TA repeat expansion outperforms MSI-H as a predictor of sensitivity to the novel WRN inhibitor MOMA-341

Anthony Tubbs, Javad Golji, Meredeth McGowan, Theresa Baker, Giulia Bottoni, Erin Brophy, Cindy Yan, Yonghong Bai, Haley Amemiya, Momar Toure, John Butler, Haoxuan Wang, Cen Gao, Timothy Guzi, Peter Hammerman, Erica Evans, Allison Drew

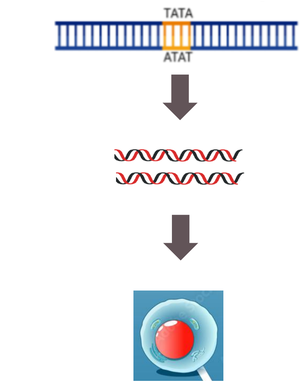
MOMA Therapeutics, Cambridge, Massachusetts, USA

Abstract

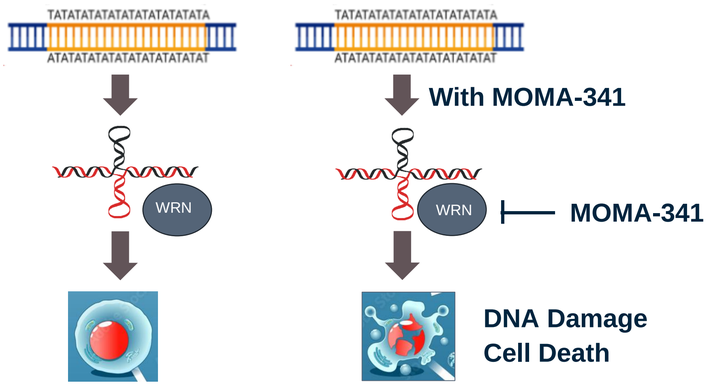
MOMA-341 is a potent and selective covalent inhibitor of the WRN helicase in clinical development for the treatment of dMMR/MSI-H tumors. The Werner syndrome helicase (WRN) is selective essential in MSI-H cell line and PDX models[1]. Since TA repeat expansions drive WRN dependency in dMMR/MSI-H tumor models[2], we hypothesized that direct, quantitative measurements of TA repeat expansions would better predict MOMA-341 responses in preclinical MSI-H tumor models than available clinical diagnostics for dMMR and MSI-H.

In contrast to dMMR or MSI-H status, direct measurement of genome-wide TA repeat expansions by long read sequencing produces a near-perfect prediction of sensitivity to WRN inhibition across a large cohort of preclinical tumor models. While MSI-H tumors with highly expanded TA repeat regions were very sensitive to MOMA-341, incomplete single agent antitumor activity was observed in MSI-H tumors with lower levels of TA repeat expansion. These incomplete tumor responses were converted to regressions with higher doses of MOMA-341 or in combination with chemotherapies such as irinotecan.

Normal Cells (MSS) — Short stable TA repeats

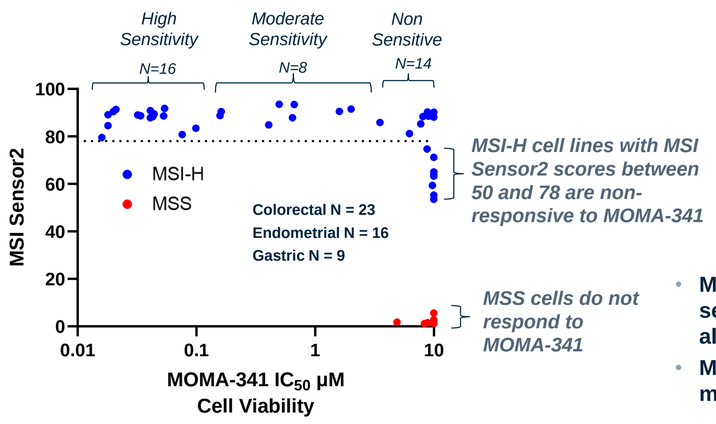


dMMR/MSI-H Tumors — Large-scale expansion of TA repeats genome-wide



MOMA-341 activity in cell line panel supports need for MSI-H biomarker refinement

Cell line sensitivity to MOMA-341 compared to MSI Score



MSI-H cell lines with MSI Sensor2 scores between 50 and 78 are non-responsive to MOMA-341

MSS cells do not respond to MOMA-341

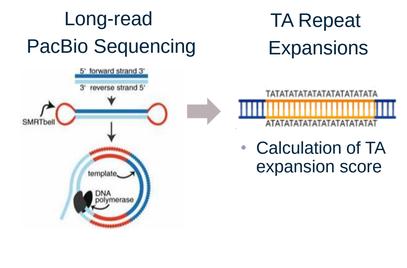
MSI Sensor 2
https://github.com/niu-lab/msisensor2
NGS-based algorithm for determining continuous MSI score (Score = % of microsatellites mutated)

2829 microsatellites analyzed
> 99% mononucleotide repeats, 0% TA repeats

- **MSI Sensor2 improves upon MSI-H to predict sensitivity to MOMA-341, but does not exclude all non-sensitive cell lines**
- **MSI Sensor2 cannot discriminate between moderate and highly sensitive MSI-H cell lines**

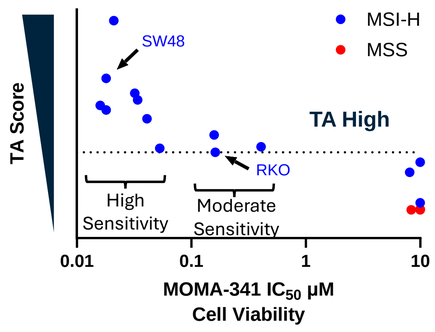
TA repeat expansions predict MOMA-341 sensitivity in preclinical MSI-H models

Determination of TA expansion score for MSI-H TA repeat expansions



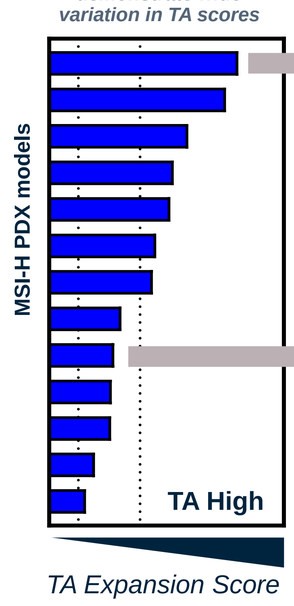
- Calculation of TA expansion score

TA expansion score determines cell line sensitivity to MOMA-341

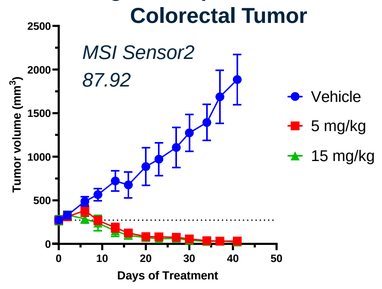


MOMA-341 monotherapy elicits tumor regressions in MSI-H PDX with high TA repeat expansions

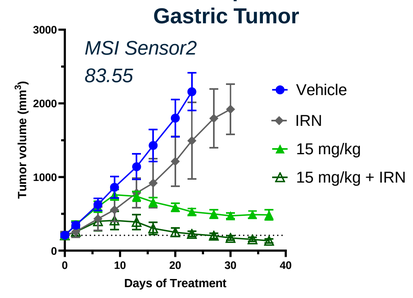
MSI-H PDX models demonstrate wide variation in TA scores



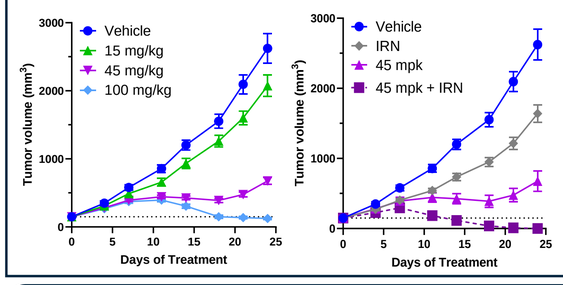
High TA Expansion Score Colorectal Tumor



Moderate TA Expansion Score Gastric Tumor



CDX with moderate TA Score (RKO) benefits from higher dose MOMA-341 or combination with irinotecan



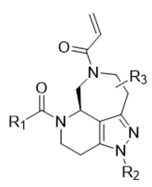
Preclinical models (PDX + cell lines) with TA Scores

Predictive Biomarker	N	Single agent Response Rate (PPV)	False Positive (FPR)	False Negative Rate
MSI-H (DNA)	28	0.63	0.37	0
dMMR (Protein)	27	0.61	0.39	0
MSI Sensor2 > 78	30	0.73	0.27	0
TA Score High	**17**	**0.94**	**0.06**	**0**

- **Direct assessment of TA repeat expansions significantly outperforms MSI-H status as a predictor of MOMA-341 single agent sensitivity**

MOMA-341 displays potent and selective activity in MSI-H cells

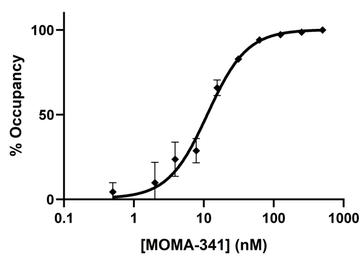
MOMA-341 is a distinct chemotype and covalent inhibitor of WRN helicase



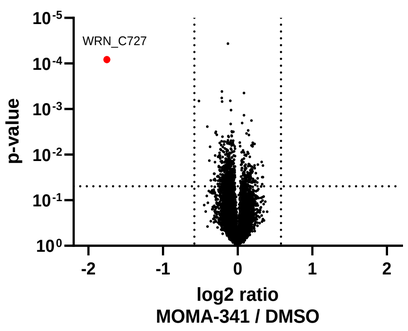
MOMA-341 demonstrates potent activity against WRN helicase

MOMA-341 biochemical activity	
WRN ATPase (10 µM ATP) (nM)	3
WRN ATPase (100 µM ATP) (nM)	7
WRN Helicase (1 mM ATP, no pre-incubation) (nM)	430
WRN Helicase kinact/KI,app ($M^{-1}sec^{-1}$)	13,058
BLM ATPase (10 µM ATP) (nM)	>50

MOMA-341 ligates WRN C727 in cells



MOMA-341 selectively ligates WRN C727 in human cells

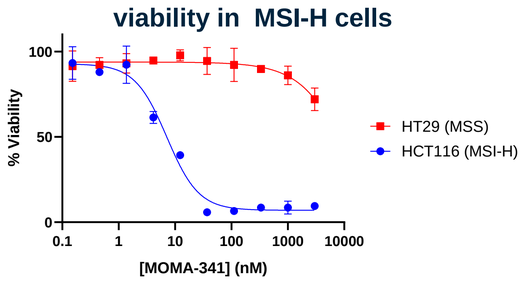


Activated T cells (Normal)

TMT-ABPP - Global Cysteine Profiling

MOMA-341 induces dose-dependent DNA damage in MSI-H cell lines

MOMA-341 induces loss of cellular viability in MSI-H cells

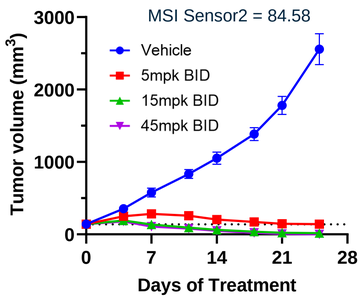


Conclusions

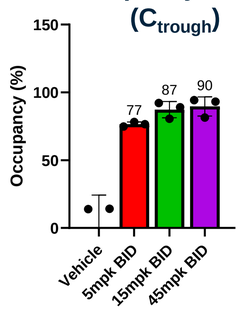
- **MOMA-341 is a potent and selective covalent inhibitor of the WRN helicase in clinical development for the treatment of dMMR/MSI-H solid tumors**
- **Direct measurement of TA repeat expansions by long-read PacBio sequencing predicts MOMA-341 activity with near-perfect accuracy in preclinical cell line and PDX models, linking response to a direct mechanistic biomarker associated with WRN sensitivity**
- **TA repeat expansions will be measured clinically in MOMA-341 Phase 1 trial to provide insight into patient responses, and may enable prediction of which patients will benefit from monotherapy vs. chemotherapy combination treatment**

MOMA-341 displays potent monotherapy in vivo activity in MSI-H CDX

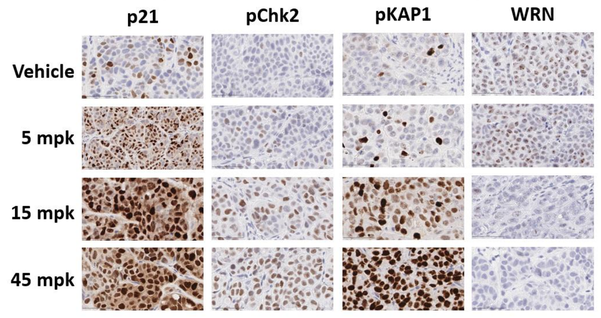
Tumor regressions in SW48 MSI-H CRC xenograft model



Dose-dependent occupancy in vivo (C_{trough})



Dose-dependent induction of DNA damage response and WRN degradation



- **MOMA-341 achieves high levels of target occupancy in vivo**
- **Monotherapy efficacy achieved at low dose in SW48 xenograft model, accompanied by dose-dependent DNA damage responses**

MOMA-341 Phase I clinical trial

- **Single agent efficacy expected**
- **Measurement of TA repeats within MSI-H tumors may enable selection for enhanced response rates**
- **Likely to combine well with anti-PD-(L)1 given orthogonal MOAs and tox/safety profiles**
- **Chemotherapy combo may increase response rates in patients with moderate TA repeat expansion**

[1] Chan, E.M., Shibue, T., McFarland, J.M. et al. WRN helicase is a synthetic lethal target in microsatellite unstable cancers. *Nature*. 2019;568:551–556.
[2] van Wietmarschen N, Sridharan S, Nathan WJ, et al. Repeat expansions confer WRN dependence in microsatellite-unstable cancers. *Nature*. 2020;586(7828):292-298.

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