MOMA-313 is a potent, selective Polθ inhibitor that enhances response to PARP inhibition in HR-deficient tumor models

Erica Evans, Michael Reutershan, Vinny Motwani, Kelly McGlynn, Yonghong Bai, Christopher Quinn, Manaswni Dhingra, Cen Gao, David Waller, Salah Nabhan, Timothy Guzi, Peter Hammerman, and Jordan Krall

MOMA Therapeutics, Cambridge, Massachusetts, USA

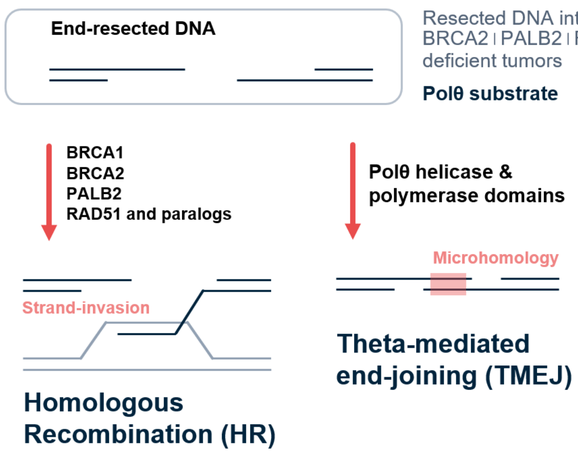
Abstract

Background:

DNA polymerase theta (Polθ) is an enzyme involved in DNA double-strand break (DSB) repair. Polθ contains an N-terminal ATPase-powered DNA helicase domain and a C-terminal DNA polymerase domain that work in tandem to repair DSBs through theta-mediated end-joining (TMEJ). In most contexts, Polθ activity is not required, as homologous recombination (HR) functions as the preferred pathway to repair DSBs that arise during DNA replication. However, genes required for HR-mediated DNA repair are commonly mutated or deleted in tumors, creating a strong dependence on Polθ-mediated TMEJ for the repair of DSBs and cell survival. MOMA-313 is a novel, potent, and selective inhibitor of Polθ helicase activity crafted to exploit the impaired DNA repair capabilities of HR-deficient tumors for potential therapeutic benefit.

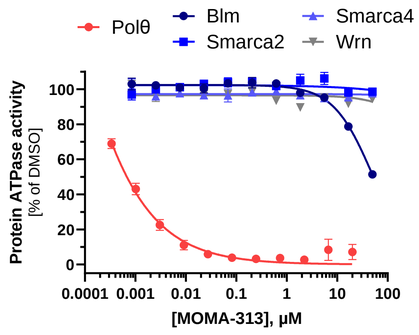
Results:

MOMA-313 is a potent inhibitor of Polθ helicase activity that strongly inhibited TMEJ repair and drove apoptosis in HR-deficient contexts in vitro and in vivo. MOMA-313 synergized with PARP inhibitors, used as standard of care therapies for HR-deficient tumors, to enhance DNA damage, apoptosis, and antiproliferative activity in HR-deficient but not HR-proficient cell lines. MOMA-313 abrogated in vivo TMEJ activity when dosed at 3-10 mg/kg twice daily and displayed antitumor activity in HR-deficient tumors when combined with the PARP inhibitor olaparib. Antitumor activity with MOMA-313 and olaparib in HR-deficient cell line xenografts and PDXs significantly exceeded the antitumor activity seen with either agent alone and was well tolerated at all doses. MOMA-313 represents a promising new therapy for HR deficient tumors and is currently in phase 1 clinical testing.



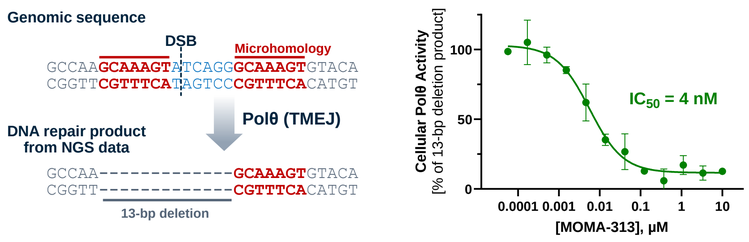
MOMA-313 displays potent and selective efficacy against HR-deficient cell lines

MOMA-313 is a potent and selective inhibitor of human Polθ ATPase activity

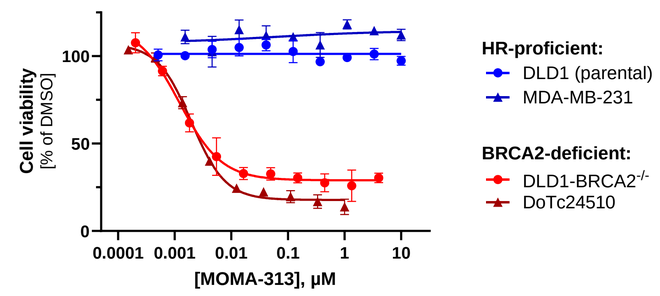


Recombinant Protein	ATPase IC_{50}
Human Polθ	0.7 nM
Human Blm	45,900 nM
Human Smarca2	> 50,000 nM
Human Smarca4	> 50,000 nM
Human Wrn	> 50,000 nM

Dose dependent inhibition of TMEJ repair product formation after targeted DNA DSB in DLD-1 cells



MOMA-313 potently inhibits the cell viability of multiple HR-deficient cell lines across multiple genotypes

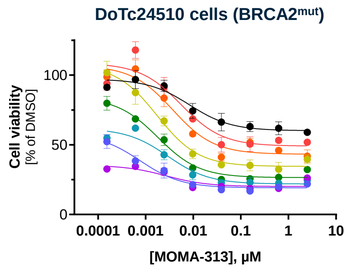


Cell Line	IC_{50}	Status	Alteration
DLD1-BRCA2$^{-/-}$	2.7 nM	HR-deficient	BRCA2-KO
DoTc24510	2.4 nM	HR-deficient	BRCA2-mut
Capan-1	534 nM	HR-deficient	BRCA2-mut
KP363T	0.2 nM	HR-deficient	RAD51C-methyl.
SNU-601	0.5 nM	HR-deficient	RAD51C-methyl.
DLD1 (parental)	> 10,000 nM	HR-proficient	---
MDA-MB-231	> 10,000 nM	HR-proficient	---

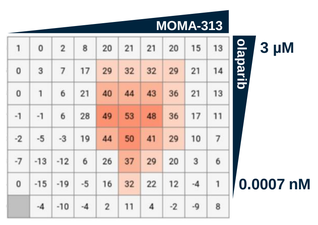
Strong selectivity profile: No activity observed in HR-proficient cell lines with MOMA-313 concentrations up to 10 µM

MOMA-313 synergizes with PARP inhibitors in HR-deficient cell lines

DoTc24510 cells (BRCA2^{mut})

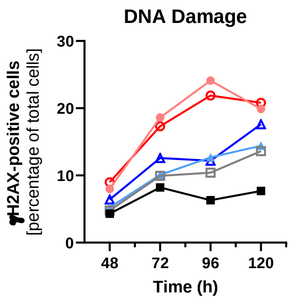


Loewe synergy matrix

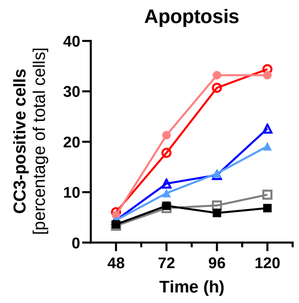


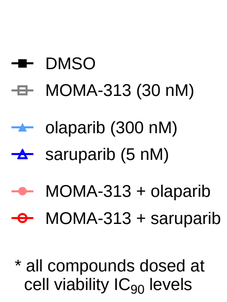
PARP inhibitor (+ MOMA-313)	Loewe synergy score	Assessment
Olaparib	14.2	Synergistic
Rucaparib	13.8	Synergistic
Niraparib	10.1	Synergistic
Veliparib	9.1	Synergistic
Talazoparib	9.6	Synergistic
Saruparib (Parp1-selective)	10.3	Synergistic

DNA Damage



Apoptosis

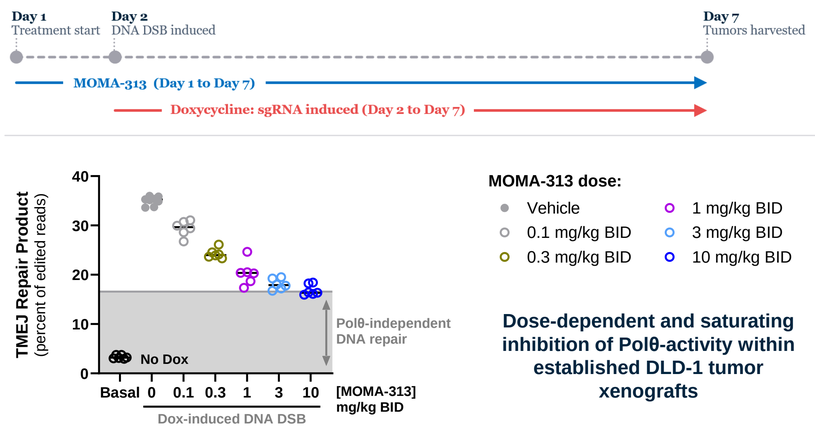




- **MOMA-313 displays class-wide synergy with PARP inhibitors against HR-deficient cells**
- **Combinations accentuate DNA damage and apoptosis even at high target coverage**
- **Strong selectivity profile: no impact of combination treatment on HR-proficient cells**

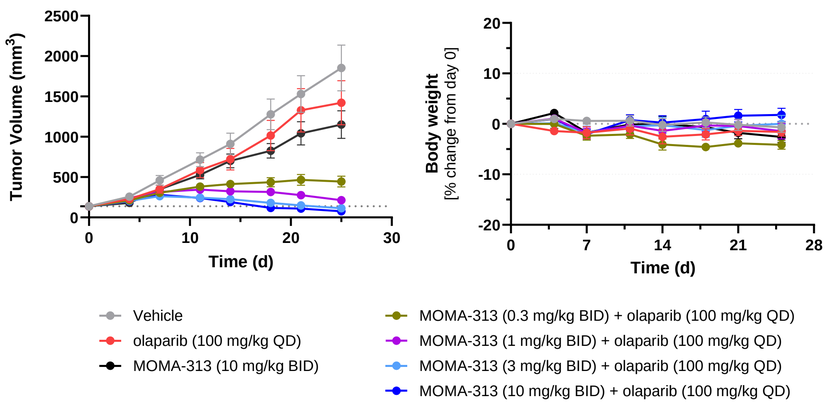
MOMA-313 inhibits in vivo TMEJ and drives tumor regressions in combination with olaparib

In vivo TMEJ assay: repair of a doxycycline-induced CRISPR-targeted DSB

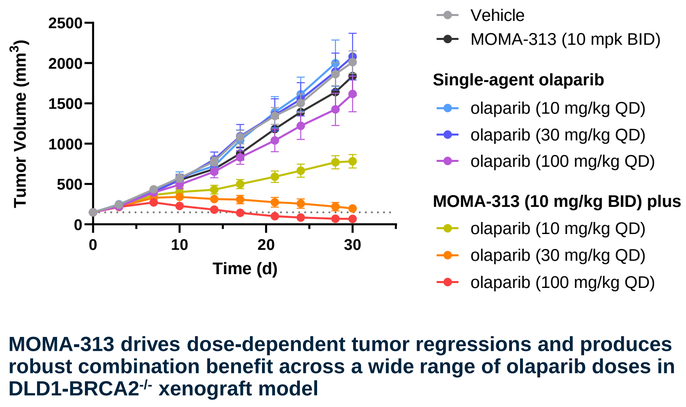


Dose-dependent and saturating inhibition of Polθ-activity within established DLD-1 tumor xenografts

MOMA-313 displays dose-dependent combination efficacy with olaparib (DLD1-BRCA2$^{-/-}$ CDX)



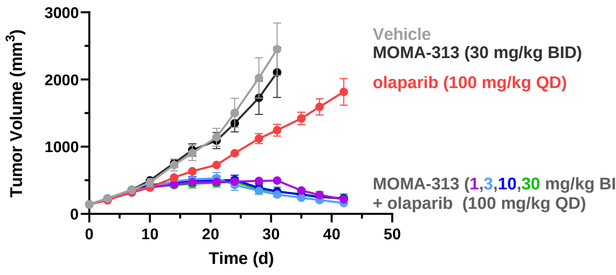
MOMA-313 retains efficacy with reduced olaparib doses



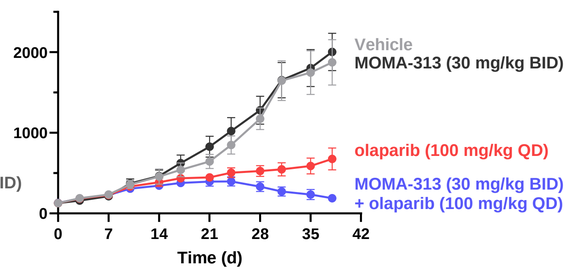
MOMA-313 drives dose-dependent tumor regressions and produces robust combination benefit across a wide range of olaparib doses in DLD1-BRCA2$^{-/-}$ xenograft model

MOMA-313 plus olaparib regresses BRCA^{mut} PDX models

BRCA2-mutant pancreatic PDX



BRCA1-mutant pancreatic PDX



- **MOMA-313 displays dose-dependent efficacy and drives tumor regressions in combination with olaparib against multiple BRCA-deficient PDX models in clinically relevant indications**
- **Combination treatment is well-tolerated at all dose-levels tested**

Summary

- **MOMA-313 is a potent and selective inhibitor of the Polθ helicase domain in clinical development for the treatment of HR-deficient tumors**
- **MOMA-313 potently inhibits Polθ-dependent TMEJ and selectively kills HR-deficient cancer cells**
- **MOMA-313 displays class-wide synergy with PARP inhibitors in vitro and drives deeper responses in HR-deficient CDX and PDX tumor models in combination with olaparib than either agent alone**
- **MOMA-313 phase 1 clinical trial initiated in August 2024 and currently enrolling (NCT06545942)**

MOMA-313 phase 1 clinical trial initiated

MOMA-313 monotherapy arm

- Locally advanced or metastatic solid tumors with prior PARP inhibitor exposure
- Genetic biomarkers of HR-deficiency eligible
- BLRM escalation design for both monotherapy and combination arms

MOMA-313 combination arm with olaparib

- Escalation: PARP inhibitor exposed or naïve solid tumors with HR deficiencies including BRCA1, BRCA2, CDK12, PALB2, RAD51B/C/D mutations
- Combination cohorts initiate after evaluation of initial MOMA-313 monotherapy dose-levels
- Expansion and optimization: PARP inhibitor-naïve metastatic CRPC, breast, or pancreatic tumors with HR deficiencies