TNG348 is synergistic with PARP inhibitors in tumor models with elevated replication stress

Abstract #4527

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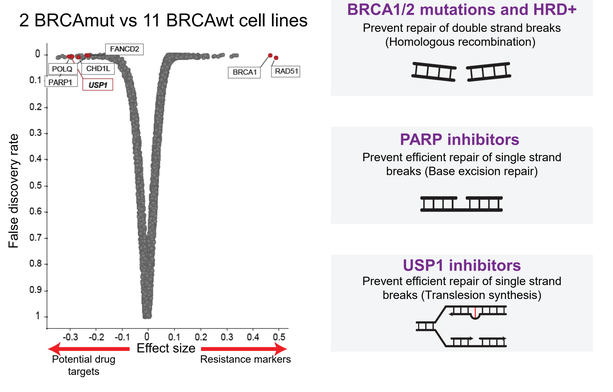
Introduction

Defective maintenance of genomic integrity is a hallmark of cancer cells that can result from oncogene-induced replication stress and by loss of DNA repair mechanisms. DNA repair deficiencies and elevated replication stress present targetable vulnerabilities for cancer treatment. Notably, BRCA1/2 mutant and homologous recombination deficient (HRD) tumors cannot repair double-strand breaks by homologous recombination and rely on alternative pathways of DNA repair. PARP inhibitors (PARPi), which are a standard of care in many BRCA1/2 mutant tumors, cause synthetic lethality with BRCA1/2 mutation by inhibiting the DNA base excision repair pathway. Despite the clinical benefit of PARPi, they are not effective in every HRD tumor and the acquisition of PARPi resistance limits long-term response. TNG348, a selective allosteric inhibitor of the deubiquitinating enzyme USP1, was specifically designed to target HRD vulnerabilities through an alternative mechanism. We previously showed that the anti-tumor activity of USP1 inhibition results from disruption of the translesion synthesis DNA damage tolerance pathway, a mechanism of action that is functionally distinct from base excision repair targeted by PARPi. Our preclinical studies show that TNG348 is active in HRD models and strongly synergizes with PARP inhibitors to drive strong anti-tumor responses. We have identified replication stress as a predictive biomarker of TNG348 response using cell line profiling and genome-wide CRISPR screens. For example, overexpression of oncogenes known to induce replication stress sensitized to the TNG348 and PARPi combination both in vitro and in vivo. These data indicate that cancer-specific elevated DNA replication stress could contribute to tumor sensitivity to TNG348 and provide additional patient stratification strategies and opportunities for indication expansion.

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

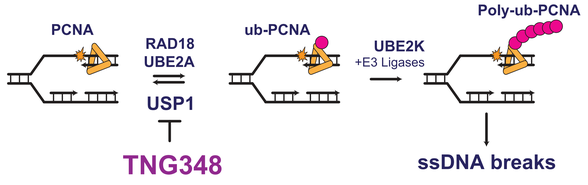


BRCA1/2 mutations and HRD+
Prevent repair of double strand breaks (Homologous recombination)

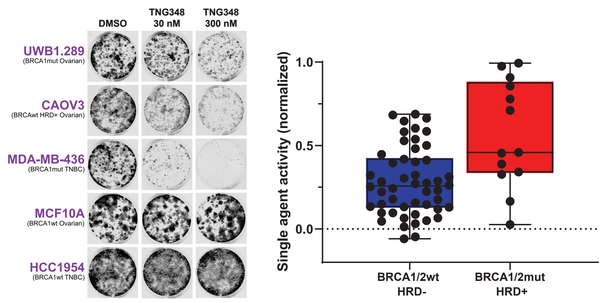
PARP inhibitors
Prevent efficient repair of single strand breaks (Base excision repair)

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

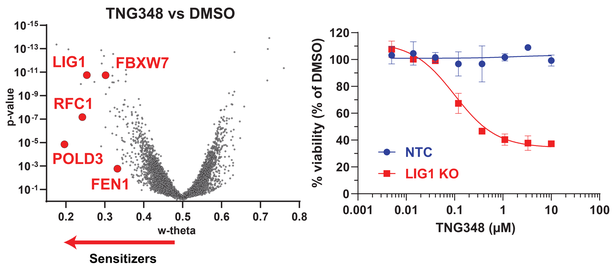


TNG348 activity is enriched in BRCA1/2mut and HRD+ cells



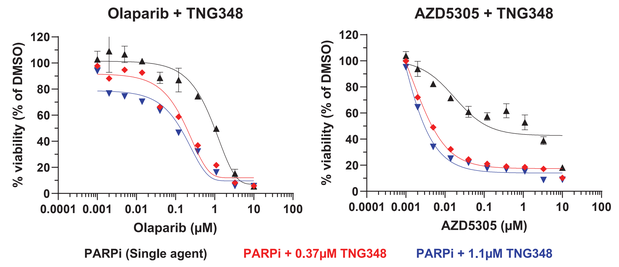
Loss of DNA replication factors sensitizes to TNG348

NCI-H1299
BRCAwt and non-HRD+ NSCLC



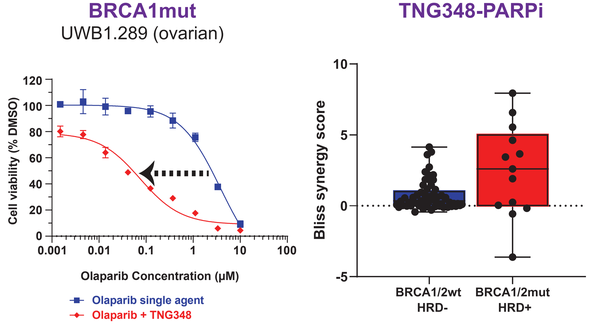
TNG348 + PARPi synergize CCNE1-amp cell line

OVCAR-3
CCNE1-amplified ovarian



TNG348 synergizes with PARPi in HRD+ cells

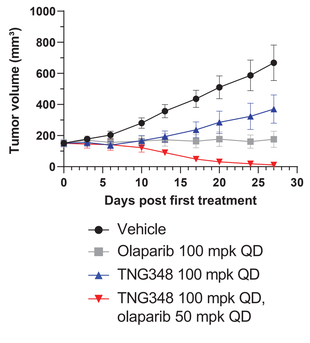
BRCA1mut
UWB1.289 (ovarian)



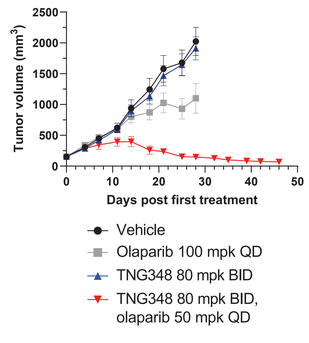
USP1i also synergize with PARPi in several non-HRD+ cancer cell lines

TNG348 synergizes in vivo with PARPi

BRCA1mut
TNBC PDX

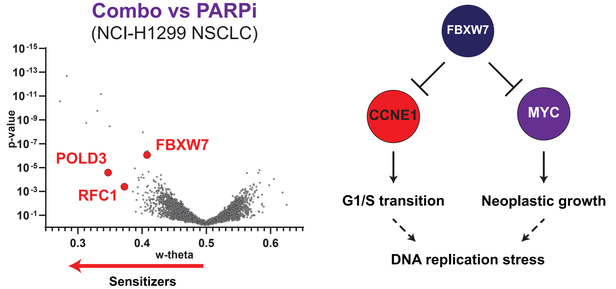


BRCA1mut
Pancreatic PDX



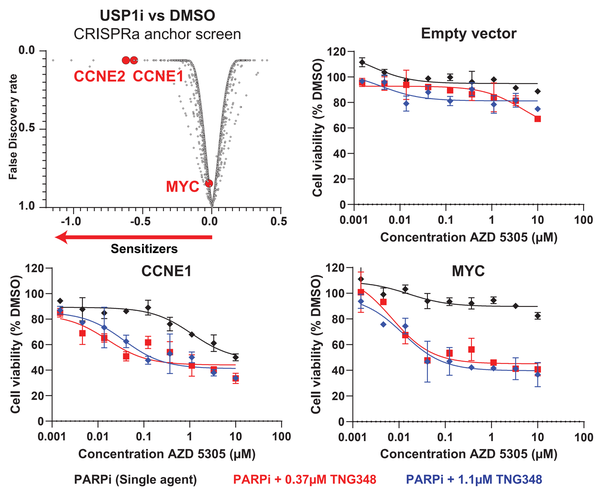
Anchor screen identifies FBXW7 KO as sensitizer to TNG348 + PARPi combination in non-HRD+ cells

Combo vs PARPi
(NCI-H1299 NSCLC)



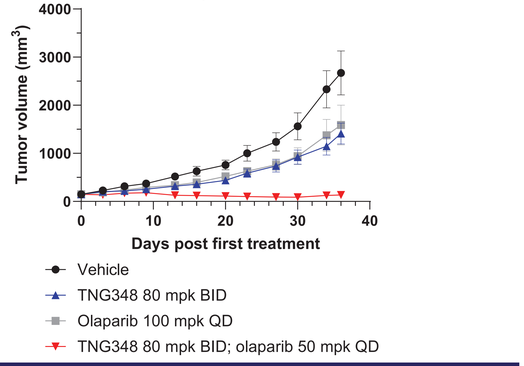
Oncogene overexpression predicts TNG348 + PARPi response

A549
BRCAwt and non-HRD+ NSCLC



CCNE1-amp CDX is sensitive to TNG348 + PARPi

OVCAR-3
CCNE1-amplified ovarian



Summary

- USP1 inhibition is synthetic lethal with BRCA1/2 mutations through a mechanism of action distinct from PARPi
- 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
- TNG348 and PARPi synergize in a subset of non-HRD+ models
- Alterations that cause DNA replication stress can sensitize to TNG348 and combination with PARPi
- CCNE1 amplification predicts response to TNG348 + PARPi in non-HRD+ tumor models
- TNG348 phase 1/2 clinical trial ongoing (NCT06065059); first patient dosed announced in January 2024

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