NDI-219216: A Non-Covalent, Potent, Selective and Highly Efficacious WRN Inhibitor with Best-In-Class Potential for the Treatment of MSI-H Tumors

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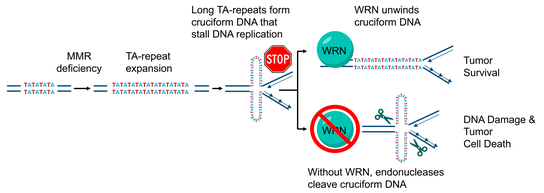
#2894

BACKGROUND

Microsatellite instability (MSI-H) is a consequence of defective mismatch repair (dMMR) in cancer and is observed in over 20 solid tumor types, with the highest prevalence in colorectal, gastric and endometrial cancers. While the treatment landscape of MSI-H is improving, substantial unmet medical need remains across several MSI-H tumor types that fail to respond, or relapse, with current standard of care therapies. Werner Syndrome Helicase (WRN) has been validated as a promising synthetic lethal drug target for MSI-H tumors, thus inhibitors of WRN may offer a novel therapeutic option for patients with MSI-H tumors.

MSI-H Tumors Require WRN Helicase Activity For Survival



METHODS

We developed covalent and non-covalent WRN inhibitor series and treated MSI-H cell lines with exemplars to assess their mechanism. Washout studies with covalent inhibitors evaluated target engagement kinetics, and dependence on WRN C727 was assessed biochemically and in cells. Prioritization of our non-covalent series during lead optimization yielded NDI-219216, which was profiled and benchmarked against clinical-stage inhibitors HRO761 (non-covalent, Novartis) and RO7589831 (covalent, Roche/Vividion).

RESULTS

Preclinical characterization of covalent and non-covalent WRN inhibitors:

- WRN inhibitors triggered dose dependent degradation of WRN protein levels, independent of inhibitor mechanism (**Fig. 1A**).
- Washout studies with covalent inhibitors demonstrated a substantial reduction (>50%) in target engagement in MSI-H cell lines within a 24h treatment period (**Fig. 1B**), explained by dynamic WRN resynthesis that may limit duration of engagement.
- Covalent, but not Nimbus non-covalent, WRN inhibitors dramatically lost potency in a biochemical assay (**Fig. 1C**) and in cells (**Fig. 1D**) when a mutation was introduced to Cysteine 727 (C727A).
- Nimbus non-covalent inhibitors were prioritized for development of a clinical candidate.

Characterization of non-covalent NDI-219216, a potential best-in-class WRN inhibitor:

- NDI-219216 displayed excellent metabolic stability, with low *in vivo* clearance, good oral bioavailability and high oral exposures in rodents and non-rodents (**Table 1**).
- NDI-219216 treatment at low doses *in vivo* led to a robust pharmacodynamic response and tumor regressions across multiple MSI-H Cell line Derived (CDX) xenograft models (**Fig. 2**).
- NDI-219216 outperformed existing clinical stage WRN inhibitors (Novartis HRO761, Roche RO7589831) across multiple MSI-H preclinical models (**Fig. 2-4**).
- NDI-219216 treatment showed broad efficacy in a diverse panel of MSI-H Patient Derived (PDX) xenograft models (**Fig. 4A**), including:
  - CRC PDX refractory to immunotherapy (**Fig. 4B**) and gastric cancer PDX refractory to chemotherapy (**Fig. 4C**).
  - MSI-H PDX tumors of ovarian (**Fig. 4D**) and endometrial (**Fig. 4E**) lineage.

Fig 1: **Characterization of Covalent and Non-covalent WRN Inhibitors**

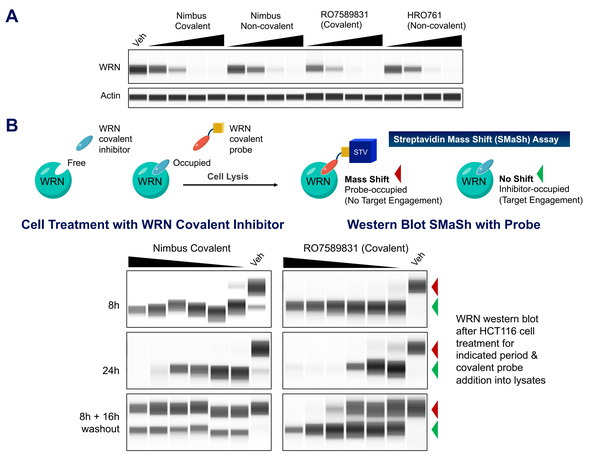


Table 1: **Drug Profile of Nimbus Non-Covalent WRN Inhibitor NDI-219216**

	Test System	NDI-219216
Mechanism		Non-Covalent
Biochemical	WRN ATPase IC_{50} (μM)	0.009
	BLM ATPase IC_{50} (μM)	>100
	WRN DNA unwinding IC_{50} (μM)	0.007
	WRN Exonuclease IC_{50} (μM)	>100
Cell 24h p21 EC_{50} MSI-H vs. MSS	MSI-H: SW48, HCT116 (μM)	0.04, 0.04
	MSS: SW620, SKCO-1 (μM)	>10
Cell 5-day Viability IC_{50} MSI-H vs. MSS	MSI-H: SW48, HCT116 (μM)	0.02, 0.02
	MSS: SW620, SKCO-1 (μM)	>10
PK	Mu CL / T1/2 (h) / Vss (L/Kg) / %F	1.8 / 1.3 / 0.2 / 84
	R CL / T1/2 (h) / Vss (L/Kg) / %F	6.8 / 3.2 / 0.7 / 80
	D CL / T1/2 (h) / Vss (L/Kg) / %F	2.4 / 6.4 / 1.1 / 52
	NHP CL / T1/2 (h) / Vss (L/Kg) / %F	0.33 / 8.0 / 0.2 / 57
Safety	hERG IC_{50} (μM)	>30
	CYP IC_{50} / TDI / PXR activation	> 30 μM/ No/ No
	Ames and MNT	Negative
	Off target and Safety panels	No Liability

Fig 2: **Daily Oral NDI-219216 Treatment Promotes Durable Tumor Regression and Complete Responses of Multiple MSI-H CDX Tumor Models *in vivo* at Low Doses**

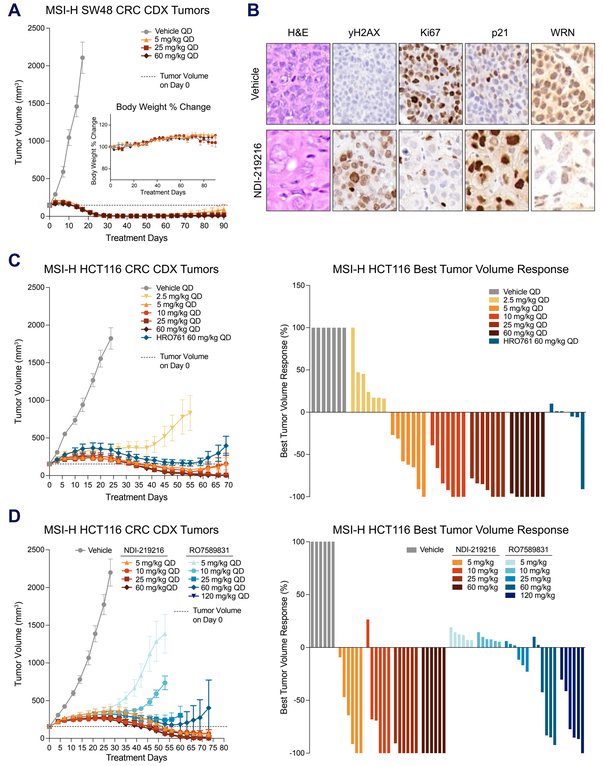
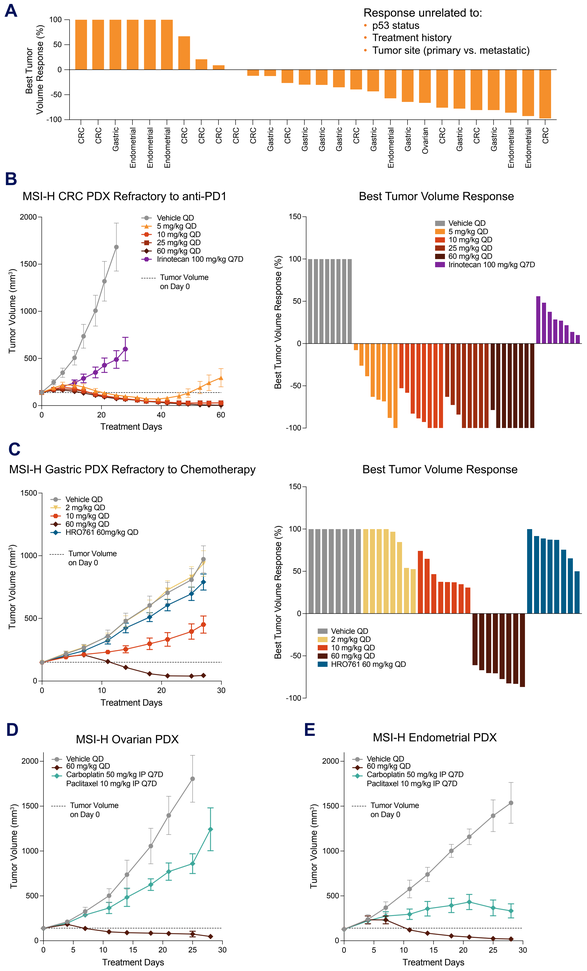


Fig 3: **NDI-219216 Treatment Promotes Regressions in Less Sensitive RKO MSI-H CDX Tumors**

Fig 4: **NDI-219216 Is Highly Efficacious Across A Spectrum of MSI-H PDX Tumor Models Which Encompass Broad Clinical Presentations**



CONCLUSIONS

NDI-219216 is a potent, selective, non-covalent WRN inhibitor with broad, best-in-class potential. It is currently being investigated in a Ph 1/2 clinical trial (NCT06898450) evaluating safety, tolerability, and preliminary anti-tumor activity in patients with advanced solid tumors.

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