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MDNA11 is a Long-Acting ‘Beta-Only’ IL-2 Agonist Exhibiting Potent Tumor Growth Control in Preclinical Models and Preferential Expansion of NK and CD8^{+} T Cells in Patients with Advanced Solid Tumors

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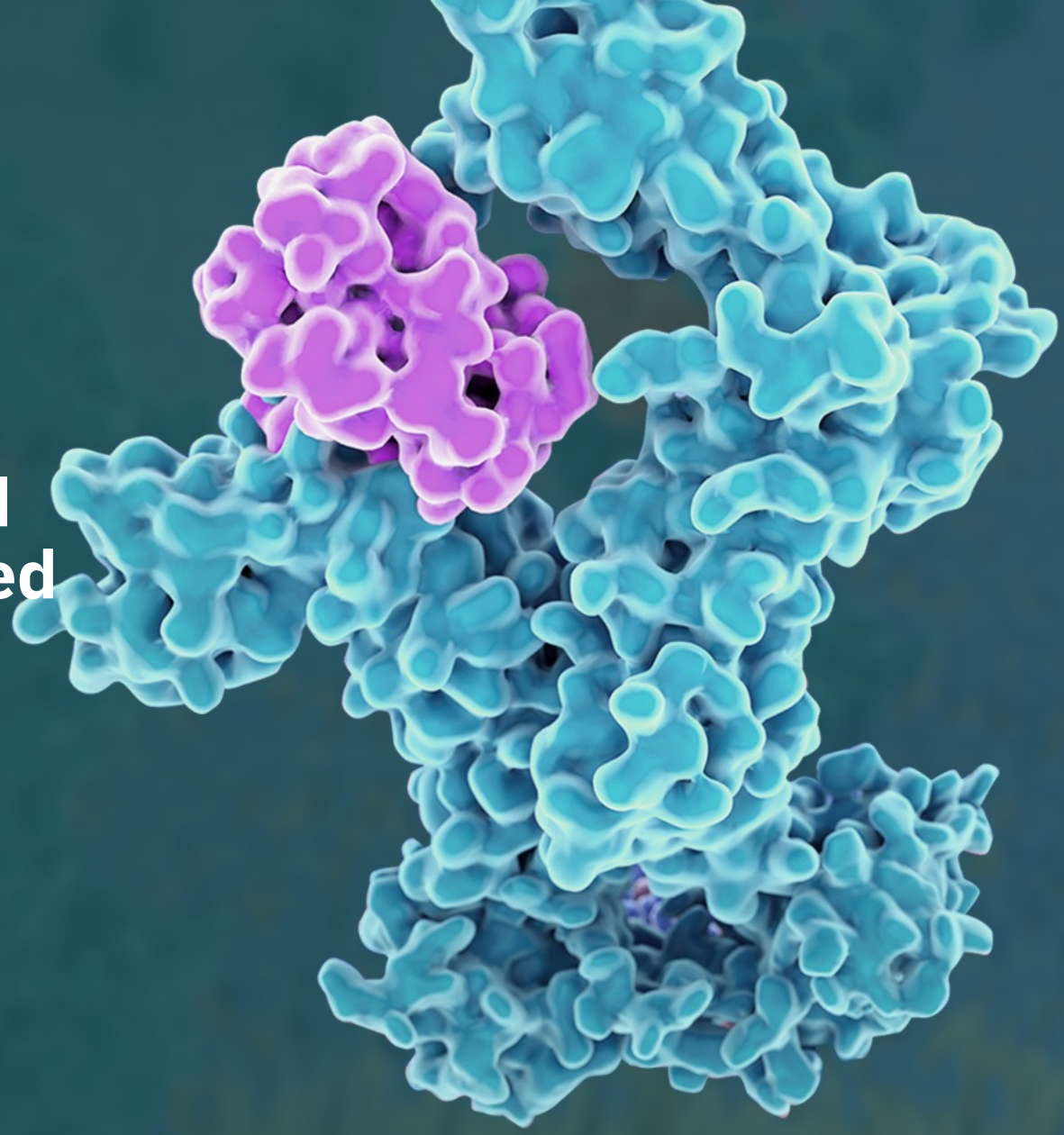
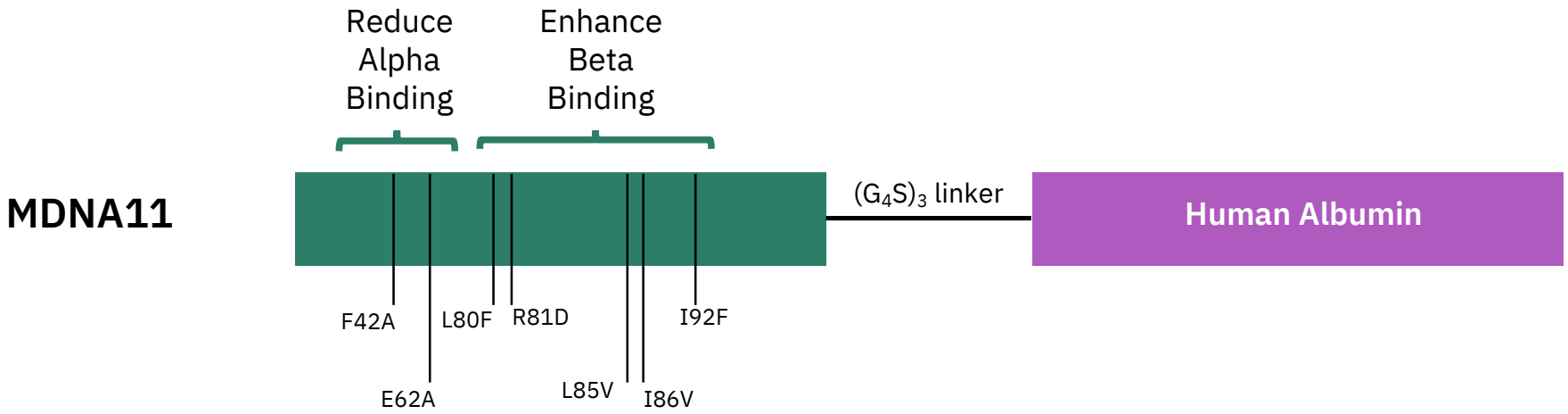


MEDICENNA

Overview of MDNA11

A long-acting ‘beta-only’ IL-2 superkine with superior receptor selectivity, designed to enhance activation of effector immune cells and reduce Treg stimulation and toxicities



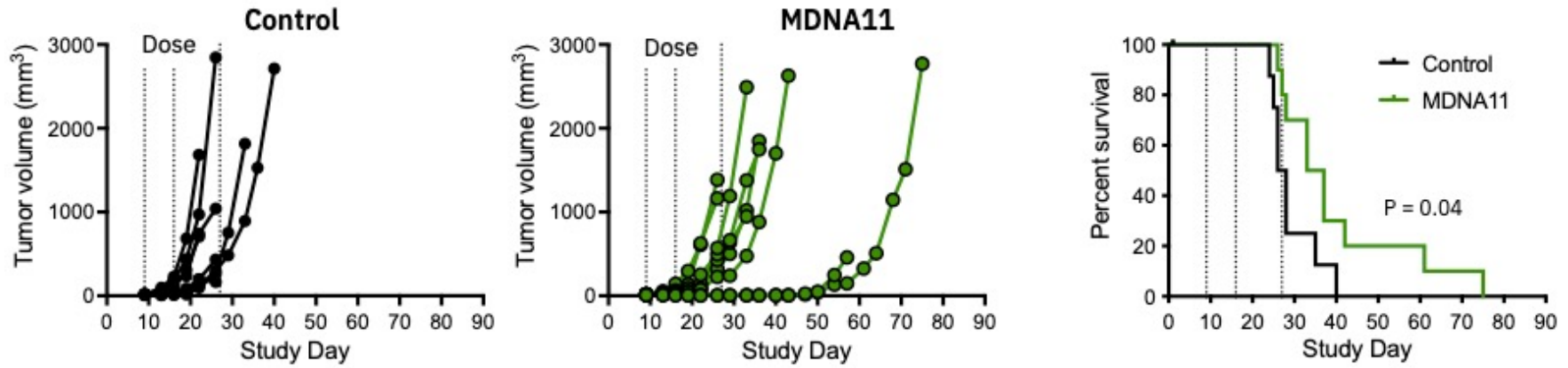
Differentiated ‘Beta-Only’ IL-2 Agonist

- Enhanced affinity for CD122
  - Potentiate CD8 T and NK cells
- No binding to CD25
  - Reduced capacity to stimulate T_{regs}
  - Improved safety profile

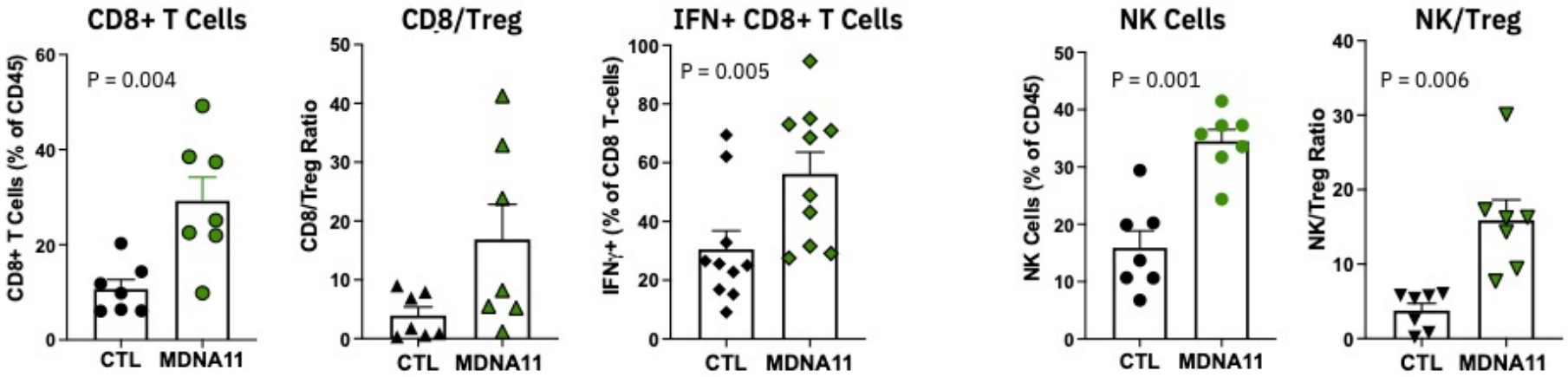
Fusion to Human Albumin

- Extends in vivo half-life
  - Reduced clearance by kidney filtration
  - Leveraging FcRn recycling
- Potential for accumulation at tumor site and tumor draining lymph nodes
  - Enhanced therapeutic response

MDNA11 Delays B16F10 Tumor Growth by Promoting TILs



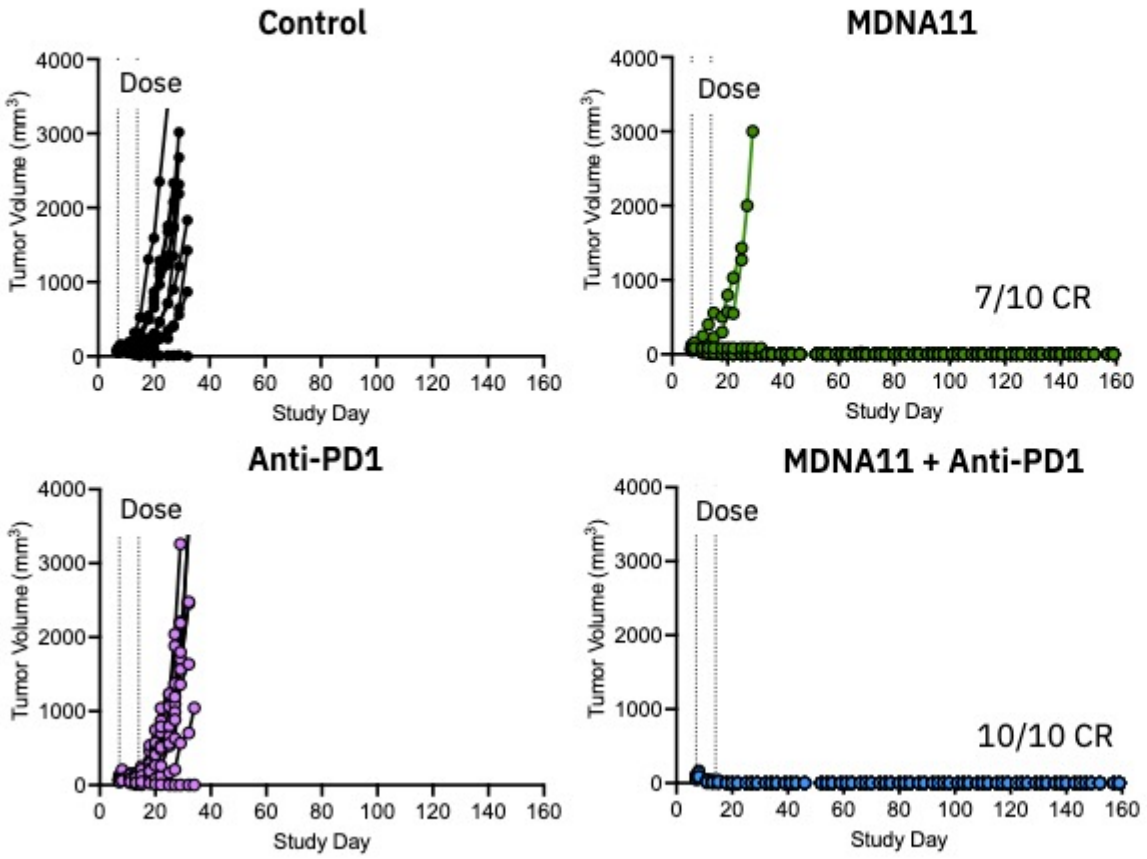
Promotion of Tumor Infiltrating CD8⁺ T and NK Cells Over Tregs



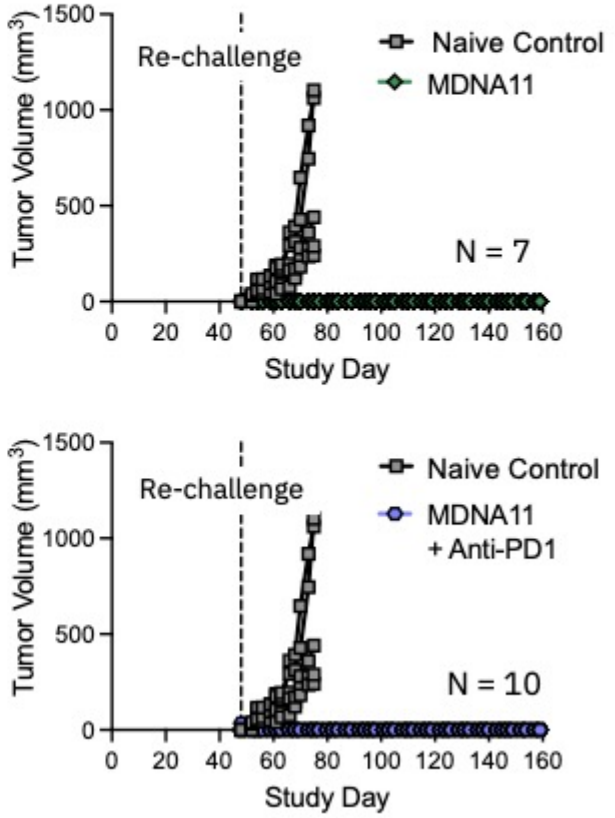
MDNA11 IP administration at 5 mg/kg (QWx3) when tumors ~20mm³. TILs analysis by flow cytometry at 6 days post dose for CD8+ T cells and 3 days post dose for NK cells

MDNA11 Exhibits Potent TGI & Synergy with Anti-PD1, Including Protection Against Re-Challenge

Complete Regression of Primary Tumors



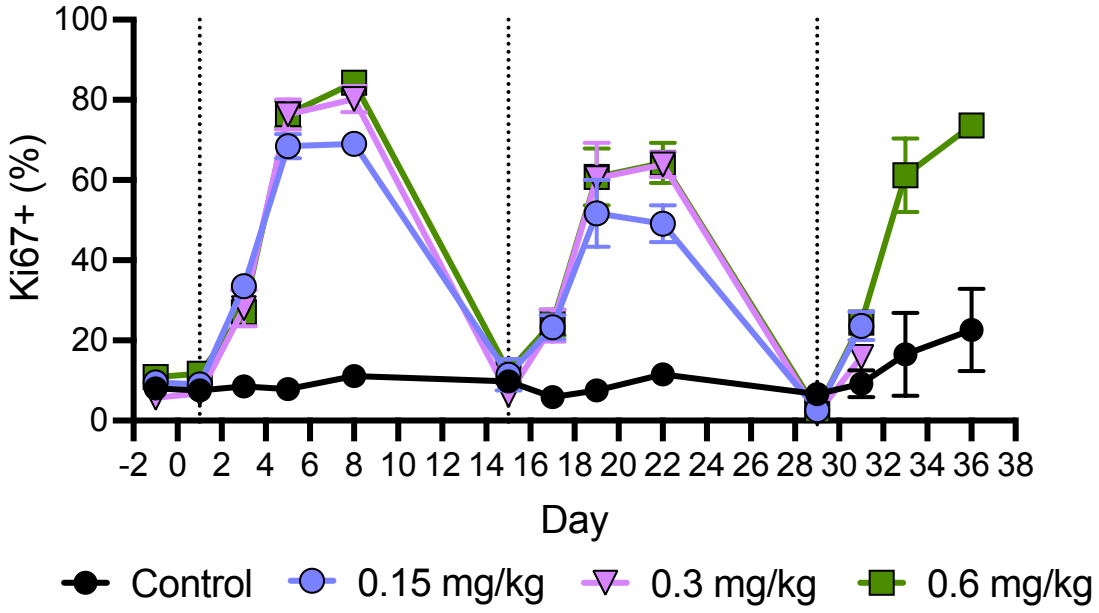
Stimulation of Memory Response



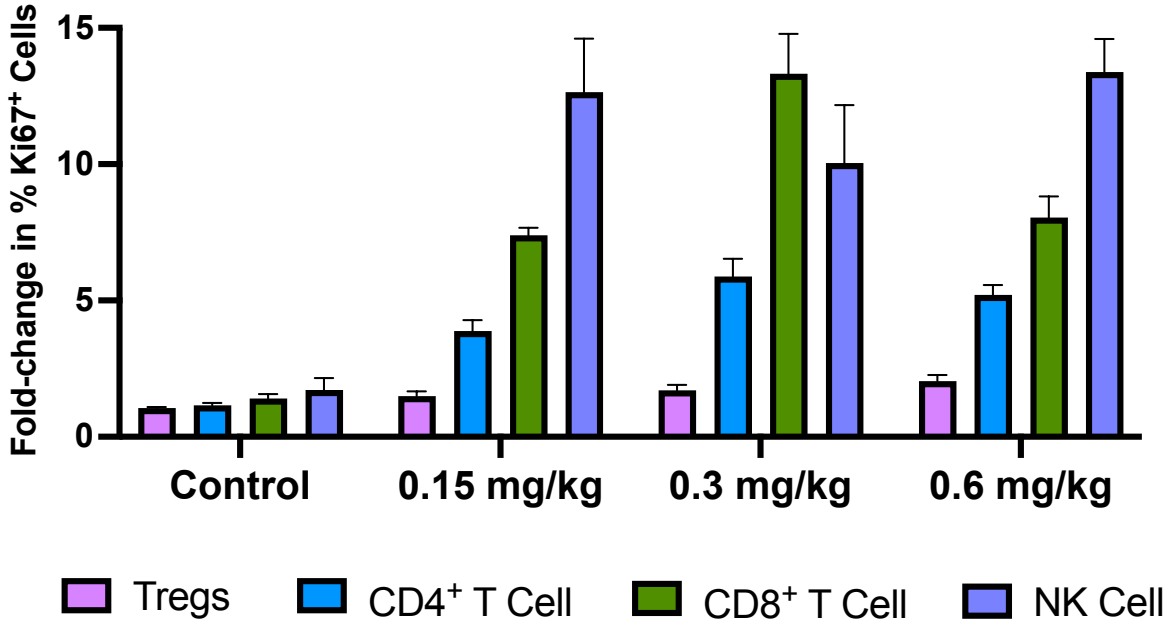
MDNA11: 2 mg/kg QWx2; anti-PD1: RMP1-14 10 mg/kg BIWx3. Tumor size at treatment start = 75 mm³

MDNA11 Induces Durable and Preferential CD8⁺ T and NK Cell Proliferation in NHP

Durable CD8+ T Cell Proliferation



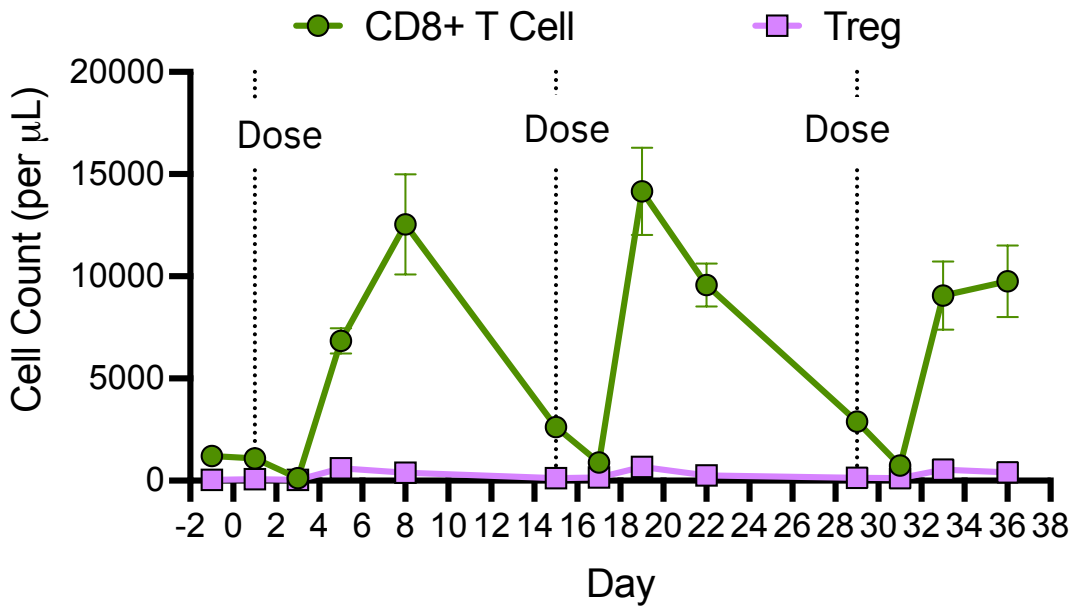
Proliferation of Immune Effector Cells But Not Tregs



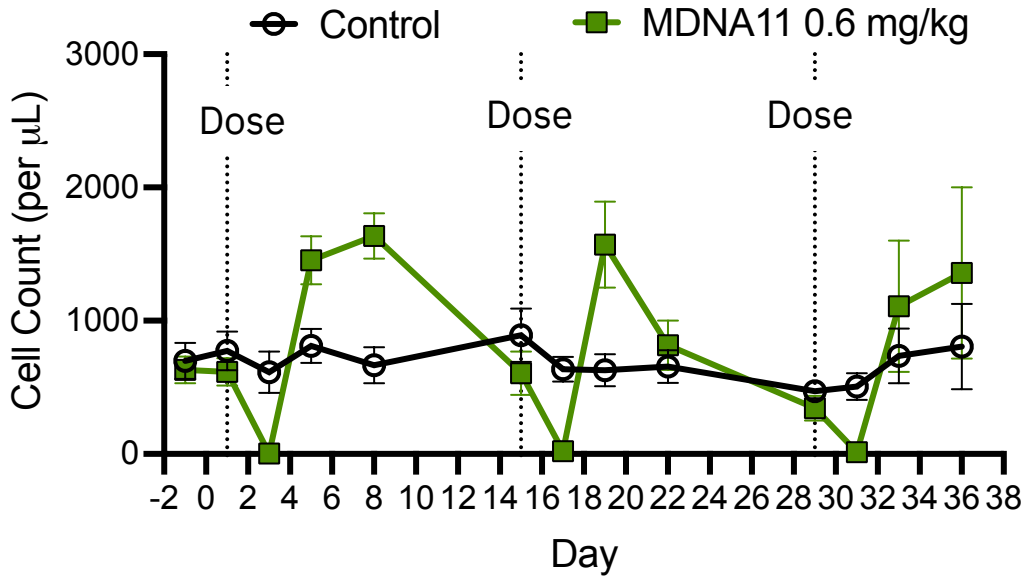
Naïve cynomolgus monkeys (male and female) treated with MDNA11 by intravenous infusion (Q2W)

MDNA11 Preferentially Expands Effector Immune Cells Over Tregs in NHP

CD8⁺ T Cells vs. Tregs (MDNA11: 0.6 mg/kg)



NK Cell Expansion



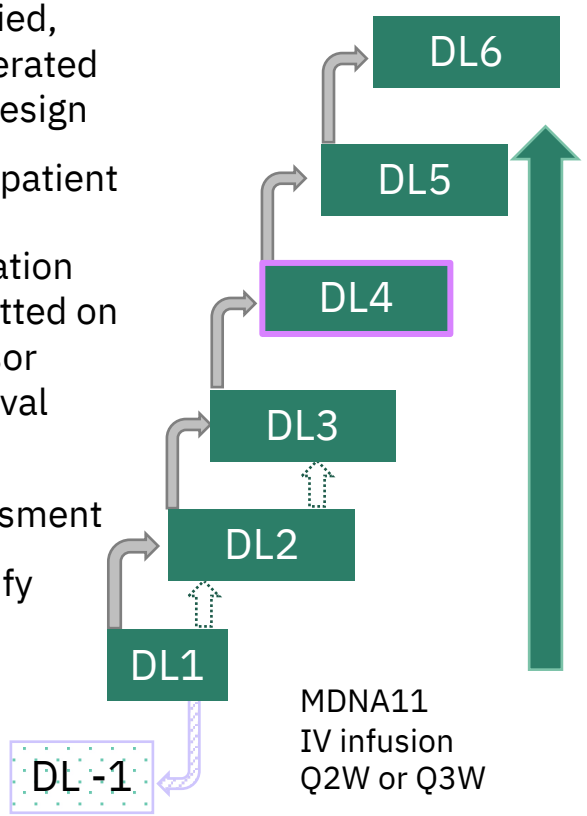
Naïve cynomolgus monkeys (male and female) treated with MDNA11 by intravenous infusion (Q2W)

Phase 1/2 ABILITY Study Schema: Enrolling Cohort 4

MDNA11 Monotherapy Dose Escalation

N ~ 20: Select tumors

- Modified, accelerated 3+3 design
- Intra-patient dose escalation permitted on sponsor approval
- DLT assessment
- Identify RP2D



MDNA11 Monotherapy Dose Expansion

N~ 30: Melanoma, RCC and other select tumors (1:1:1)

MDNA11 administered alone at RP2D via IV infusion Q2W or Q3W

Signals of anti-tumor activity

MDNA11 + CPI Dose Expansion

N~ 30: Melanoma, RCC and other select tumors (1:1:1)

Safety run-in

MDNA11 administered at RP2D in combination with CPI via IV infusion Q3W (planned)

Signals of anti-tumor activity

Endpoints:

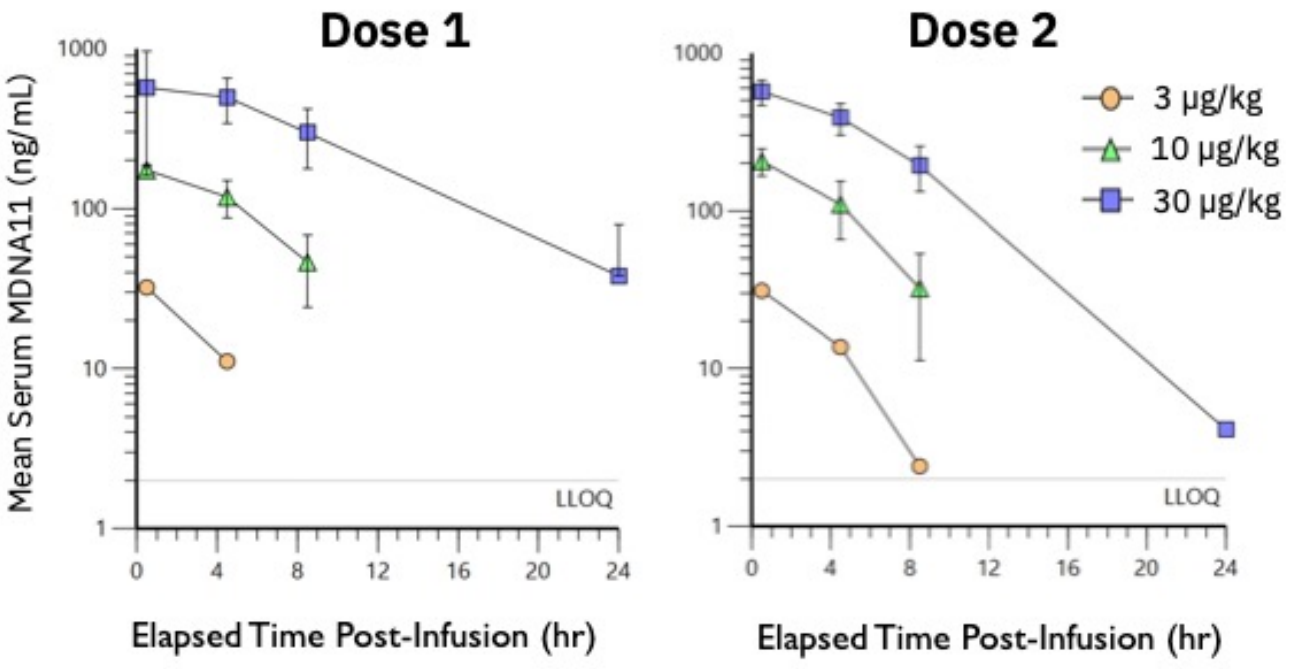
- ORR (RECIST 1.1)
- Clinical Benefit Rate (CBR) (CR+PR+SD)
- Survival EPs (TTE Analysis): PFS/OS
- Disease Control Rate (DCR)
- Duration of Response (DoR)
- Time to Relapse (TTR)

Pharmacodynamic Assessment:

- Immune Cell Profiling (Blood)
- Serum Cytokines
- Multiplex Immunofluorescence (Paired tumor biopsies)
- NanoString Gene Expression (Paired tumor biopsies)

MDNA11 PK in Patients with Advanced Solid Tumors

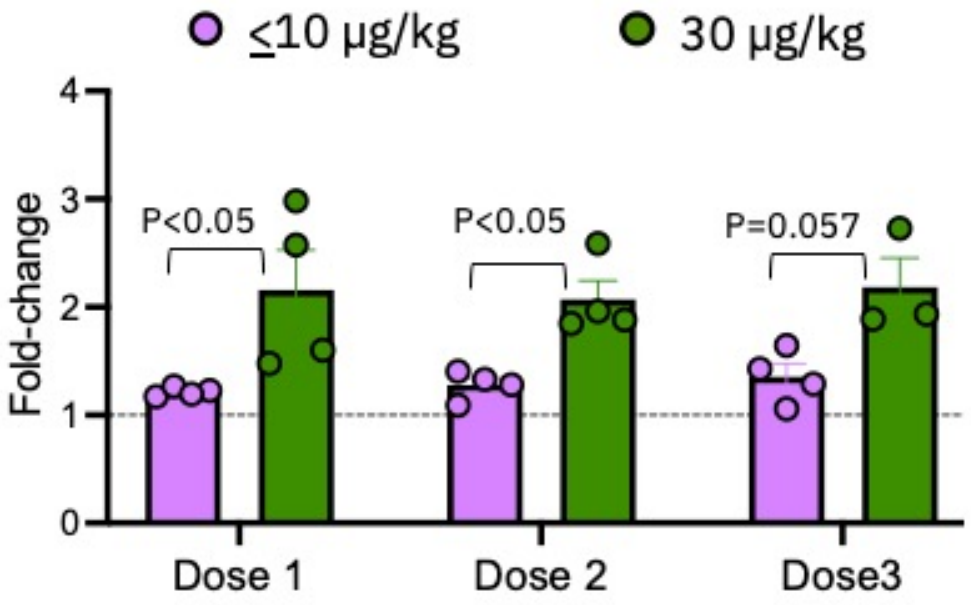
Consistent PK profile for each dose cycle suggests absence of ADA



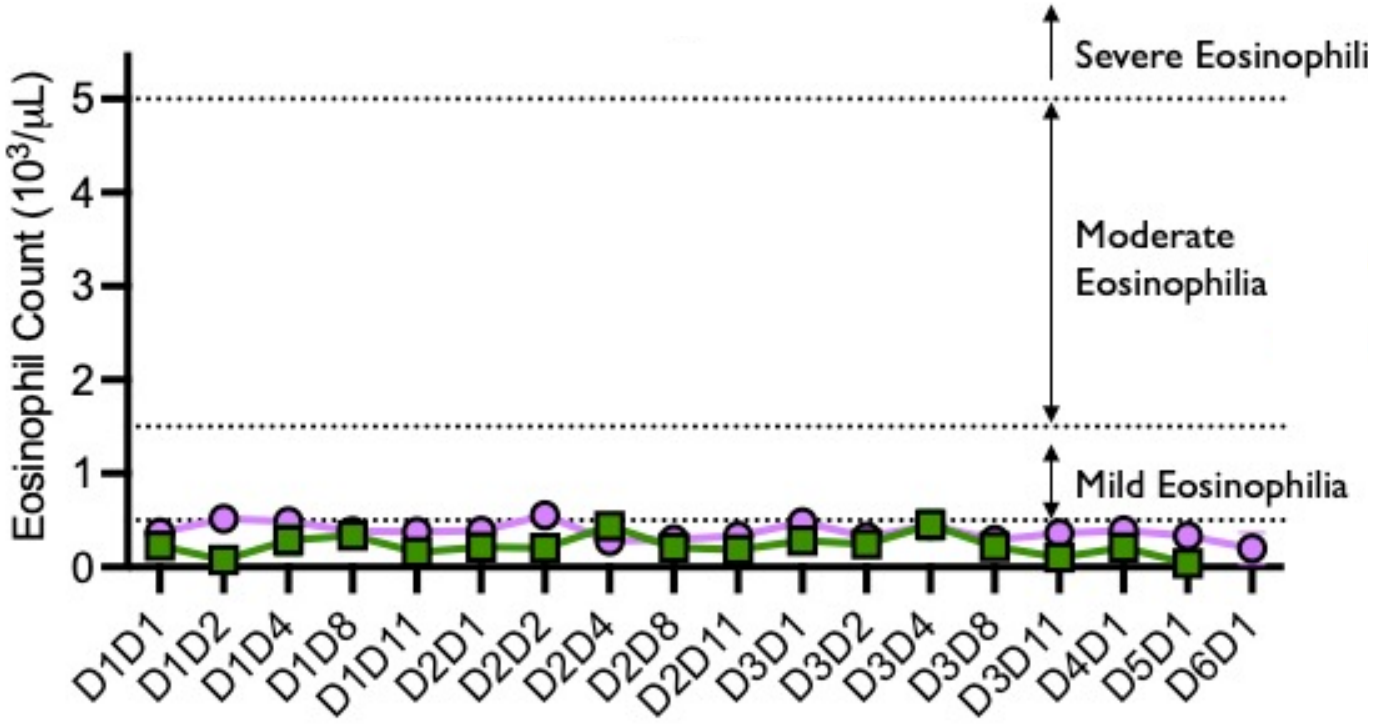
	Cohort 1 3 µg/kg (N = 1)	Cohort 2 10 µg/kg (N = 3)	Cohort 3 30 µg/kg (N = 2)
Dose 1			
Cmax (ng/mL)	32.2	174	615
AUClast (h.ng/mL)	94.7	957	6,470
Overall Mean (3 doses)			
Cmax (ng/mL)	30.6	190	655
AUClast (h.ng/mL)	102	924	5,318

Lymphocyte Expansion Without Eosinophilia

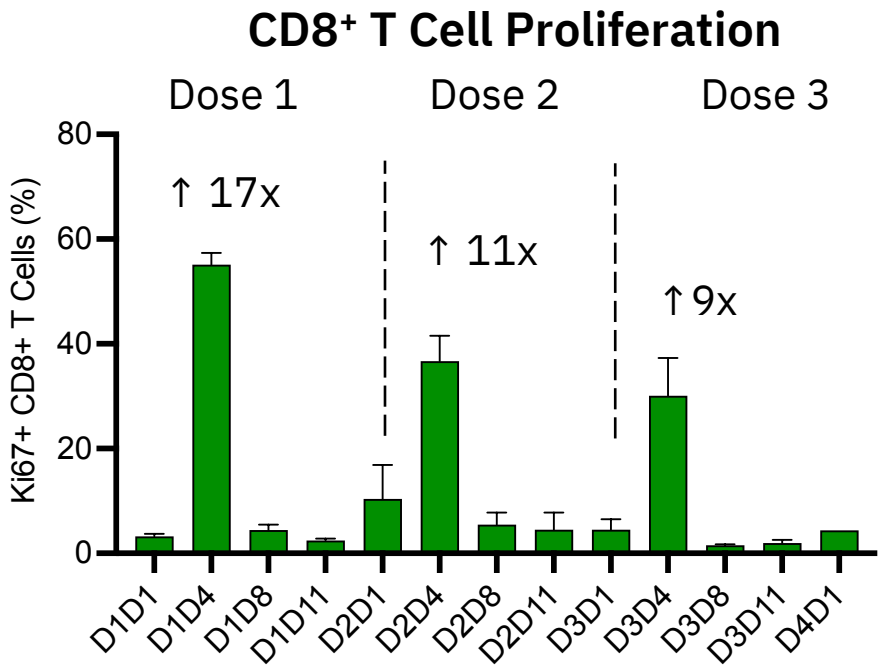
Dose-Dependent Increase in Lymphocytes

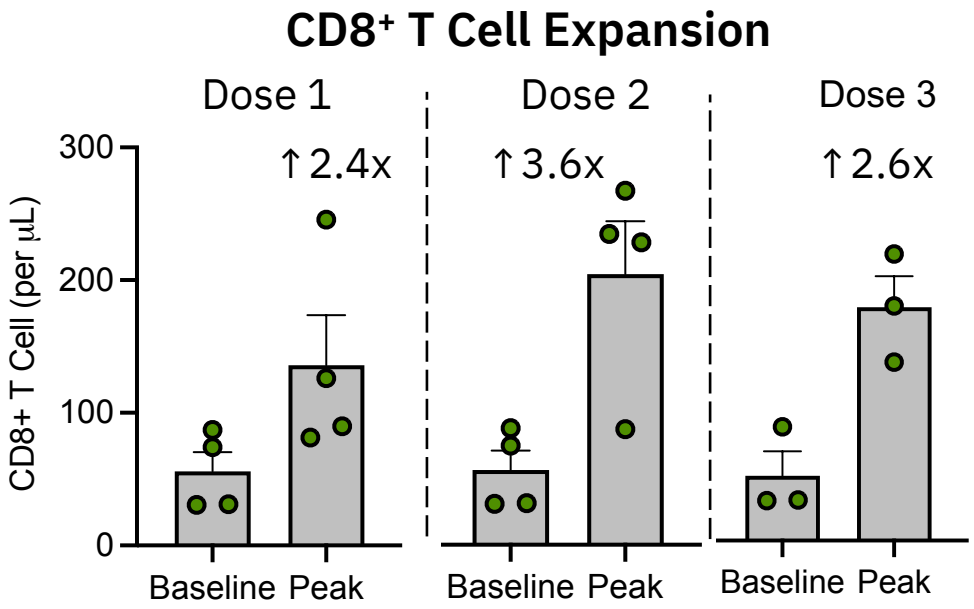


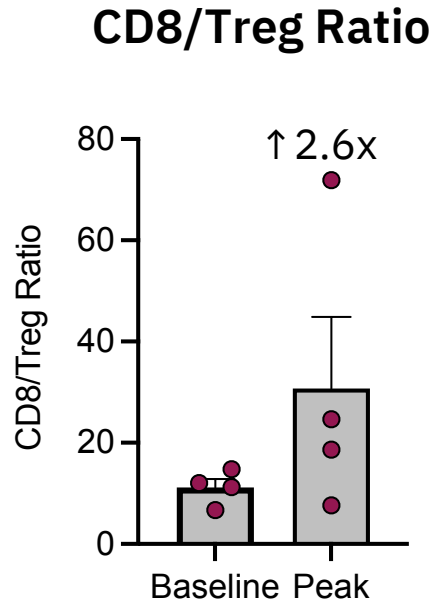
No Eosinophil Increase Compared to Baseline



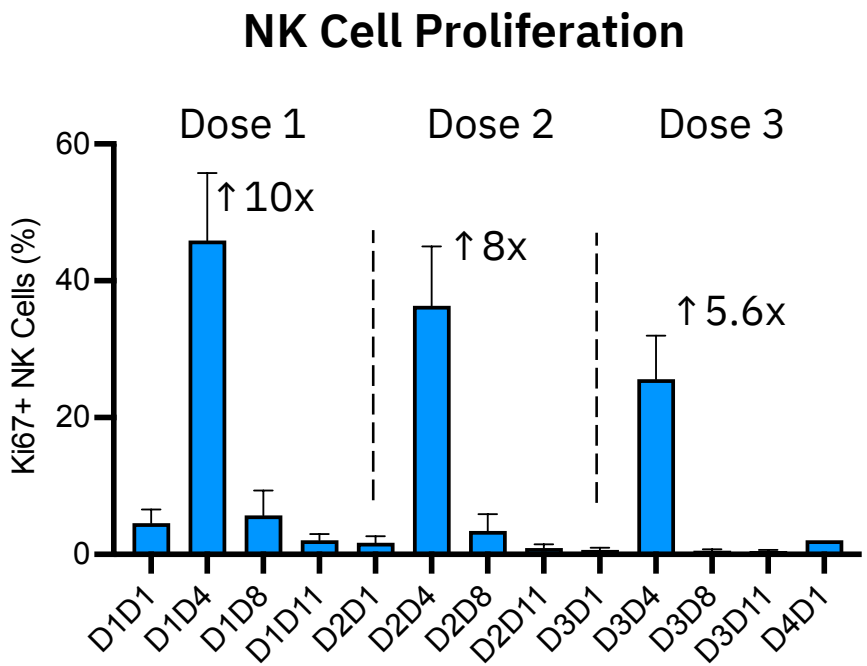
MDNA11 Preferentially Induces Proliferation & Expansion of CD8⁺ T Cells Over Tregs

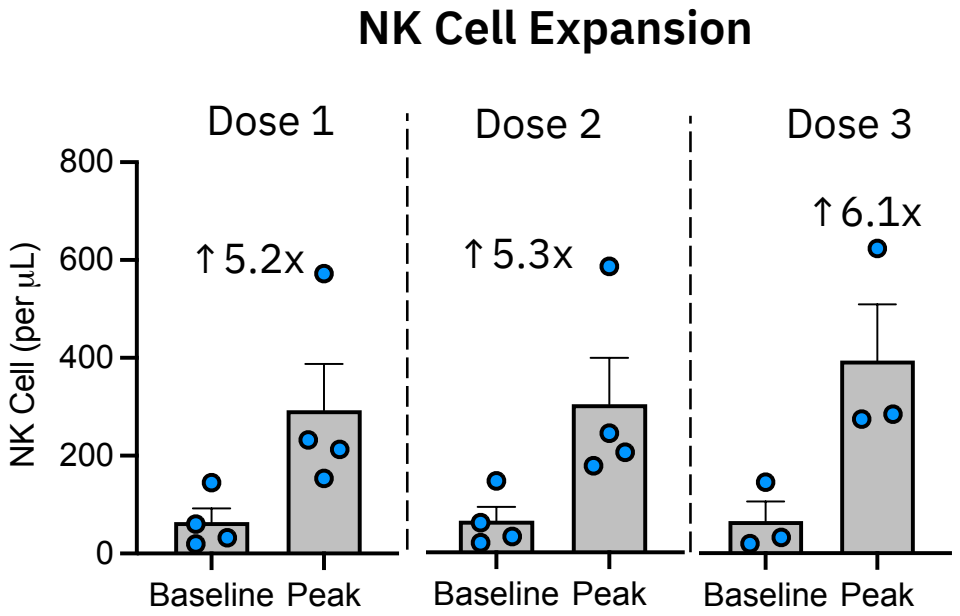


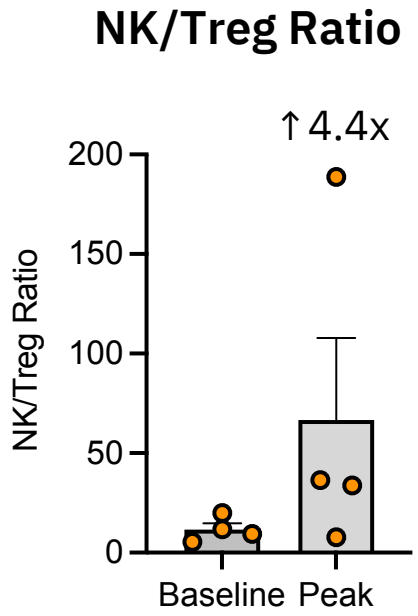




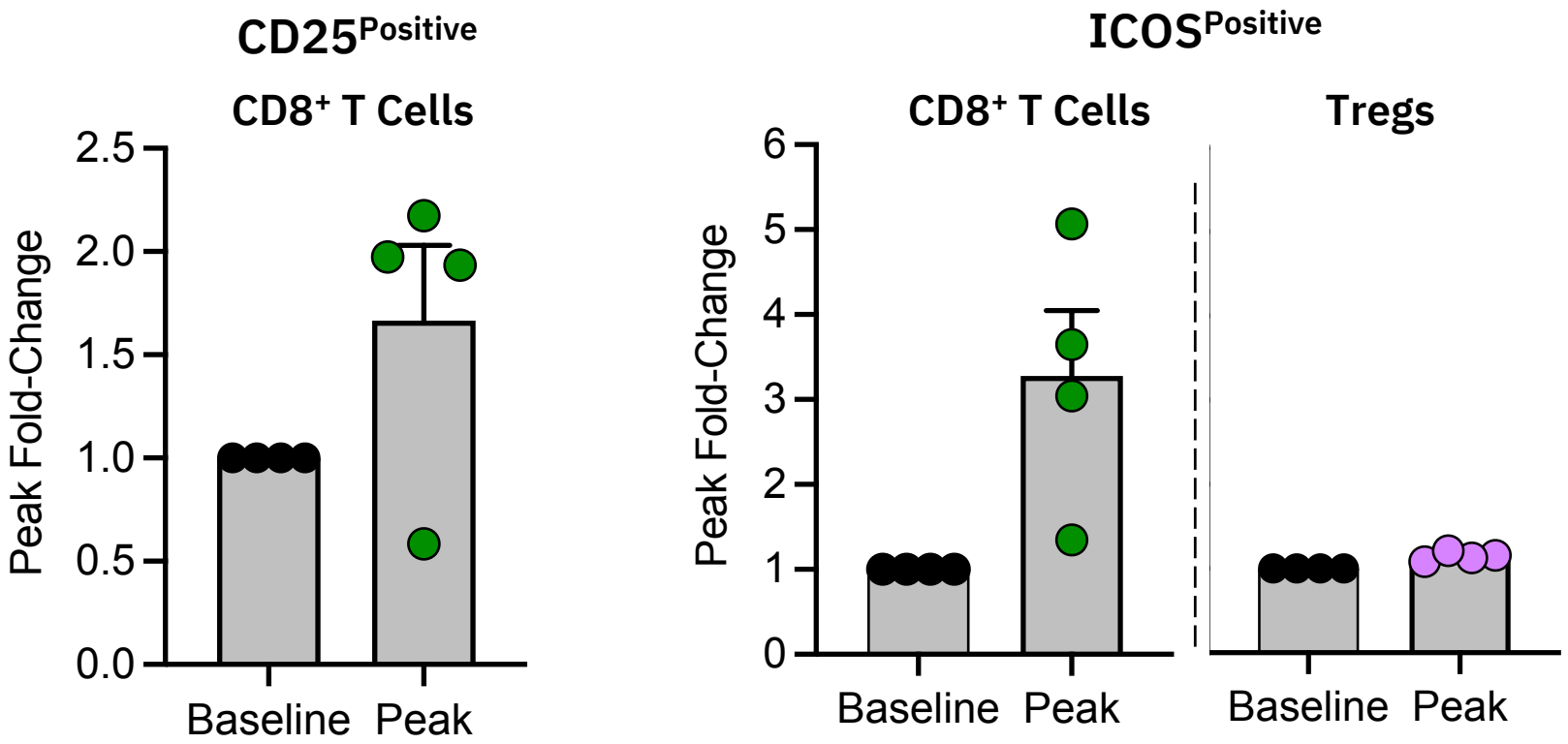
MDNA11 Preferentially Induces Proliferation & Expansion of NK Cells







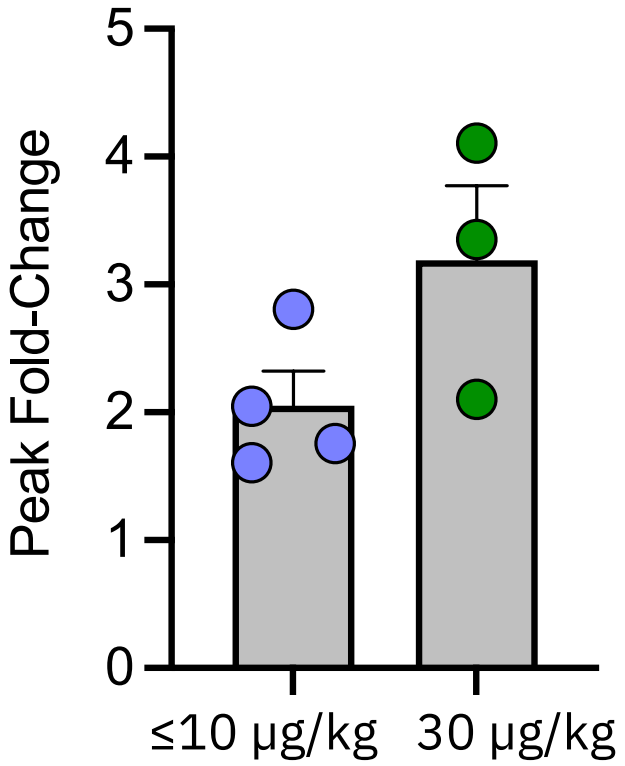
CD8⁺ Cell Activation/Stimulation Without ICOS Induction on Tregs



- ICOS is an inducible stimulatory molecule
- High dose rhIL-2 induces ICOS expression on Tregs in melanoma patients
- Increased ICOS^{positive} Tregs are associated with lack of therapeutic response

(Sim et al., J Clin Invest, 2014)

Dose-Dependent Increase in Circulating Granulysin Expressing Cells



- Granulysin is a cytolytic molecule expressed by CD8+ T and NK cells that mediates tumor cell killing
- Increased granulysin expression is associated with reduced risk of cancer progression (Kishi et al., Cancer Immunol Immunotherapy, 2002)
- Increased granulysin expression is associated with reduced risk of colorectal cancer relapse (Pages et al., N Engl J Med, 2005)

Epiontis validated epigenetic qPCR assay on whole blood samples

Highlights

- MDNA11 monotherapy and in combination with immune check-point inhibitor exhibit potent tumor growth inhibition in syngeneic tumor models by promoting tumor infiltration of effector immune cells and development of memory response
- MDNA11 induces dose-dependent expansion of lymphocytes in patients with advanced solid tumors but does not promote eosinophilia
- MDNA11 induces $CD8^+$ T and NK cell proliferation and expansion but not Tregs
- Evidence of MDNA11 elicited $CD8^+$ T cell activation (CD25) and stimulation (ICOS)
- No observed increase in $ICOS^+$ Tregs, which are highly immune suppressive and associated with lack of response to IL-2 immunotherapy
- Dose-dependent increase in number of circulating granulysin expressing cells, which are involved in tumor cell killing and associated with favorable clinical outcome
- No dose limiting toxicities have been reported to date in ABILITY study even at the 30 µg/kg dose level

Active Clinical Sites

Gallipoli Medical Research Foundation
Brisbane, Australia
PI: Victoria Atkinson

Chris O'Brien Life House
Sydney, Australia
PI: Jenny Lee

Cabrini Hospital
Melbourne, Australia
PI: Gary Richardson

Scientia Clinical Research
Sydney, Australia
PI: Charlotte Lemech

Icon Cancer Center
Brisbane, Australia
PI: Jim Coward

Princess Margaret Hospital
Toronto, ON, Canada
PI: Philippe Bedard

Gabrail Cancer Center Research
Canton, OH, USA
PI: Nashat Gabrail

Orlando Health Cancer Institute
Orlando, FL, USA
PI: Sajeve Thomas