Synergistically Engaging a β-Selective IL-2 Agonist with PD-1/PDL-1 Blockade in a Bifunctional Superkine, MDNA223

MEDICENNA

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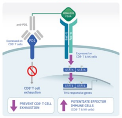
Poster # A005

Bifunctional MDNA223: Combining Effector Immune Cell Activation and Immune-Checkpoint Blockade



MDNA223 (Anti-PD1-MDNA109FEAA) is a novel Bifunctional SuperKines for ImmunoTherapy (BiSKIT) with key differentiating features:

- cis-binding to IL-2Rβ and PD-1 on the same CD8⁺ T cell
- synergy between IL-2 agonism (stimulate CD8⁺ T cell function) and PD-1/PD-L1 blockade (prevent CD8⁺ T cell exhaustion)

MDNA109FEAA is a 'beta-enhanced' IL-2 superkine with no IL-2Rα binding, designed to:

- preferentially activate CD8⁺ T and NK cells over Tregs
- overcome toxicities associated with IL-2Rα engagement on non-immune cells (e.g., pulmonary endothelial cells)

MDNA223 Exhibits Enhanced IL-2Rβ Selectivity and Potentiates Preferential Stimulation of CD8⁺ T Cells Over Tregs in Human PBMCs

Increase Affinity for IL-2Rβ and No Binding to IL-2Rα

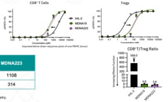
Receptor Binding (K_D, nM)	IL-2Rβ (CD122)	IL-2Rα (CD25)
IL-2-Fc	3540	32
MDNA223	11.3	No binding

SPR performed using immobilized IL-2-Fc and MDNA223

pSTAT5 EC_{50} (pM)	rhIL-2	MDNA109FEAA-Fc (MDNA19)	MDNA223
CD8⁺ T cells	2068	509	1108
Tregs	3.9	112	314

Average EC_{50} of 3 unique PBMC donors
PBMCs rested in complete media prior to stimulation for 15 min. Analysis by flow cytometry.

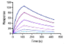
Enhanced stimulation of CD8⁺ T cells while reducing activity of immune suppressive Tregs



MDNA223 Retains PD-1 Affinity and PD-1/PD-L1 Blockade

Surrogate mouse MDNA223 (with anti-mPD1) was used in all studies

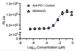
High-Affinity Mouse PD-1 Binding



	K_D(nM)
MDNA223	102

SPR performed using immobilized PD1 and MDNA223

Potent Blockade of PD-1/PD-L1 Mediated Exhaustion

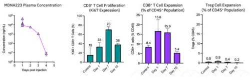


	EC_{50} (nM)
Anti-mPD1	4.7
MDNA223	6.2

Promega PD-1/PD-L1 cell-based reporter assay

MDNA223 Induces Durable Proliferation and Expansion of CD8⁺ T Cells

Pharmacodynamic (PD) effects extend beyond duration of serum exposure (PK)
Preferential expansion of circulating CD8⁺ T cells over Tregs

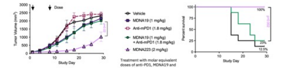

MDNA223 Plasma Concentration
Concentration (ng/mL)
Days post injection
CD8⁺ T Cell Proliferation (Ki67 Expression)
15
33
70
38
CD8⁺ T Cell Expansion (% of CD45⁺ Population)
8.4
16.6
15.9
5.4
Treg Cell Expansion (% of CD45⁺ Population)
0.5
0.9
0.4
0.2
Control
Day 1
Day 7
Day 10

Mice (C57Bl/6) received single dose of MDNA223 (2 mg/kg) by intra-peritoneal injection on Day 0

Superior Efficacy and Survival Benefit with MDNA223 in Multiple Syngeneic Tumor Models

MDNA223 is more effective than co-administration of anti-mPD1 and MDNA19 in tumor growth control

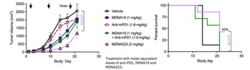
CT26 Colon Cancer Model (highly immunogenic; 'Hot')



Treatment with molar equivalent doses of anti-PD1, MDNA19 and MDNA223.

IP treatment QWx2, Avg tumor size at initiation of dosing: 127 mm3
Statistical analysis by the non-parametric Mann Whitney test (efficacy)
Statistical analysis by the non-parametric Mantel Cox test (survival)

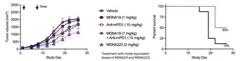
B16F10 Melanoma Model (poorly immunogenic; 'Cold')



Treatment with molar equivalent doses of anti-PD1, MDNA19 and MDNA223.

IP treatment QWx3, Avg tumor size at initiation of dosing: 30 mm3
Statistical analysis by the non-parametric Mann Whitney test (efficacy)
Statistical analysis by the non-parametric Mantel Cox test (survival)

E0771 Triple Negative Breast Cancer Model ('Cold' Tumor)

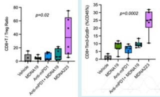


Treatment with molar equivalent doses of MDNA19 and MDNA223.

IP treatment QWx2, Avg tumor size at initiation of dosing: 80 mm3

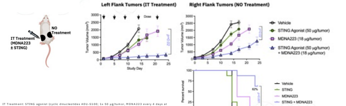
MDNA223 Enhances Tumor Infiltration of Functionally Active CD8⁺ T Cells in B16F10 Melanoma

- CD8⁺T cell expansion favored over Tregs
- Significant upregulation of Granzyme B in the CD8⁺T cell population with MDNA223 compared to co-administration of MDNA19 and anti-mPD1



Mice received single molar equivalent dose of dose of MDNA223 (2 mg/kg), MDNA19 (1 mg/kg) and anti-mPD1 (1.8 mg/kg) Ip and samples were collected on Day 7 for analysis
Statistical analysis by one-way ANOVA Kruskal Wallis Test

MDNA223 Synergizes with STING Agonist to Enhance Anti-Tumor Abscopal Effect in Bilateral CT26 Tumor Model


NO Treatment
IT Treatment (MDNA223 ± STING)
Left Flank Tumors (IT Treatment)
Right Flank Tumors (NO Treatment)
Dose
Tumor Volume (mm³)
Study Day
Vehicle
STING Agonist (50 µg/tumor)
MDNA223 (18 µg/tumor)
STING Agonist (50 µg/tumor) + MDNA223 (18 µg/tumor)
Percent survival
62%
STING
MDNA223
STING + MDNA223

IT Treatment: STING agonist (cyclic dinucleotides ADU-S100; 1x 50 µg/tumor, MDNA223 every 4 days at 18 µg/tumor.
Avg tumor size at start of dosing: 75 mm3.
Statistical analysis by the non-parametric Mann Whitney test on study day 17 (efficacy)
Statistical analysis by non-parametric Mantel Cox test (survival)

Step-Up Dosing Increases Tolerability and Enhances Tumor Response in CT26 Colon Carcinoma Model

➤ Step-up dosing increases MDNA223 tolerability to > 8 mg/kg on a QW schedule

Treatment with MDNA223 IP QWX4. Avg tumor size at initiation of dosing: 35 mm3
Statistical analysis by the non-parametric Mann Whitney test (efficacy)
Statistical analysis by the non-parametric Mantel Cox test (survival)

SUMMARY

Characterization of MDNA223 shows:

- Potent IL-2 agonism and effective PD-1/PD-L1 blockade in one bi-functional construct
- Durable pharmacodynamics extending well beyond plasma exposure, supporting a QW administration schedule
- Superior efficacy and extended survival over co-administration of anti-PD1 and MDNA19 in multiple immunologically 'hot' and 'cold' syngeneic tumor models.
- Preferential tumor infiltration of CD8⁺T cells and maintenance of cytotoxic activity
- Synergy with pro-inflammatory agonist (STING) to enhance tumor inhibition and induce abscopal effect

Strategies to Broaden Therapeutic Index of MDNA223:

- Step-up dosing increased tolerability, enabling high dose administration to enhance therapeutic response
- Engineering of a conditionally attenuated version of MDNA223 completed and characterization on-going.