Neoadjuvant administration of MDNA11, a long-acting IL-2 Superkine, prevents metastasis, protects against tumor rechallenges and provides long-term survival in an orthotopic model of breast cancer

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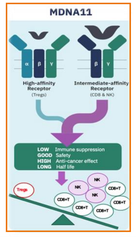
MDNA11: A Long-acting 'β-enhanced Not-α' IL-2 Superkine

Engineered to overcome key limitations of high dose rhIL-2

Engineered IL-2 — Linker — Human Albumin

Enhanced β-binding + No α-binding + Albumin-fusion → Superior Anti-cancer Response

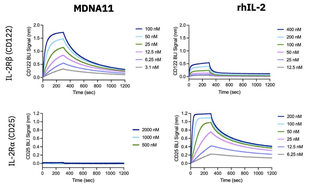
Potentiate activation of CD8+ T & NK cells | *Reduce* stimulation of Tregs & improve safety | *Half-life extension and increased tumor exposure*



MDNA11 demonstrates a favorable safety profile and encouraging single-agent anti-tumor response in patients with advanced solid tumors (ongoing Phase 1/2 ABILITY Study)

MDNA11: Enhanced Receptor Selectivity

Enhanced β-binding + abrogated α-binding favors immune effector cell activation



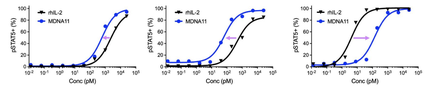
K_D (nM)	MDNA11	rhIL-2
IL-2Rβ (CD122)	6.6 ± 0.1	210 ± 30
IL-2Rα (CD25)	No Binding	24 ± 1

Receptor affinity by bio-layer interferometry (Octet)

Merchant et al., JITC (2021)

MDNA11: Preferential pSTAT5 Activation in CD8+ T and NK Cells

Potency in immune suppressive Tregs greatly reduced with MDNA11 vs. rhIL-2



EC_{50} (pM)	CD8+ T Cells	NK Cells	Tregs
MDNA11 (N = 3)	463.8 ± 141.6	68.9 ± 9.3	160.3 ± 21.7
rhIL-2 (N = 4)	3389.5 ± 1571.1	201.5 ± 175.6	5.6 ± 3.1
MDNA11 vs rhIL-2	↑ 7.4x	↑ 2.9x	↓ 28.6x

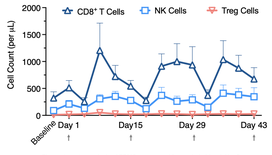
Human PBMC stimulated with MDNA11 or rhIL-2 for 15 minutes; pSTAT-5 assessment by flow cytometry

Merchant et al., JITC (2021)

MDNA11 Preferentially Expands CD8+ T and NK Cells

MDNA11 at 90 µg/kg (IP Q2W) in patients with advanced solid tumors

[Data from ongoing Phase 1/2 ABILITY study]



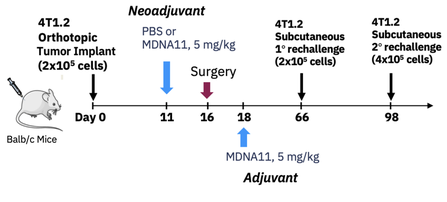
Flow cytometry analysis of PBMCs processed from whole blood; N = 8.

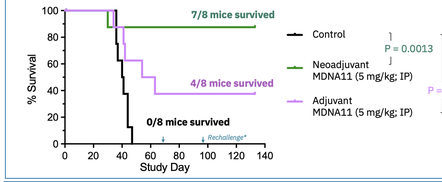
To et al., SITC (2024)

Results: Neoadjuvant Treatment with MDNA11 in Orthotopic Model of Triple Negative Breast Cancer (TNBC)

Significant Survival Benefit with a Single Neoadjuvant MDNA11 Treatment

Study Schema:



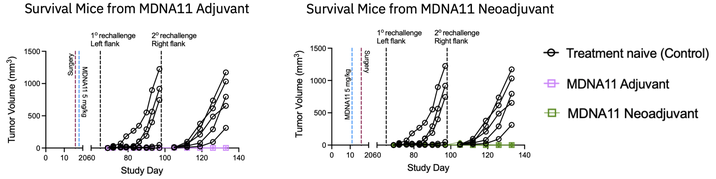


- Mice in control and MDNA11 adjuvant groups died of metastasis.
- Single dead mouse in MDNA11 neoadjuvant group had no metastasis.

** Rechallenge was performed in surviving mice, 7 and 4 respectively in the neoadjuvant and adjuvant group*

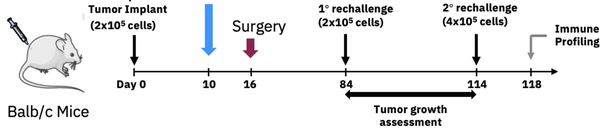
MDNA11 Promotes Memory Response Against Tumor Rechallenges

Mice rechallenged by subcutaneous 4T1.2 implant (Days 66 and 98) without any additional treatment



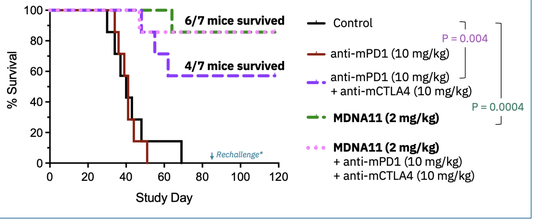
Single agent MDNA11 is more Effective than Combination of Immune Checkpoint Inhibitors

Study Schema:



** Rechallenge was performed in surviving mice,6, 6 and 4 respectively in the MDNA11, Anti-mPD1 + Anti-mCTLA4 + MDNA11 and Anti-mPD1 + Anti-mCTLA4 group*

Low Dose Neoadjuvant MDNA11 is Sufficient to Achieve Survival Benefit

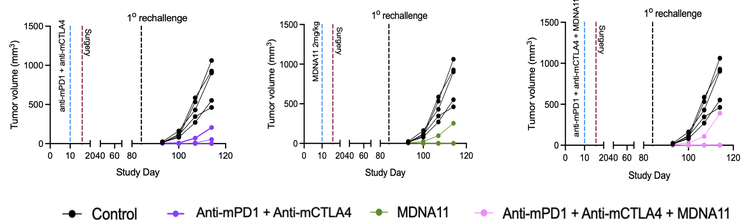


MDNA11 Exhibits Superior Neoadjuvant Effect and Long-Term Survival than Combination of Anti-mPD1 and Anti-mCTLA4

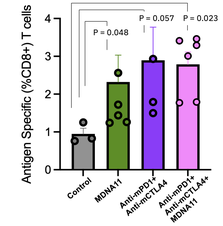
Neoadjuvant Anti-mPD1 + Anti-mCTLA4
Tumor growth in **2/4 (50%)** rechallenged mice

Neoadjuvant MDNA11
Tumor growth in **1/6 (17%)** rechallenged mice

Neoadjuvant Anti-mPD1 + Anti-mCTLA4 + MDNA11
Tumor growth in **1/6 (17%)** rechallenged mice

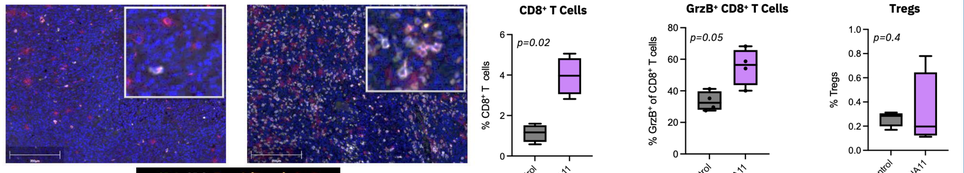


MDNA11 Promotes Antigen-Specific CD8+ T Cells that Protect Against Tumor Rechallenge



Following the second rechallenge with 4T1.2 cells on Day 114, spleen from mice were collected 4 days later (i.e., day 118) and processed for flow cytometric analysis of antigen specific CD8+T cells (T-select H-2Ld MuLV gp70 tetramer)

Single Neoadjuvant Treatment with MDNA11 Promotes Tumor Infiltrating CD8+ T Cells



Balb/c mice were treated with PBS or MDNA11 (5 mg/kg) and tumors were collected 5 days after for mIF analysis

Summary

- Single neoadjuvant treatment with MDNA11 provided significant survival benefit in an orthotopic model of TNBC by preventing metastasis
- MDNA11 promotes tumor infiltration of cytotoxic (Grzb+) CD8+ T cells with no increase in immune suppressive Tregs
- Neoadjuvant MDNA11 as well as combination of immune checkpoint inhibitors promote development of antigen-specific memory response that protects against tumor re-challenge.
- Neoadjuvant MDNA11 monotherapy is more effective than the combination of anti-mPD1 + anti-mCTLA4 in prevention of metastasis and extending survival