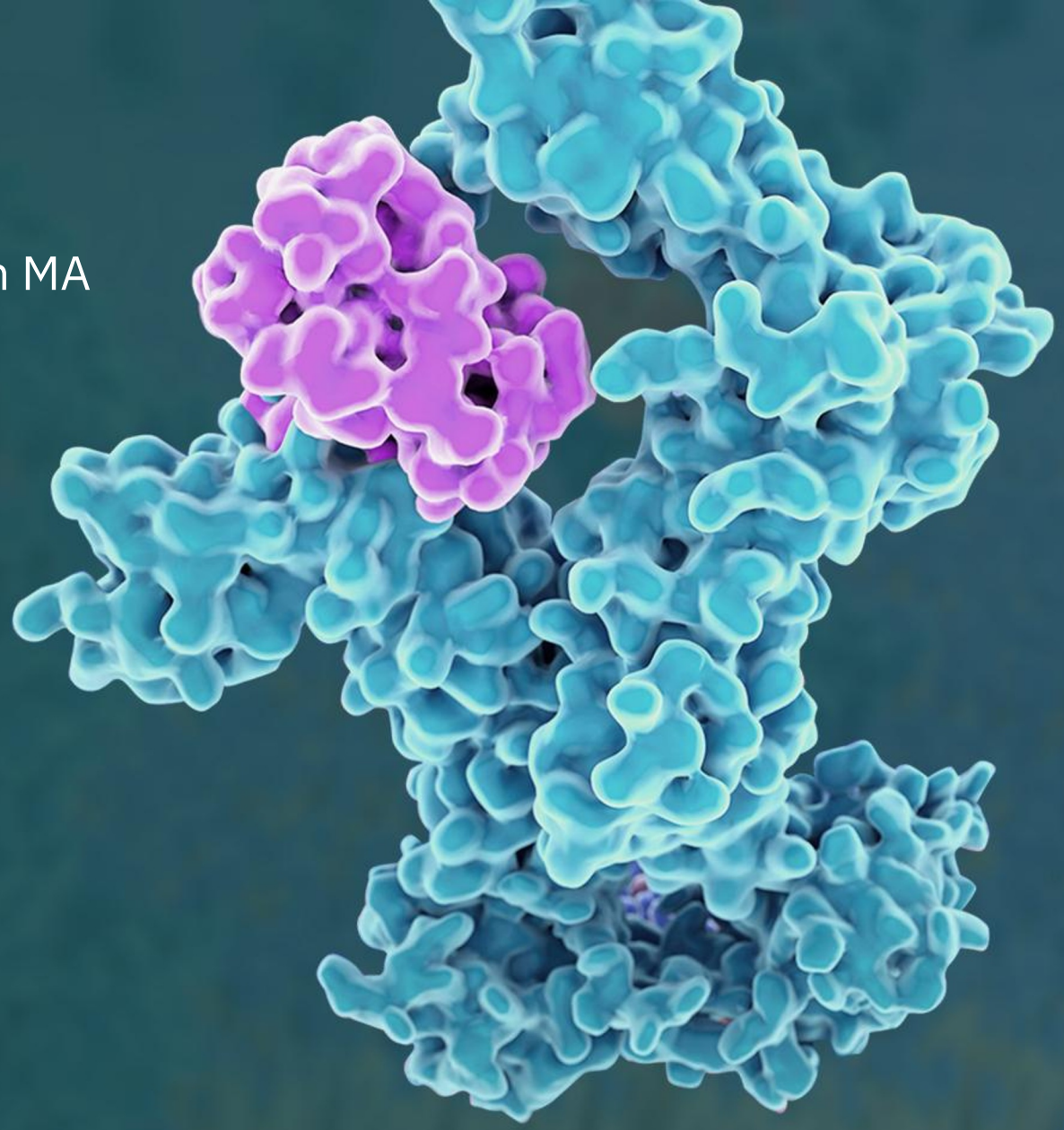
July 27, 2022

Cytokine-Based Drug Development Summit, Boston MA

Co-Stimulation of Adaptive and Innate Immune Cells to Achieve Clinical Benefit with MDNA11, a Long-Acting 'Beta-only' IL-2 Super-Agonist

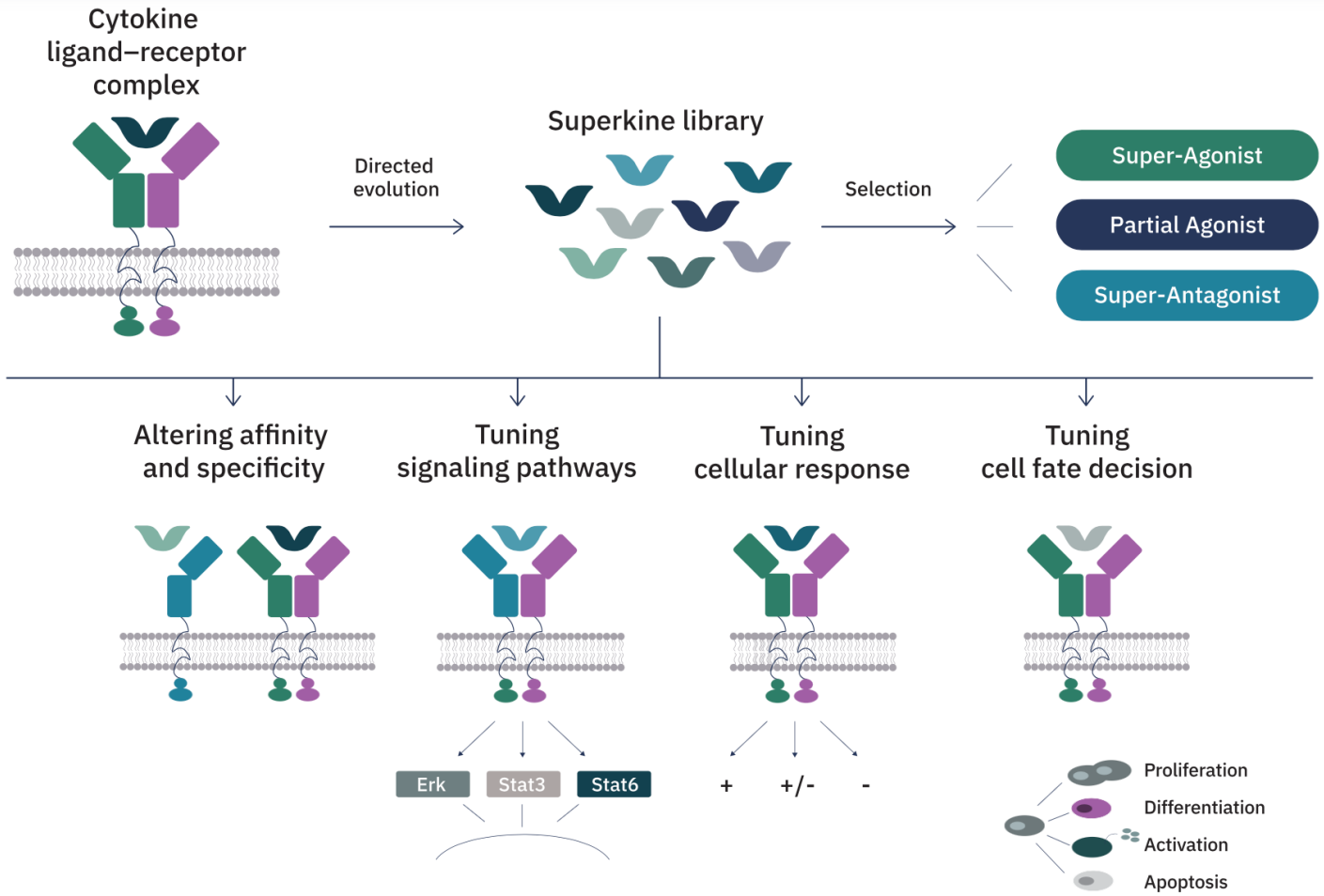


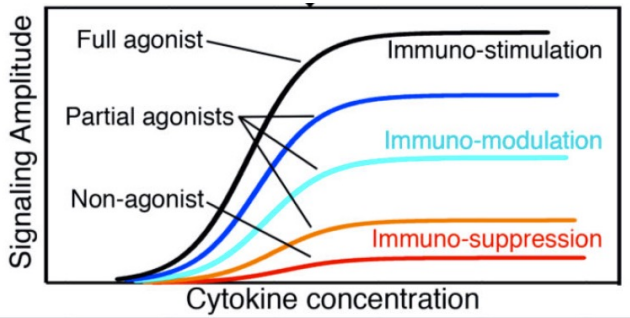
Fahar Merchant, PhD
President & CEO
Medicenna Therapeutics

MEDICENNA

Directed Evolution + Yeast Display = Tunable Superkines

- Platform has generated a library of Superkines with diverse immune modulating capabilities





Overview of Superkine Platform

Superkine Platform:
Drug Discovery Engine

- Directed evolution **enhances the desired properties** of IL-2, IL-4, & IL-13 to generate Superkines
- Protein fusion can **improve PK, add an MOA, or confer new capabilities** to Superkines
- IL-2, IL-4 , & IL-13 are known to modulate immune activity against **2,000 different diseases**

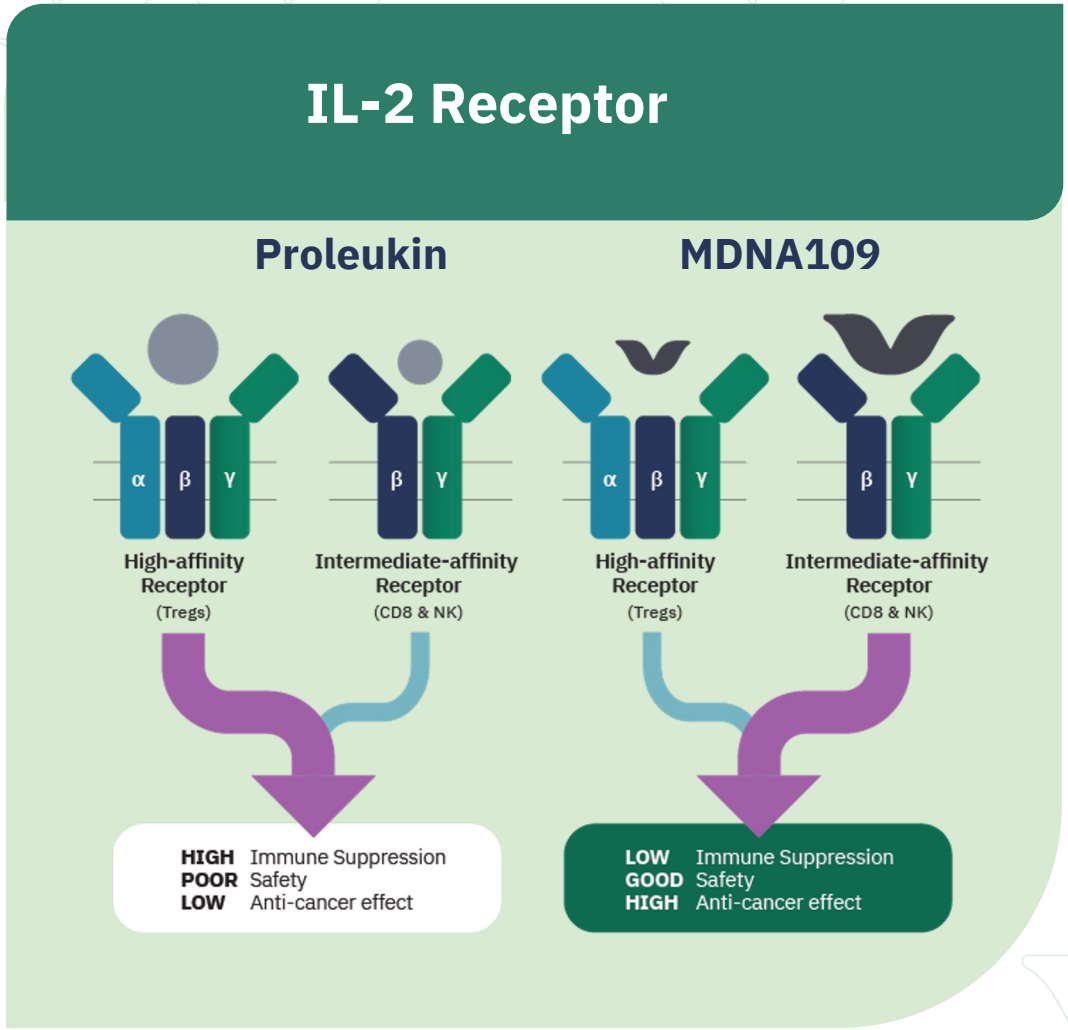
MDNA11: "Beta-only" & Long-acting IL-2 Super-agonist in Phase 1/2

- Super-agonist against IL-2R, a **clinically validated anti-cancer target**
- Enhanced IL-2Rβ binding and lack of IL-2Rα affinity position MDNA11 to be **best-in-class**
- **Preferential stimulation** of $CD8^+$ T and NK Cells
- **Synergistic** with immune checkpoint inhibition
- Strong memory response with **low immunogenicity** risk

BiSKIT Platform:
Bifunctional **S**uper**K**ines for **I**mmuno**T**herapy

- Fusion of two Superkines or a Superkine and an antibody (e.g. a checkpoint inhibitor)
- Incorporate **two synergistic MOAs** into a single molecule

Targeting IL-2 Receptor Subunits in Cancer Therapy



- **The IL-2 receptor (IL-2R) consists of three subunits**
  - CD25 (IL-2Rα)
  - CD122 (IL-2Rβ)
  - CD132 (IL-2Rγ)

- **Stimulation of CD122**
  - Key for the activation of cancer-killing immune cells such as CD8+ T cells, naïve T cells, and NK cells.

- **Stimulation of CD25**
  - Leads to the activation of immunosuppressive Tregs, which abrogate the anti-tumour response
  - Causes extreme toxicity (i.e., pulmonary edema, VLS)

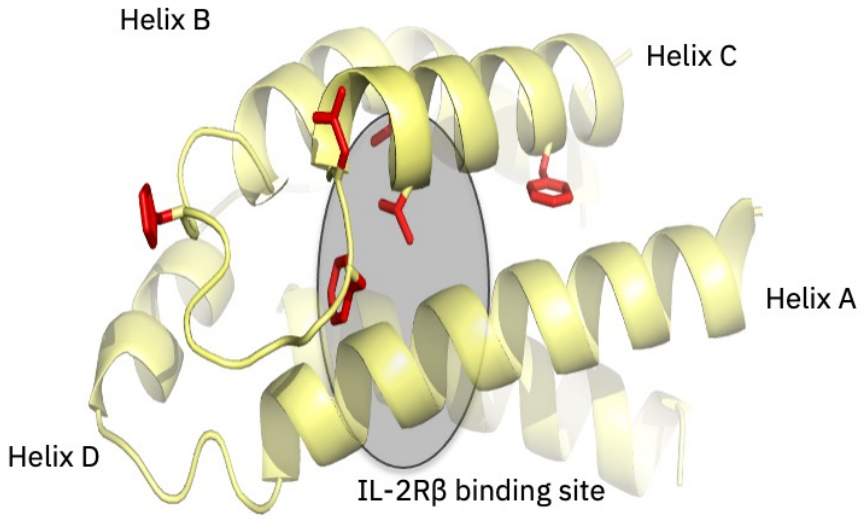
Proleukin® (recombinant human [rh] IL-2), which selectively stimulates CD25, is approved for the treatment of metastatic melanoma and renal cell carcinoma

MDNA109 is a First-Generation IL-2 Super-Agonist

LETTER

nature

Exploiting a natural conformational switch to engineer an interleukin–2 'superkine'



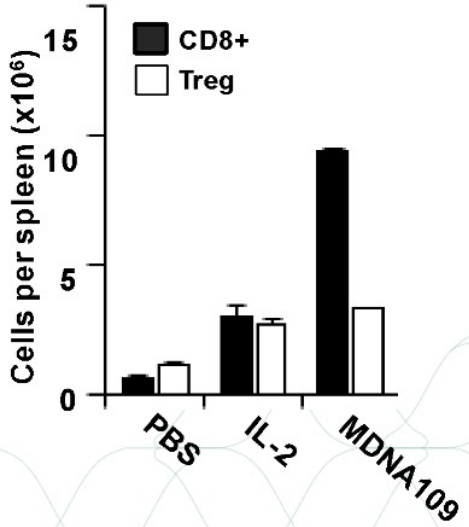
Core Mutations: L80F, R81D, L85V, I86V, I92F

Levin et. al, Nature, 2012 484(7395): 529–533.

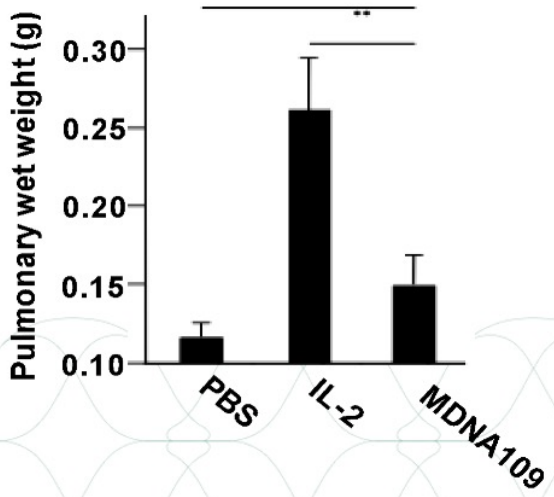
Enhanced Affinity for CD122 (IL-2Rβ); Retains binding to CD25 (IL-2Rα)

SPR data K_D (nM)	CD122 (IL-2Rβ)	CD25 (IL-2Rα)
IL-2	280	6.6
MDNA109	1.4	6.6

Selective Expansion of CD8⁺ T-cells over T_{regs}



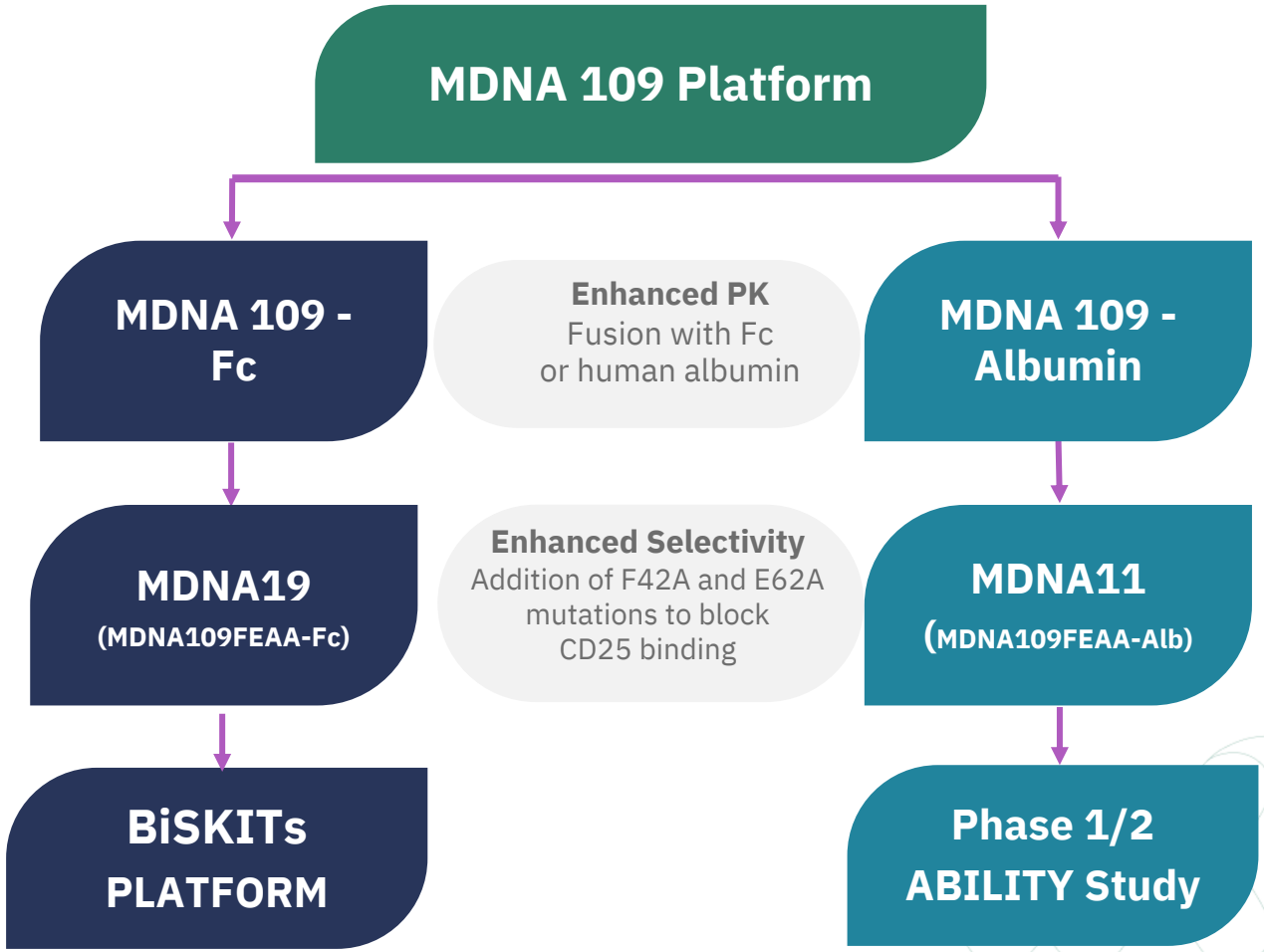
Reduced Adverse Side Effects



Mice were dosed with 20 µg of IL-2 or MDNA109 (IP, for 5 days).
Data shown above based on analysis performed on day 6

MDNA109 Has Been Engineered to Optimize PK & Selectivity

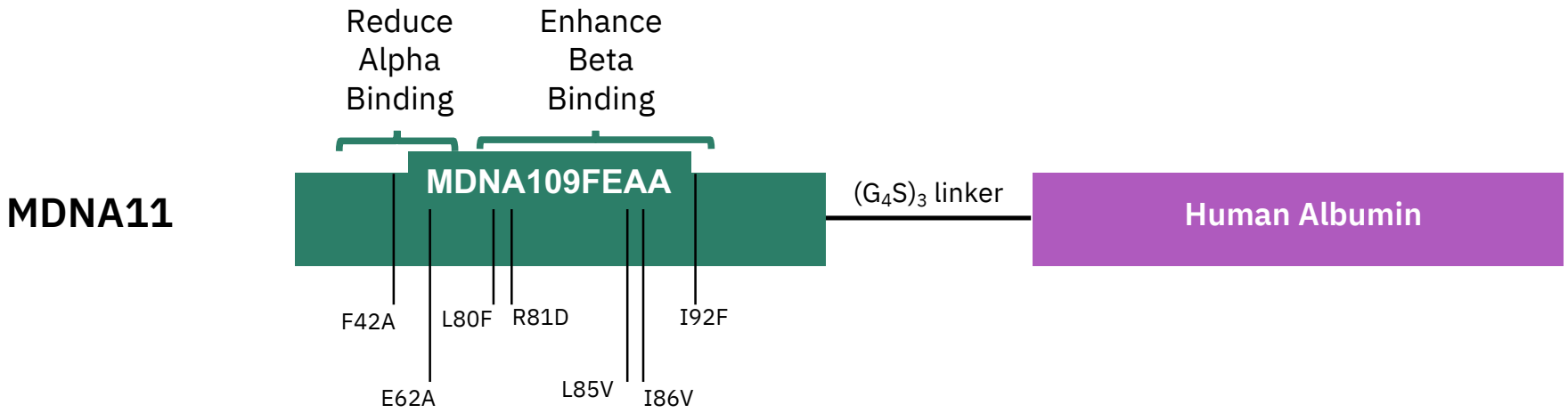
- MDNA11 Has Enhanced IL-2Rβ Affinity, No IL-2Rα Binding, Extended Half-Life and Improved Bioavailability



	Affinity for IL-2Rβ K_D(nM)	Affinity for IL-2Rα K_D(nM)
rhIL-2	280	6.6
MDNA109	1.4	6.6
MDNA11	6.6	No binding

Key Differentiators of MDNA11

- Does not rely on Pegylation or steric hindrance to modulate activity
- Ease of manufacture ensuring consistent batch to batch reproducibility
- Highly versatile backbone aiding design of bespoke immune modulation



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

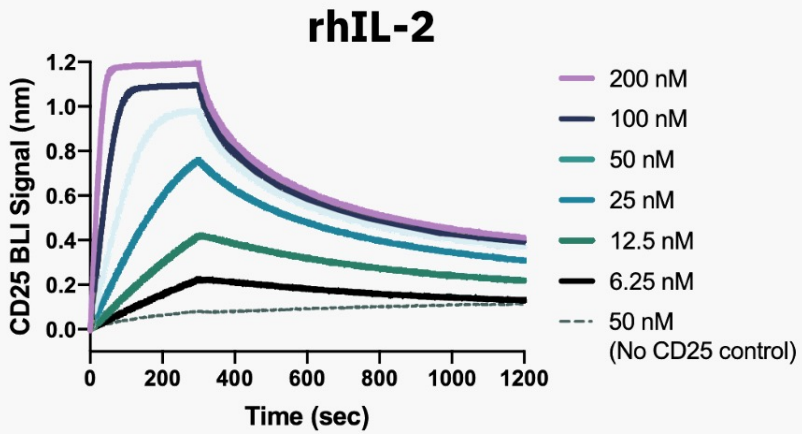
Fusion to Human Albumin

- 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

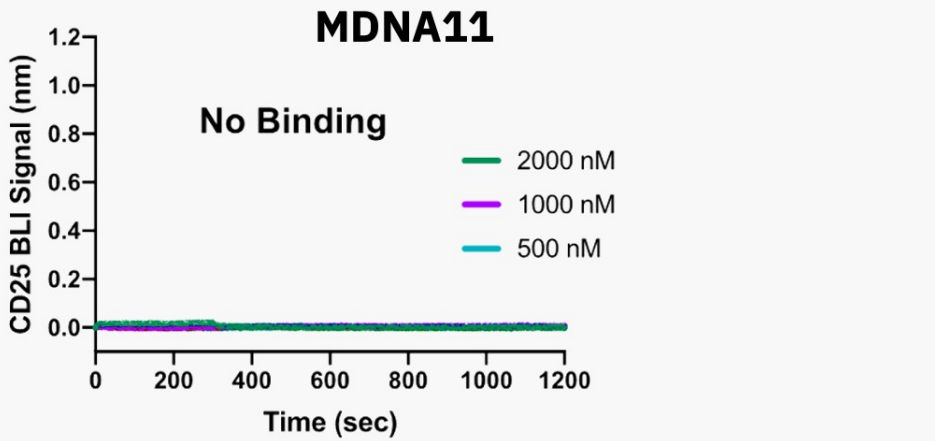
MDNA11 Receptor Binding is Highly Selective Unlike IL-2

- No IL-2Rα (CD25) Binding and Enhanced Affinity and Selectivity for IL-2Rβ (CD122) Compared to rhIL-2

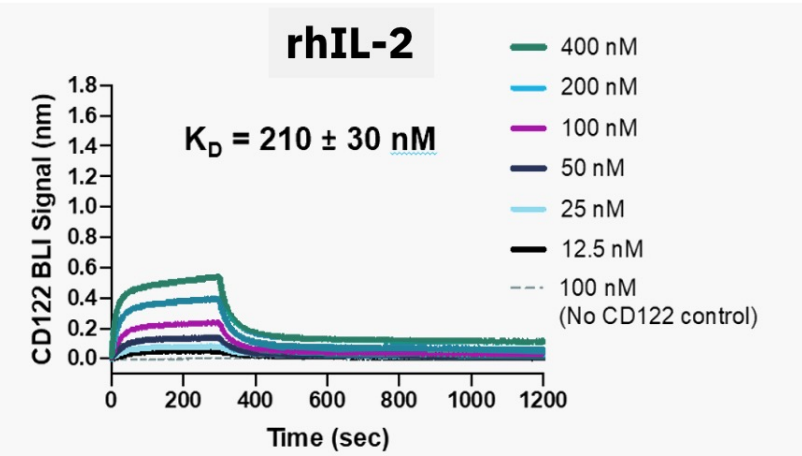
IL-2Rα



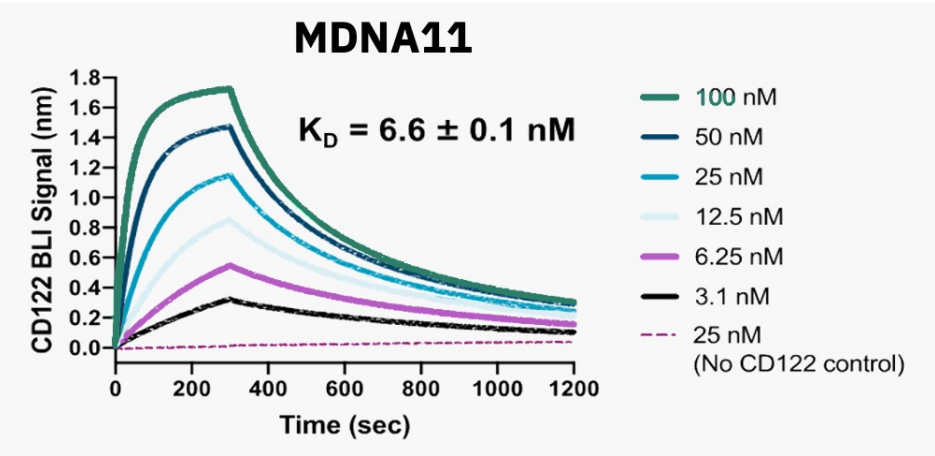
IL-2Rα



IL-2Rβ

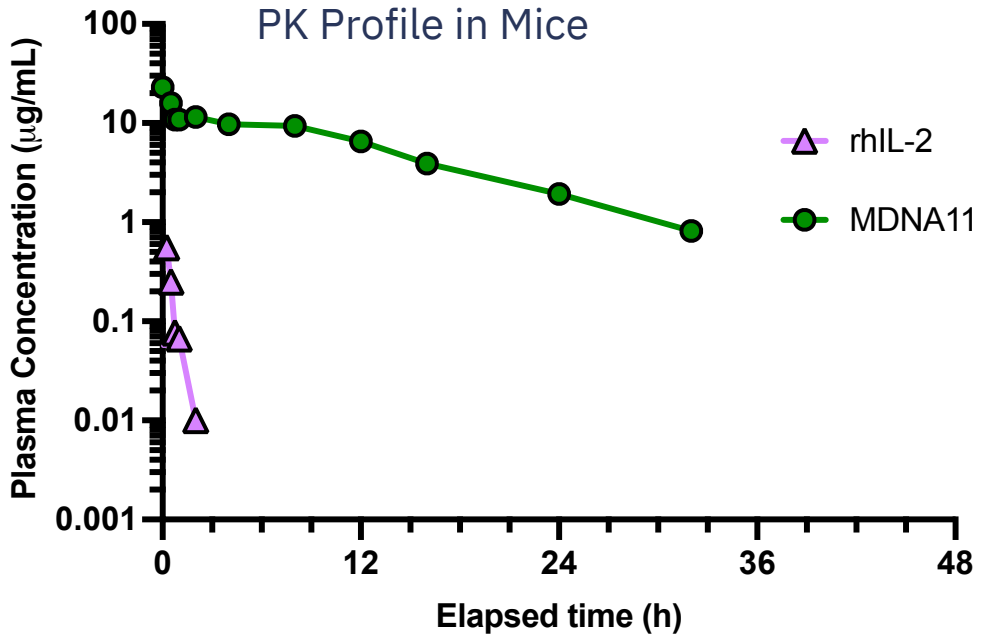


IL-2Rβ



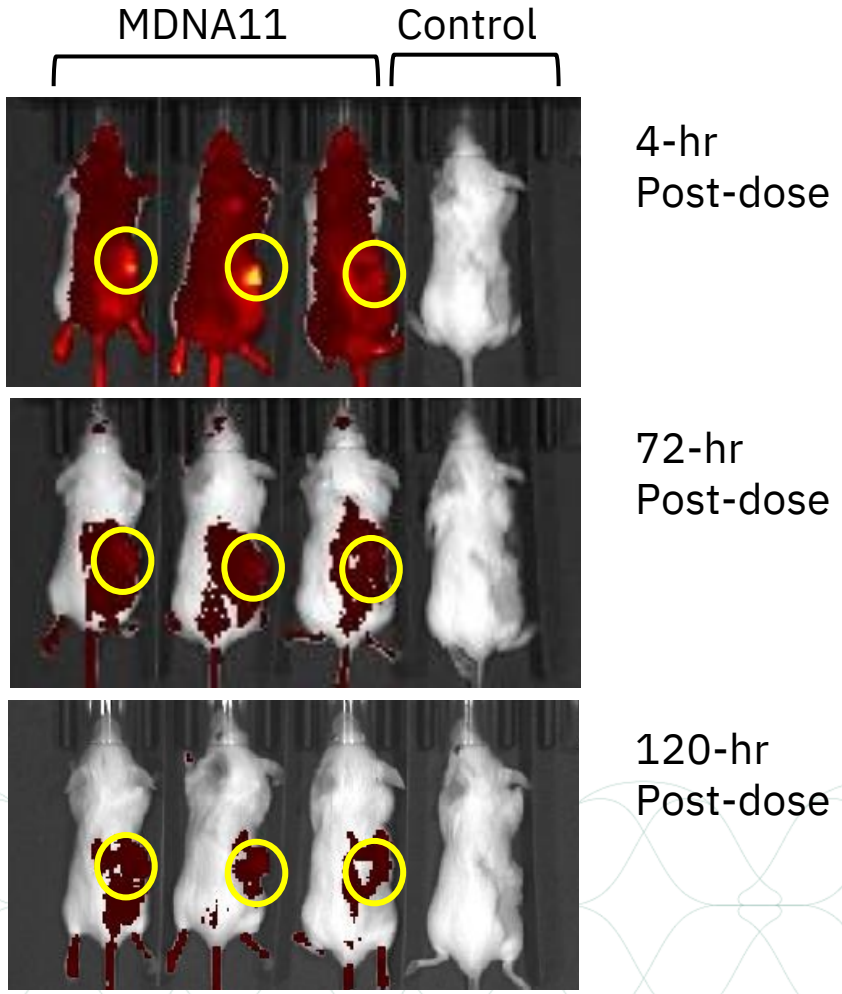
MDNA11 Exhibits Durable Tumor Accumulation In Vivo

- Improves Half-Life by ~25 fold in mice and tumor bioavailability for at least 120 hours



	C_{max} (µg/mL)	AUC (µg.hr/mL)	T_{half} (hr)
rhIL-2	5.77	1.07	0.28
MDNA11	23.02	182.3	6.83

Naive C57Bl/6 mice IV dosed at 1 mg/kg IV



MDNA11 Localization in CT26 Tumor Bearing Mice

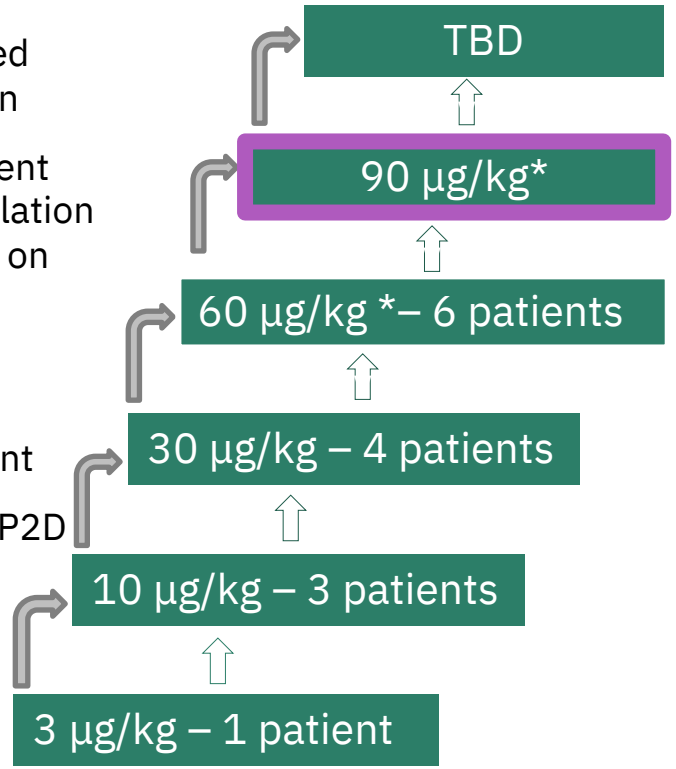
MDNA11 labelled w/VivoTag800; IV dose: 1 mg/kg; Tumor size: 150-200 mm^3

Phase 1/2 ABILITY Study Schema: Enrolling DL5

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~ 40: 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:

- Safety/Tolerability
- 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)

PK and PD Assessment:

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

*Step-up dosing utilized: two priming doses of 30µg/kg given before the target dose

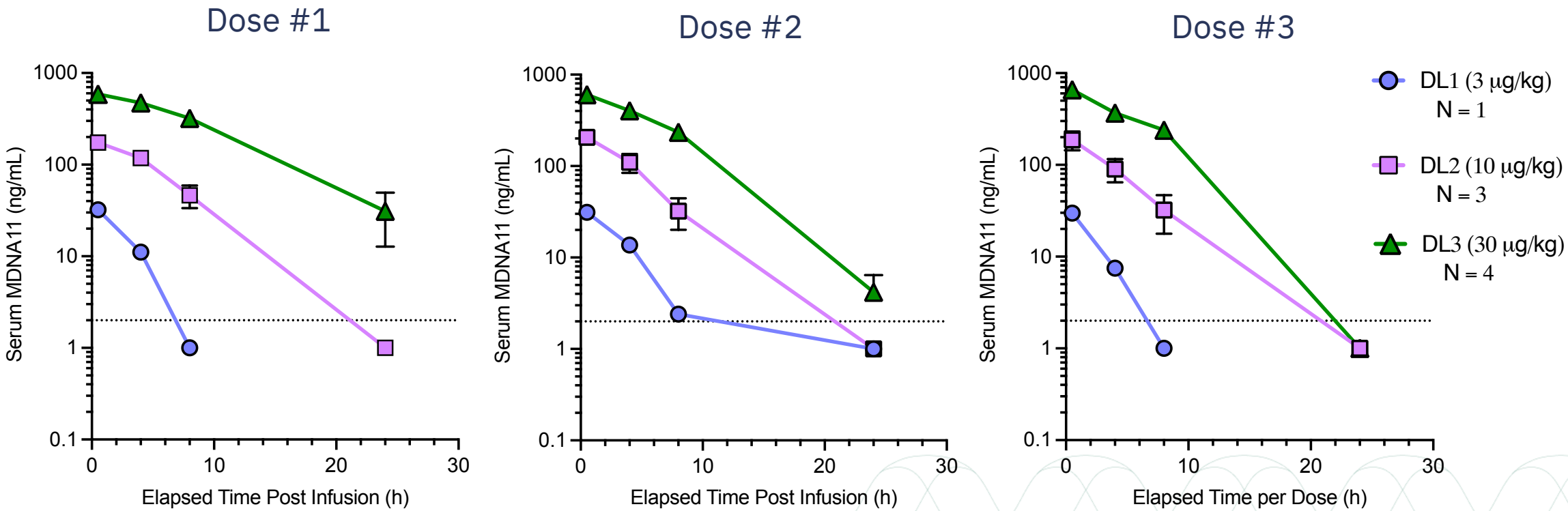
Protocol Version 5

Patient Characteristics (N = 14, as of July 21, 2022)

Demographics/Performance	
Age (mean, yrs)	60.5
Male (%)	11/14 (79%)
Female (%)	3/14 (21%)
Baseline ECOG = 0	9/14 (64%)
Baseline ECOG = 1	5/14 (36%)
Primary Cancer Diagnosis	
Melanoma	7/14 (50%)
Renal Cell Carcinoma	1/14 (7%)
Pancreatic	2/14 (14%)
Sarcoma	2/14 (14%)
Squamous Cell Carcinoma	1/14 (7%)
Gastro-esophageal Adenocarcinoma	1/14 (7%)
Prior Systemic Therapies	
Lines of systemic therapies	1-4
Prior use of immunotherapy	11 /14 (79%)
Prior use of targeted therapy	4/14 (28%)
Prior use of chemotherapy	6/14 (43%)

MDNA11 PK Profile in Patients with Advanced Solid Tumors

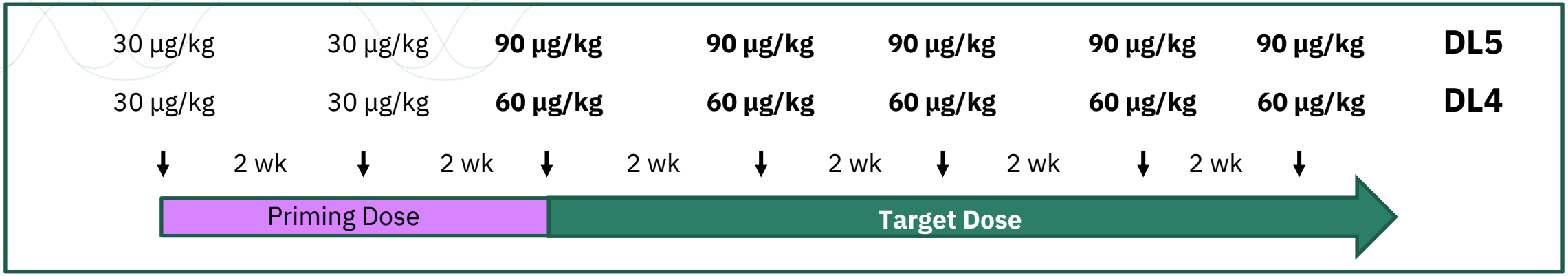
- Highly similar PK plots following each of 3 repeat doses suggest no immunogenicity; ADA testing ongoing
- Dose-dependent increase in C_{max} and AUC



Summary of Key PK Parameters

	DL1: 3 µg/kg (N = 1)	DL2: 10 µg/kg (N = 3)	DL3: 30 µg/kg (N = 4)
Dose 1			
C_{max} (ng/mL)	32.2	174 ± 13.4	611 ± 188
AUC_{last} (h.ng/mL)	94.7	957 ± 187	5,497 ± 2,768
Dose 2			
C_{max} (ng/mL)	31.2	206 ± 40.5	604 ± 82.1
AUC_{last} (h.ng/mL)	130	969 ± 306	4,458 ± 1,373
Dose 3			
C_{max} (ng/mL)	29.8	188 ± 75	659 ± 259
AUC_{last} (h.ng/mL)	82.1	847 ± 387	3,434 ± 780

Step Up Dosing (SUD) Strategy Implemented Starting at DL4



Objective:

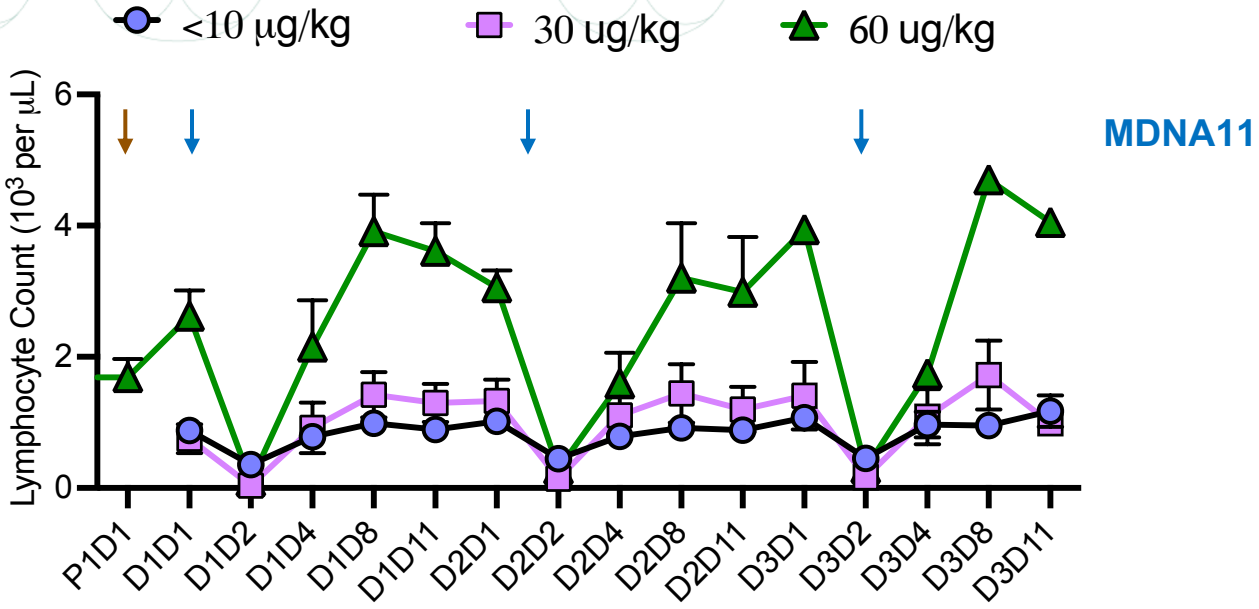
- To pre-emptively mitigate the risk of potential toxicities during dose escalation in order to safely reach higher doses and achieve the best therapeutic response

Rationale:

- SUD is adopted in clinical trials to deliver the highest achievable dose (Carlo-Stella et al., Hematological Oncology 2021; Trudel et al, Blood 2021; Hutchings et al., Blood 2020; Bartlett et al., ASCO 2019)
- A study in mice with MDNA11 demonstrated a > 2.5-fold increase in tolerability with SUD compared to a fixed dose administration

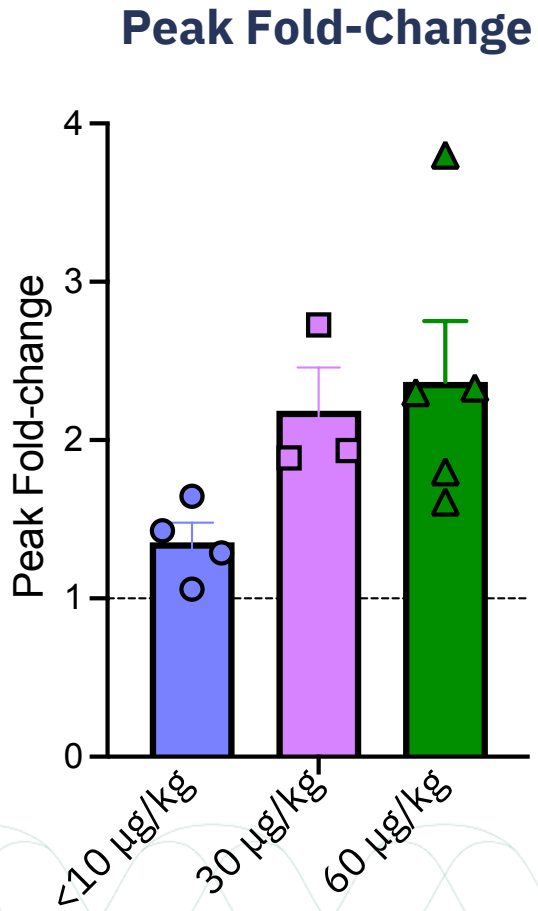
MDNA11 Induces Lymphocyte Expansion

- Expansion of circulating lymphocytes irrespective of baseline count



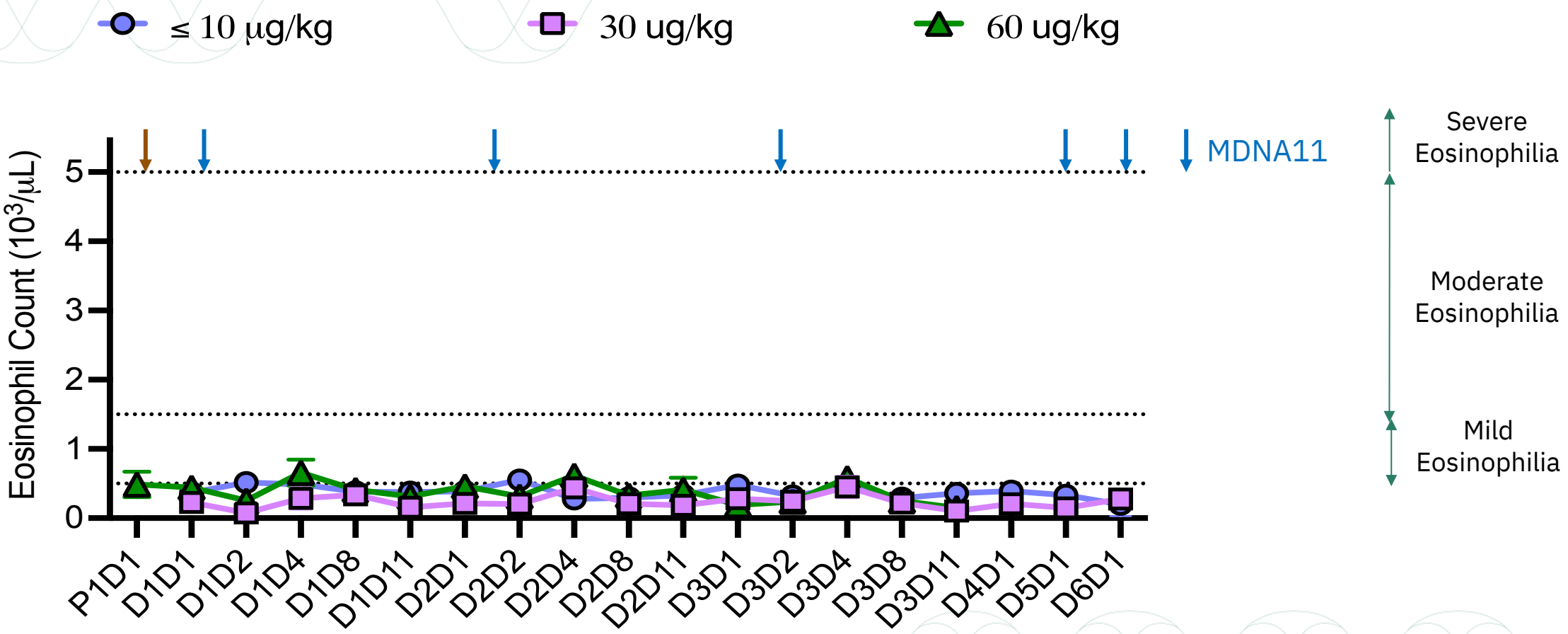
	Average AUC (day.10^3 cells/µL) (Average of Dose 1 & 2)
< 10 µg/kg	3
30 µg/kg	4.8
60 µg/kg	12.2

DL4 patients received 2 priming doses (30 µg/kg Q2W) prior to target dose (60 µg/kg Q2W)
AUC measured as area between minimum lymphocyte count values



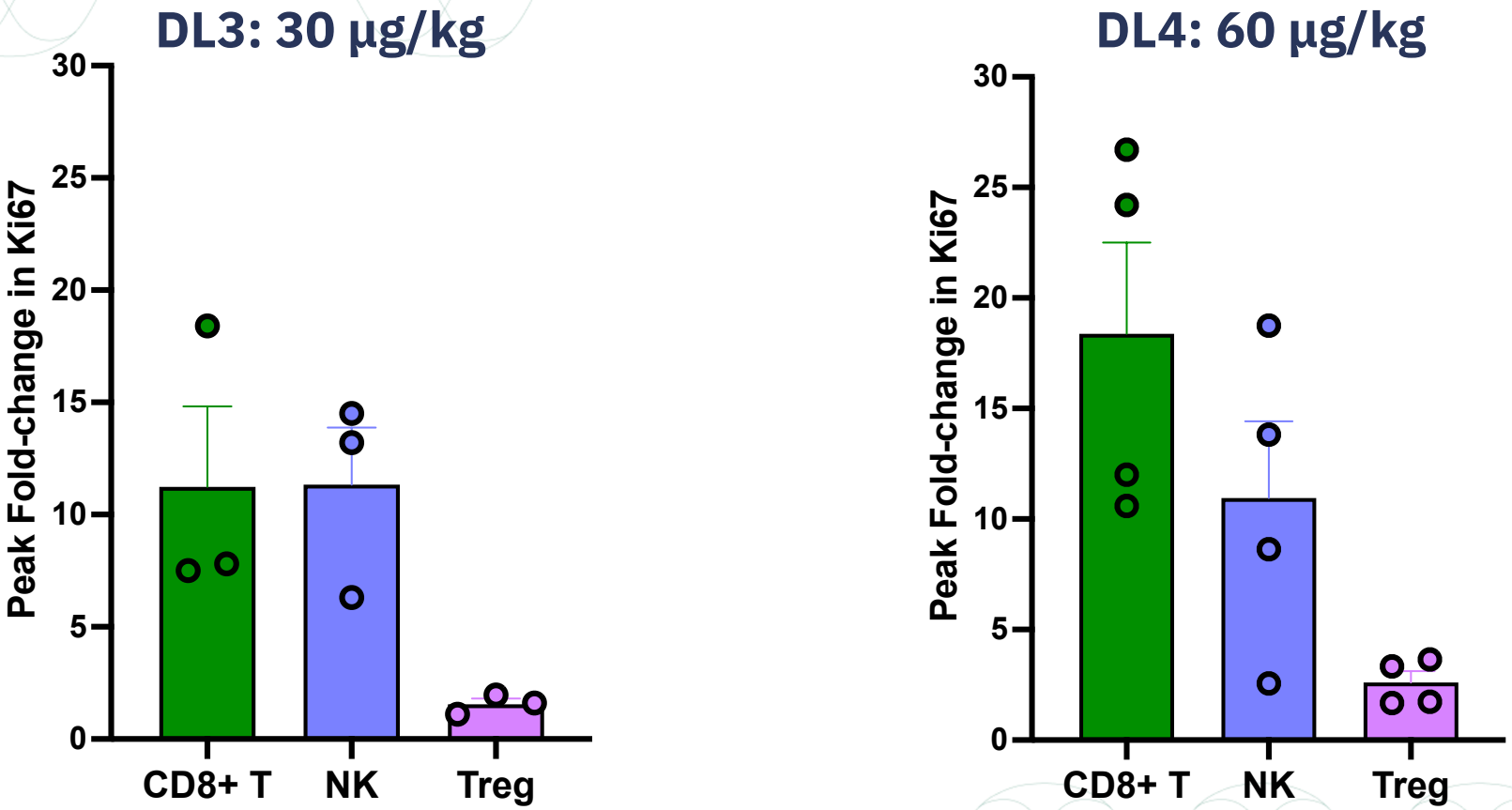
Peak fold-change relative to baseline
For < 10 µg/kg and 30 µg/kg, peak data for Dose 3
For 60 µg/kg, peak data for Target Dose 1

No Evidence of Eosinophilia (Associated with VLS)



DL4 patients received 2 priming doses (30 µg/kg Q2W) prior to start of target dose of 60 µg/kg (Q2W)

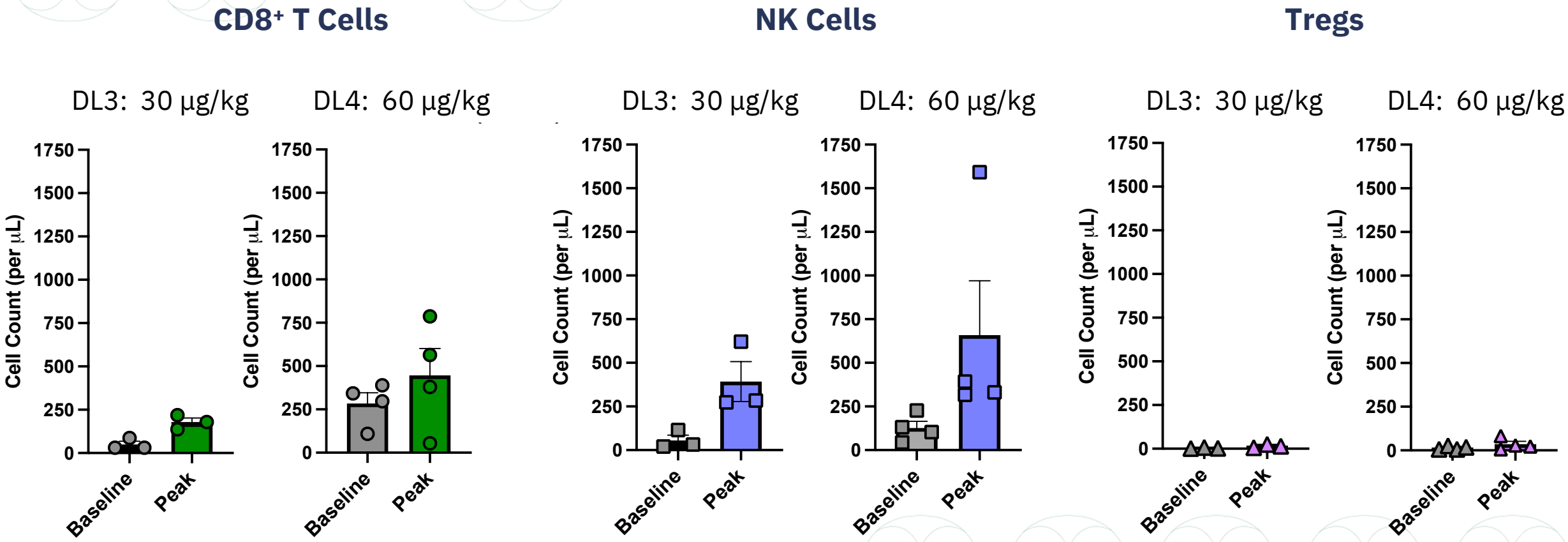
MDNA11 Preferentially Stimulates CD8+T & NK Cell Proliferation (Ki67)



Peak fold-change relative to respective baseline (D1D1 for DL3; P1D1 for DL4)
DL4 patients received 2 priming doses (30 µg/kg Q2W) prior to start of target dose of 60 µg/kg (Q2W)
DL3 data based on 3rd dose cycle

MDNA11 Preferentially Expands CD8⁺T and NK Cells Over Tregs

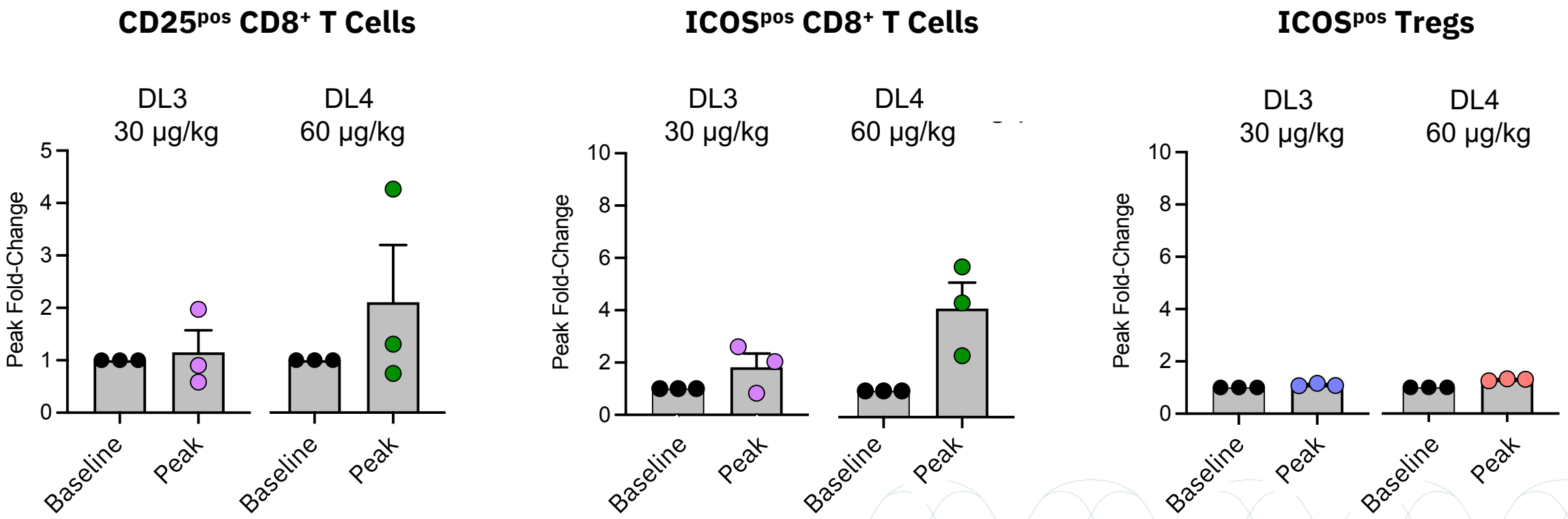
- Increase in number of CD8+ T and NK cells with minimal change in Treg counts



DL4 patients received 2 priming doses (30 µg/kg Q2W) prior to start of target dose of 60 µg/kg (Q2W).
DL3 data based on 3rd dose cycle; DL4 data based on 1st dose

CD8+ T Cell Activation Without ICOS Induction on Tregs

- Upregulation of CD25 and ICOS indicate CD8+ T cell activation
- High dose rhIL-2 stimulates ICOS expression on Tregs and is associated with lack of therapeutic response*

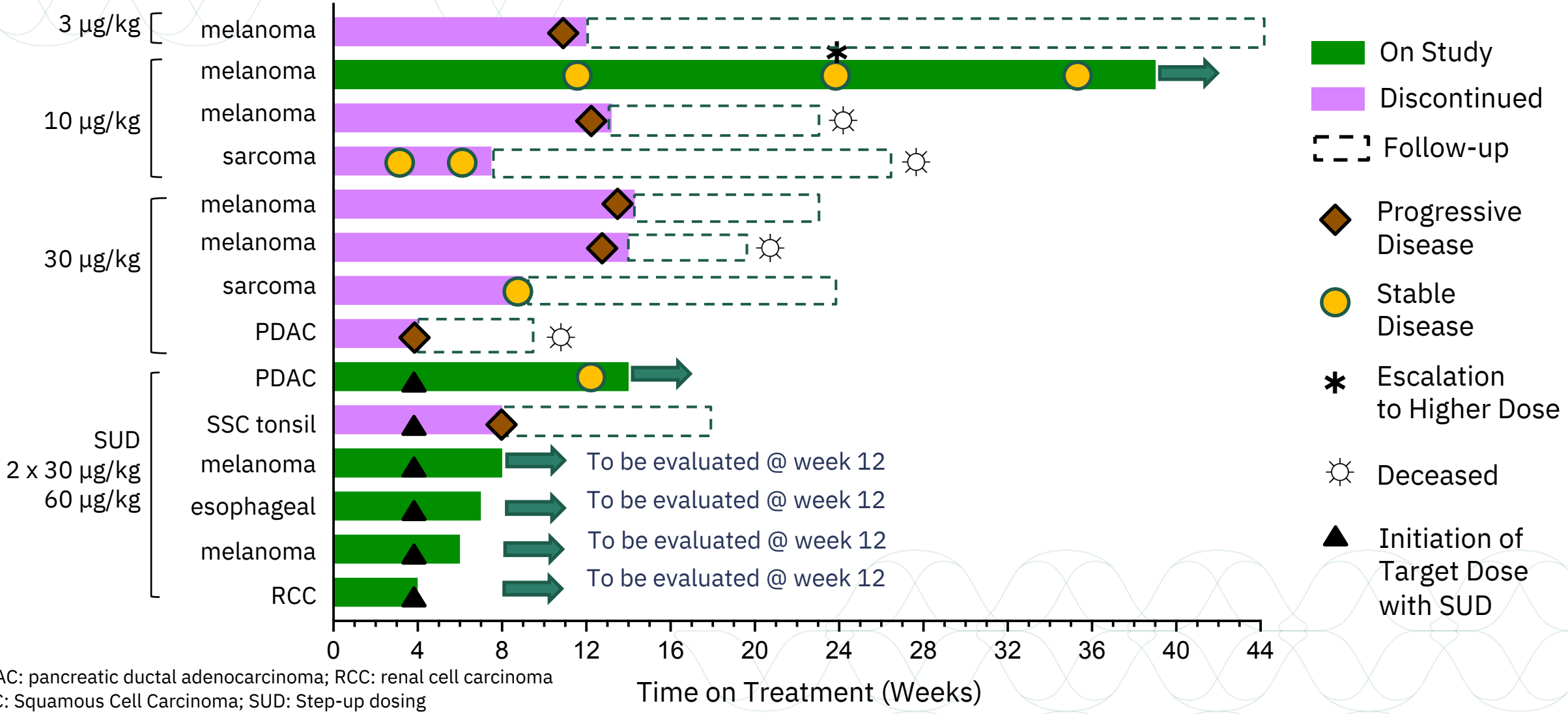


DL4 patients received 2 priming doses (30 µg/kg Q2W) prior to start of target dose of 60 µg/kg (Q2W).
DL3 data based on 3rd dose cycle; DL4 data based on 1st dose
Relative to baseline (D1D1 for DL3; P1D1 for DL4)

(*Sim et al., J Clinical Investigation, 2014)

Duration of Treatment and Summary of Response

- Tumor Control Observed in 4 of 10 Evaluable Patients



PDAC: pancreatic ductal adenocarcinoma; RCC: renal cell carcinoma
SSC: Squamous Cell Carcinoma; SUD: Step-up dosing

As of July 21, 2022

MDNA11 is a Potentially Best-in-Class IL-2 Therapy

"Beta-only" IL-2 Super-Agonist	• **High affinity for IL-2Rβ (CD122) and lack of affinity for IL-2Rα (CD25)** enhances therapeutic efficacy and improves safety profile • Competing IL-2 agents have comparatively low affinity for IL-2Rβ
Strong CD8⁺ T-cell and NK Cell Expansion with Clean Safety	• **~7.5 fold more potent on effector T cells and ~28 fold less potent on T_{regs} when compared to native IL-2** • Preliminary Phase 1/2 data demonstrated **preferential stimulation of CD8⁺ T and NK cells, with acceptable toxicity** (no DLTs, no evidence of cytokine release syndrome or vascular leak syndrome)
Extended Half-Life	• Fusion to albumin scaffold extends half-life that allows for a **highly convenient dosing** schedule (Q2W) • Albumin fusion provides **additional benefit for localizing MDNA11** at the tumor site and tumor draining lymph nodes
Synergistic with Immune Checkpoint Inhibition	• **Induced 100% tumor regression in preclinical models** when co-administered with anti-CTLA4 and anti-PD1 • **Strong memory response with low immunogenicity risk**, both as a monotherapy and in combination with anti-CTLA4 and anti-PD1

IL-2 Superkines Independently Validated Across Diverse Treatment Modalities

Science Signaling
nature chemical biology
nature

Levin et al., Nature (2012)
Moraga et al., Science Signaling (2015)
Junttila et al., Nature Chem Biol (2012)

Naked Interleukins (NaIL Cancer™)

PNAS Immunity
Journal for ImmunoTherapy of Cancer

Mitra et al., Immunity (2015)
Rafei et al., CICON (2019)
Rafei et al, ASCO (2020)
Wolf et al, PNAS (2022)
Sharma et al, AACR (2022)
Merchant et al., JITC (2022)

Long-Acting Interleukin Agonists or Antagonists (LAILA™)

Merchant & To, AACR (2021)
Merchant, Designer Cytokines (2021)
To et al, AACR (2022)

Checkpoint Inhibitors Fused to Cytokines (CheCK Cancer™)

nature COMMUNICATIONS

Sun et al., Nat Comm (2019)

Superkines Targeted with Antibodies (STAb Cancer™)

nature COMMUNICATIONS

Hsu et al., Nat Commun (2021)

Metalloprotease Activated SuperKines (MASK™)

CLINICAL CANCER RESEARCH

Sampson et al., ASCO (2020)
Ellingson et al, Clin Cancer Res (2021)

Fusion to Pro- or Anti-apoptotic Payloads (Empowered Superkines™)

To et al., ENA 2020
Merchant & To, AACR (2021)
Moraga et al., eLife (2017)

Dual Specific Cytokines (DUCK Cancer™)

Merchant & To, AACR (2021)
Merchant, Designer Cytokines (2021)

IL-13 directed Cell Engagers (ICE™)

Quixabeira et al., Front Immunol (2021)
Brog et al., Cancer Immunol Res (2022)

Cellular therapies and Oncolytic Viruses armed with Cytokine Therapies (CONVICT™)

CANCER IMMUNOLOGY RESEARCH

ACKNOWLEDGEMENTS

- We are very grateful to the patients enrolled in the study and their friends and family
- All Investigators and their teams for exceptional support at:
  - Gallipoli Medical Research Foundation (GMRF), Brisbane, Australia
  - Chris O'Brien Lifehouse (COBLH), Sydney, Australia
  - Scientia, Sydney, Australia
  - ICON, Brisbane, Australia
  - Princess Margaret Hospital, Toronto, Canada

Thank You