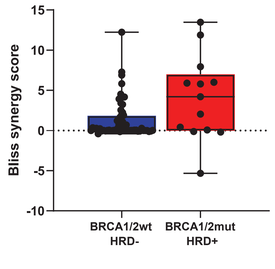
BRCA1mut
UWB1.289 (ovarian)



TNG348-PARP1/2i

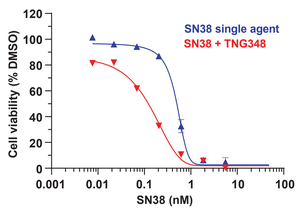


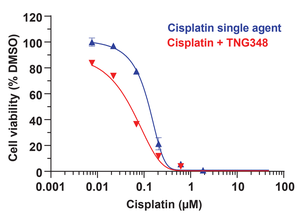
TNG348-PARP1i



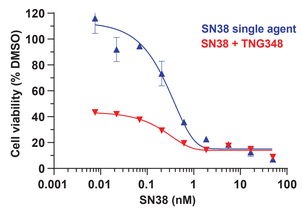
TNG348 synergizes with DNA damaging agents

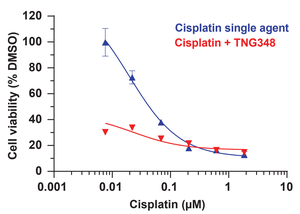
Ovarian
UWB1.289 (BRCA1mut)





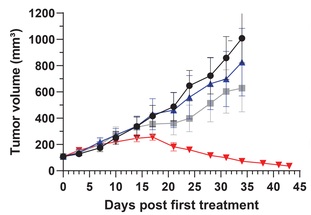
TNBC
MDA-MB-436 (BRCA1mut)



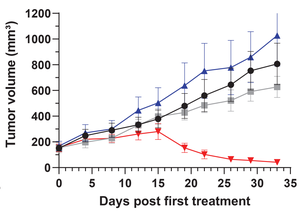


TNG348 synergizes *in vivo* with PARPi

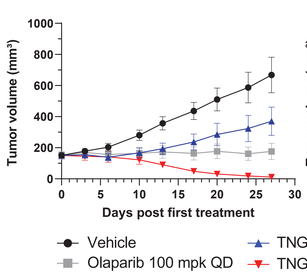
BRCA1mut
TNBC PDX



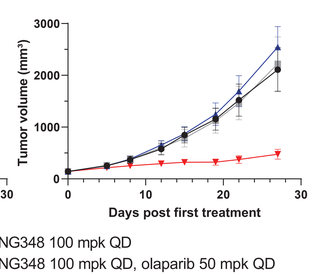
BRCAwt HRD+
TNBC PDX

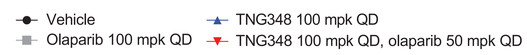


BRCA1mut
Parental PARPi-sensitive
TNBC PDX



BRCA1mut
Acquired PARPi resistance
TNBC PDX





- **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**

SUMMARY

- USP1 inhibition is synthetic lethal with BRCA1/2 mutations through a mechanism of action distinct from PARPi
- TNG348 is 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
- FDA clearance of IND for TNG348 announced in September 2023

ACKNOWLEDGEMENTS

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