

MDNA113 is a Masked Conditionally Activated Tumor-targeted Anti-PD1-IL-2^{SK} with Superior Safety & Therapeutic Properties



MDNA113: Designed to Maximize Therapeutic Response with Optimal Tolerability

Targeting Domain
Specific and high-affinity binding to decoy receptor **IL-13Rα2**, a tumor associated antigen (TAA)

Masking Domain
Attenuates systemic immune stimulation by >10,000-fold by sterically hindering IL-2^{SK} engagement with IL-2R

Protease Sensitive Linker (PSL)
Cleavage by matrix metalloproteases (MMPs) releases Masking Domain, unmasking IL-2^{SK}

Anti-PD1
Bivalent, commercial block-buster, anti-PD1

IL-2^{SK}: "β-enhanced, not-α" IL-2
Identical to IL-2 in MDNA11 currently in Phase 1/2 ABILITY-1 Study (NCT05086692) showing best-in-class single agent activity

Optimal Binding to Tumor, CD8⁺ T, γδT and NK Cells but not Tregs
Ko Masked: IL-13Rα2 (0.49 nM) > PD1 (4.5 nM) > IL-2Rβ (No binding) > IL-2Rα (No binding)
Ko Unmasked: PD1 (6.5 nM) = IL-2Rβ (7.4 nM) > IL-2Rα (No binding)

MOA-1: MMP Cleavage Activates IL-2^{SK} Within the TME

Intact PD-1/PDL-1 Blockade

Restoration of IL-2 Activity by MMP

MOA-2: Anti-PD-1 Binding to PD-1⁺ T Cells Facilitates cis-binding and IL-2R Signaling Without MMP Activity

PD-1 Negative CD8⁺ T Cells (Systemic Abundance)

PD-1 Positive CD8⁺ T Cells (TME Abundance)

IL-13Rα2 is Selectively Expressed in Solid Tumors and TME: Associated with High MMP Levels and Poor Survival

Retention in IL-13Rα2 Tumors Maximizes MMP Cleavage

IL-13Rα2 Positive Tumors (%)

Liver	~80%
Breast	~75%
Glioblastoma	~70%
Ovarian	~65%
Pancreatic	~60%
Colon	~55%
Kidney	~50%
Mesothelioma	~45%
Prostate	~40%
Lung	~35%
Head & Neck	~30%
Melanoma	~25%

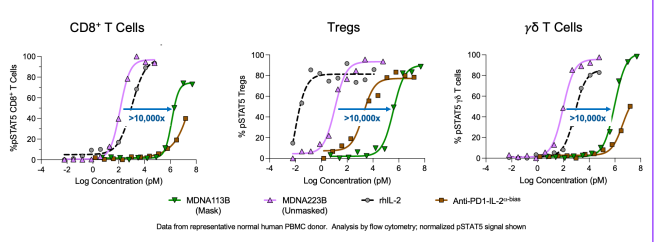
□ Normal tissues have low to no IL-13α2 expression
□ Globally affects at least 2 million cancer patients every year

Summary

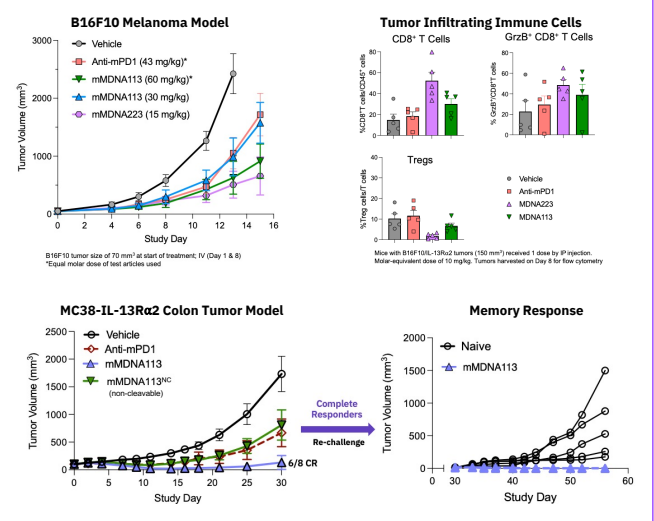
Background and Design Features of MDNA113:

- First-in-Class **Bifunctional SuperKine Immunotherapy (BiSKIT™)** supercharges PD-1 with an IL-2^{SK} that has shown clinical activity in anti-PD1 resistant patients
- MDNA113 incorporates a commercially validated anti-PD1
- Tumor targeting is used to maximize conditional activation of masked IL-2^{SK}
- MDNA113 shows **>10,000x attenuated IL-2R agonism** without impacting PD1/PDL-1 blockade
- MOA 1:** Accumulation in **IL-13Rα2^{pos} tumors** maximizes MMP cleavage to fully restore IL-2^{SK} potency
- MOA 2:** cis-binding to PD-1 facilitates IL-2R engagement by causing receptor proximity thereby restoring IL-2^{SK} potency independent of MMP activity
- Demonstrates efficacy in multiple murine tumor models without systemic toxicity
- MDNA113 was well tolerated at 10-50 mg/kg in non-human primates, with PK similar to approved anti-PD-1s, without Treg expansion or dose-limiting toxicities
- A single 1.4mg/kg dose of anti-PD-1 × IL-2^{SK}-bias bispecific caused a 200-fold expansion of Tregs, severe toxicity and weight loss with 2nd dose withheld due to on-going adverse events
- MDNA113 was well tolerated at >30x higher exposure than anti-PD-1 × IL-2^{SK}-bias and supported repeat dosing, showing a substantially wider therapeutic window

10,000-Fold Blockade of pSTAT5 Signaling in Human PBMCs Demonstrates Superior Masking Capacity



MDNA113 Shows Tumor Growth Inhibition in Multiple Syngeneic Models

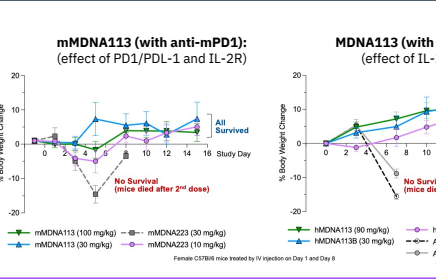


Well-tolerated at Doses up to 50 mg/kg in NHP

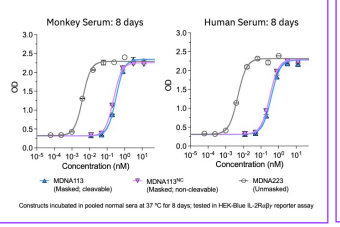
Test Construct	Dose	Clinical Observations
MDNA113 (Masked)	10 mg/kg (n = 2)	1 of 2 monkeys experienced diarrhea (7 days)
	30 mg/kg (n = 2)	No abnormal findings
	50 mg/kg (n = 1)	Monkey experienced diarrhea (7 days)
MDNA223 (Unmasked)	2 mg/kg (n = 2)	1 of 2 monkeys experienced diarrhea (5 days)
Anti-PD1-IL-2^{SK}-bias	1.4 mg/kg (n = 1)	Skin erythema in eye and inguinal regions (> 9 days) Decreased appetite (> 9 days) Decreased activity (7 days)

Naive cynomolgus monkeys; IV infusion

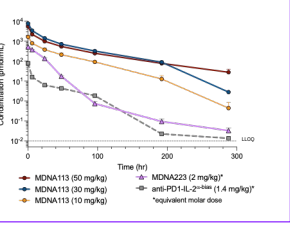
Well-Tolerated in Mice to at Least 100 mg/kg



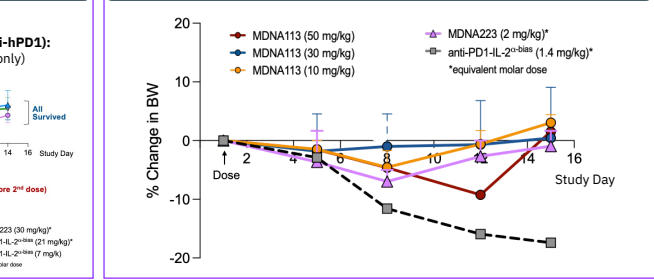
Stable in Sera for at Least 8 Days



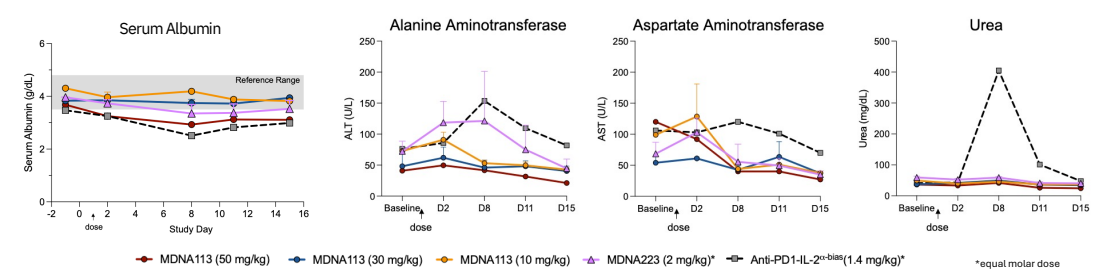
Prolonged Exposure in NHP vs Anti-PD1-IL-2^{SK}-bias



Body Weight in NHP Maintained with High Dose MDNA113



NHP: Unlike anti-PD1-IL-2^{SK}-bias MDNA113 has Minimal Effect on Serum Albumin, Liver Enzymes and Urea



Dampened Systemic Immune Activation in NHP with MDNA113

