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Early Results of an IL-2 Superkine (MDNA11) from the Phase 1/2 ABILITY Study in Advanced Solid Tumors

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CONFLICT OF INTEREST STATEMENT

I hereby declare that I do not conduct activities that would involve a conflict of interest with CME-accreditable training, but that in the past 2 (two) years I have received the funding listed below from the following sources:

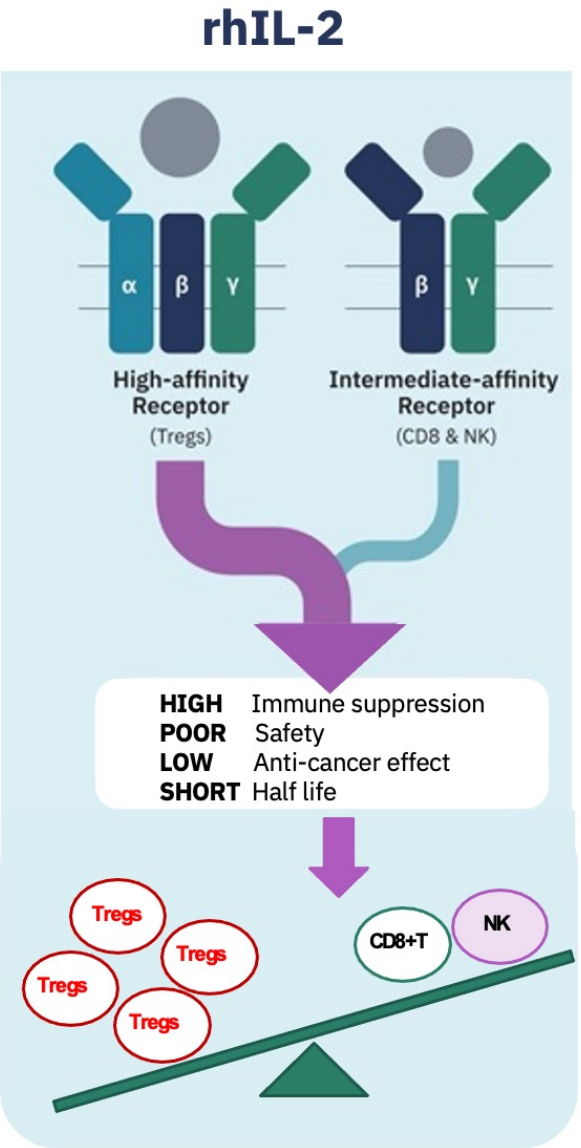
1. **Employment/other financial – University of Oxford, Imbria, Weatherden**
2. **Research/grant funding – SBI Pharmaceuticals**
3. **Advisory role – Medicenna Therapeutics**

Biology of IL-2 and High Dose IL-2 Immunotherapy

- **IL-2, a 15 kDa multi-faceted cytokine with dual immune functions**:
  - immunostimulation – proliferation and generation of effector and memory T cells and NK cells
  - immune suppression - promoting generation, survival and functional capacity of Tregs

- **High dose recombinant human IL-2 (HD-rhIL-2, aldesleukin) can result in durable complete tumor remission as monotherapy** in a subset of patients with metastatic melanoma and renal cell carcinoma (RCC)

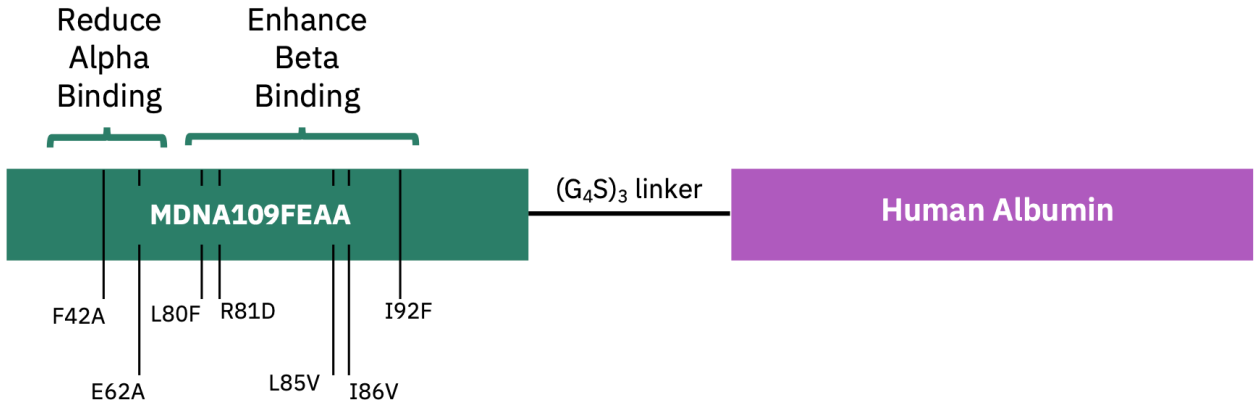
- **However, its broad clinical use is limited by**:
  - very short half life and requirement for frequent high doses
  - severe toxicities necessitating specialist center administration
  - preferential stimulation of Tregs and lower potency on effector immune cells (i.e. CD8⁺ T and NK cells)

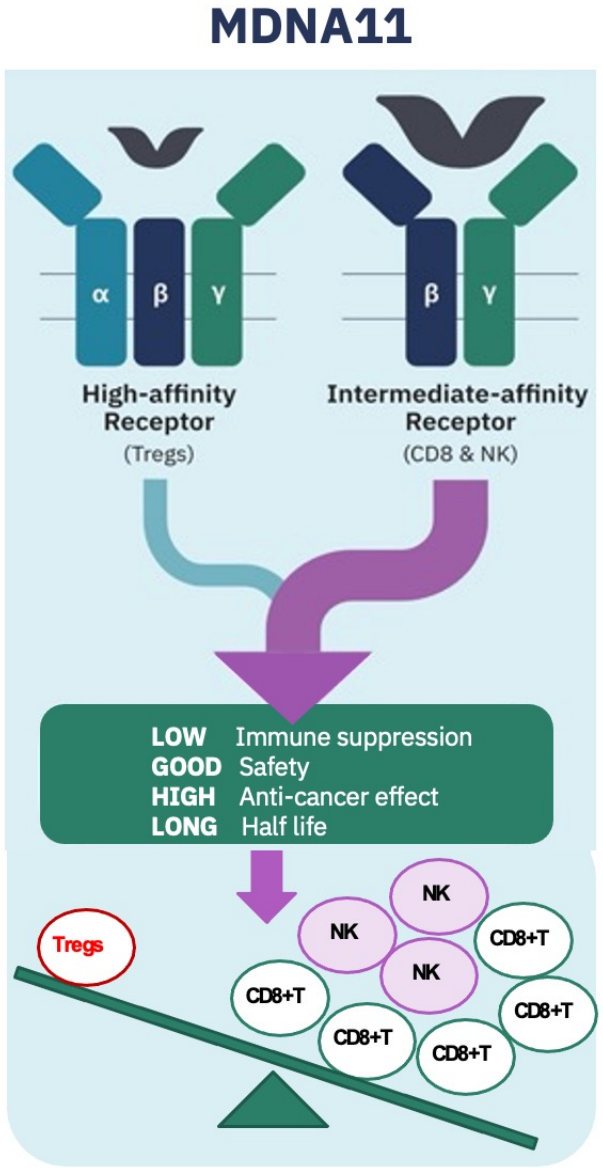


MDNA11: A Long-acting, Next-generation, β-only IL-2 Superkine

Superior selectivity with enhanced 'β-only' pharmacology

Enhanced PK profile & tumor accumulation



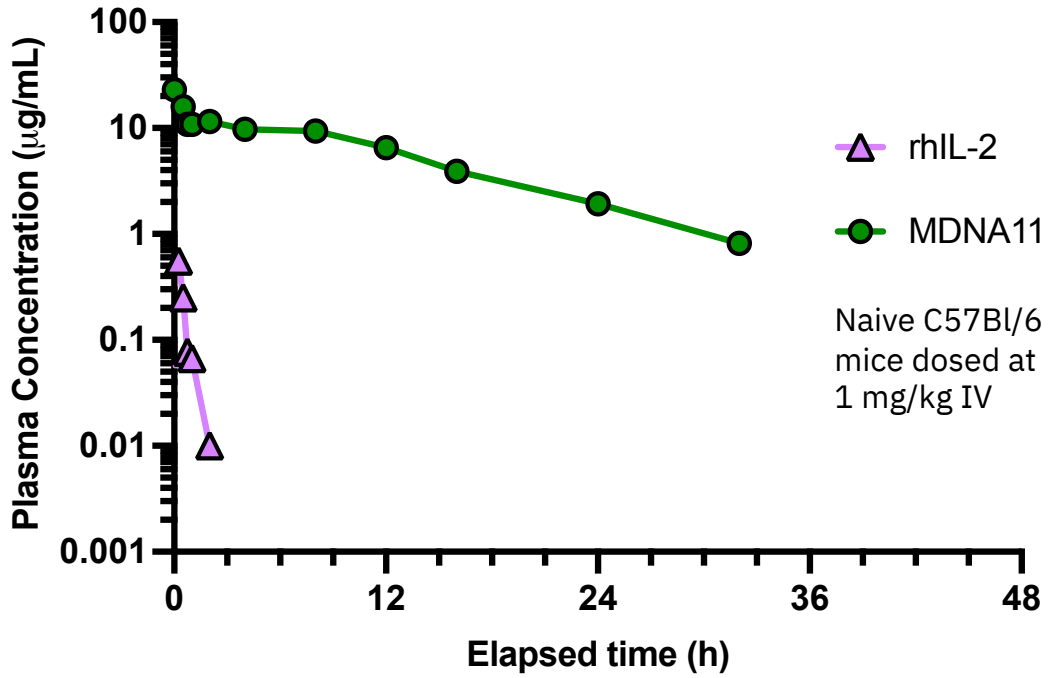


- **MDNA11 - engineered to overcome key limitations of HD rhIL-2:**
  - ↑ affinity to IL-2Rβ (CD122) - Potentiate effector cell activation
  - Abolish binding to IL-2Rα (CD25) - ↓Treg stimulation & toxicities
  - Fusion to human albumin to overcome rapid renal clearance, increase half-life and promote tumor accumulation
- **MDNA11 exerts potent anti-tumor and memory responses in multiple tumor models as monotherapy and combined with ICI**

Merchant et al., *JITC* 2022

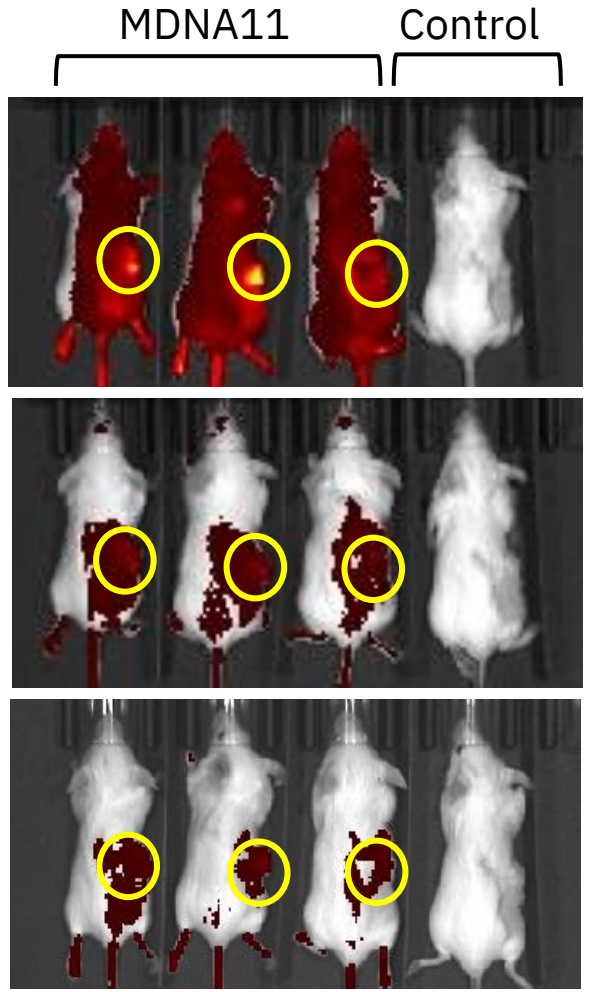
MDNA11 Durably Accumulates In Solid Tumors In Vivo

PK Profile in Mice



	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

MDNA11 Imaging in CT26 Tumor Model



MDNA11 labelled with VivoTag800; IV dosing (1 mg/kg); Tumor size: 150-200 mm^3

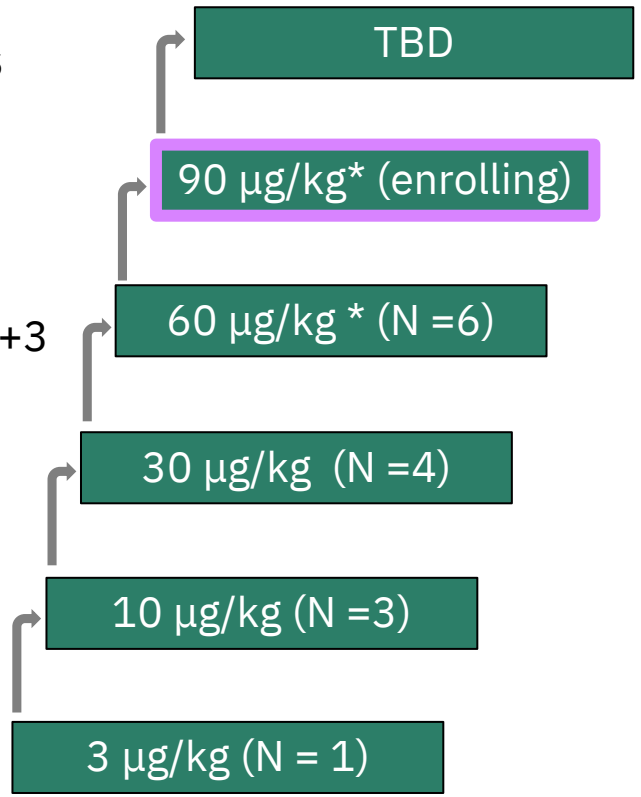
- **Tumor exposure of MDNA11 is > 15x longer than its serum half-life**

ABILITY MDNA11 FIH Trial (A Beta-only IL-2 ImmunoTherapY)

MDNA11 Monotherapy Dose Escalation

Advanced solid tumors
IV Infusion, Q2W

- Modified, accelerated 3+3 design
- Safety and tolerability
- Determine MTD, RP2D
- Anti-tumor activity



*Step-up dosing utilized:
two priming doses of 30 µg/kg (Q2W) prior to the indicated target dose

MDNA11 Monotherapy Dose Expansion

N~ 40
(Melanoma, up to N = 20)

Single agent MDNA11 at RP2D via IV infusion Q2W

Signals of anti-tumor activity

MDNA11 + Pembrolizumab Dose Expansion

N~ 40
(Melanoma, up to N = 20)

Safety run-in

MDNA11 administered at RP2D in combination with pembrolizumab via IV infusion

Signals of anti-tumor activity

- Design: First-in-human, open-label study of MDNA11 as single agent & with pembrolizumab
- Patient population: Patients with treatment-refractory advanced solid tumors

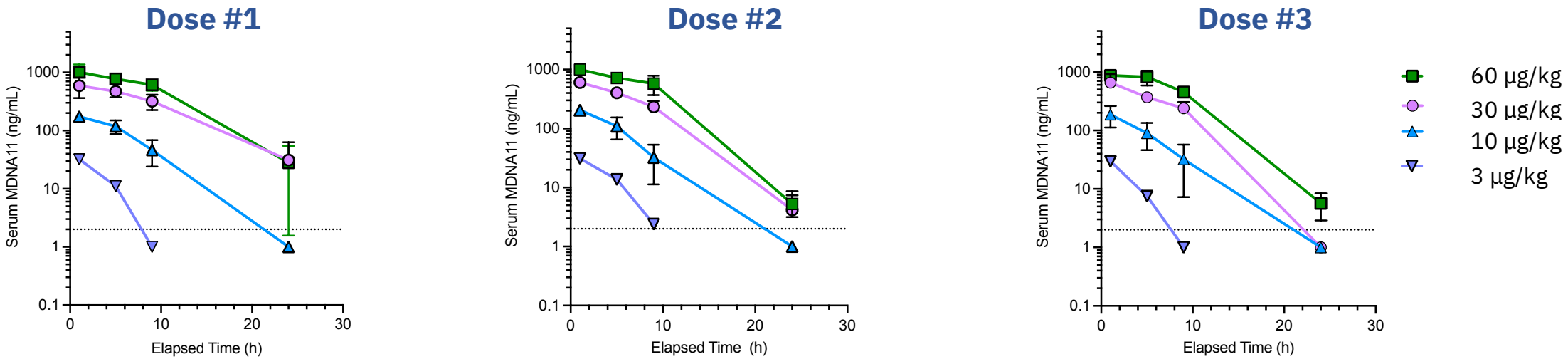
Baseline Patient And Tumor Characteristics

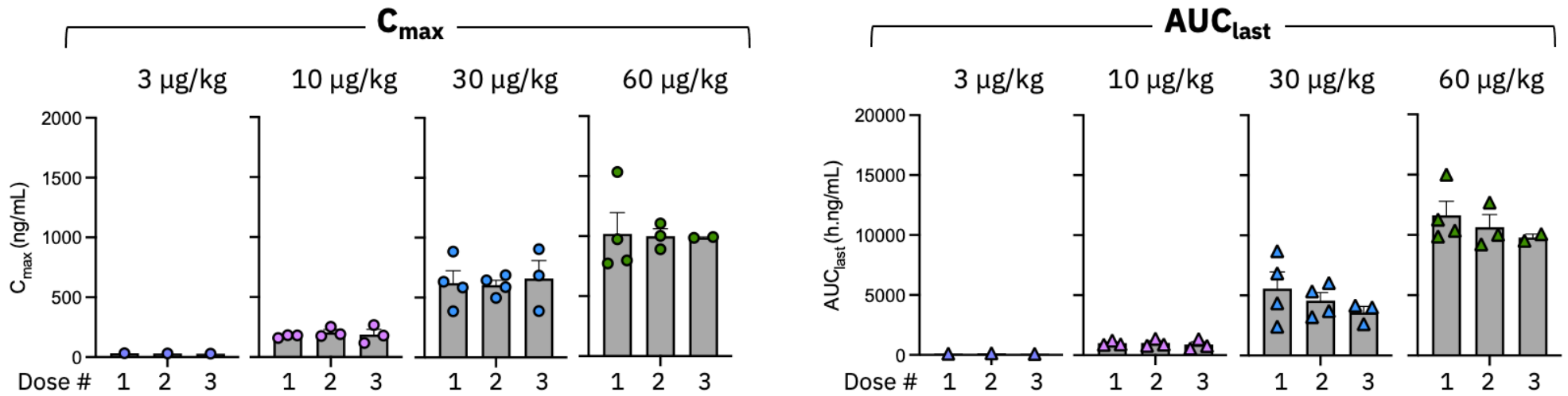
Demographics/Performance status	N=14
Age, median years (range)	63 (27-78)
Male, n (%)	11 (79%)
Baseline ECOG = 0, n (%)	10 (71%)
Baseline ECOG = 1, n (%)	4 (29%)
Primary Tumor Type	**N, %**
Melanoma	7 (50%)
Renal Cell Carcinoma (non-clear cell)	1 (7%)
Pancreatic Ductal Adenocarcinoma (PDAC)	2 (14%)
Sarcoma	2 (14%)
Squamous Cell Carcinoma	1 (7%)
Gastro-esophageal Adenocarcinoma	1 (7%)
Prior Anti-cancer Systemic Therapies	**N, %**
Prior Lines of Therapy: 1-2	9 (64%)
Prior Lines of Therapy: 3-4	5 (36%)
Immunotherapy	11 (79%)
Targeted therapy	4 (28%)
Chemotherapy	7 (50%)

- Data from all patients enrolled in Cohorts 1-4

Clinical PK of MDNA11

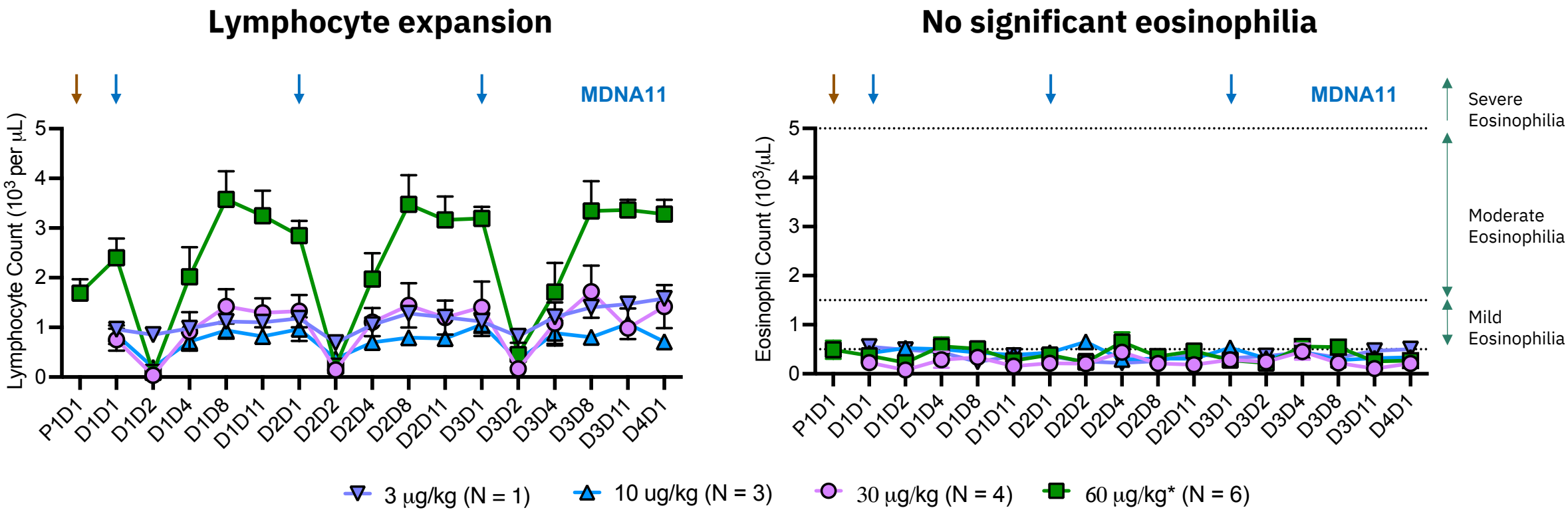
- MDNA11 PK exhibits saturable rapid clearance and a slower parallel linear clearance process
- **Dose-dependent increase in exposure (C_{max} & AUC_{last}) with low variability between doses**





MDNA11 Induces Sustained Peripheral Lymphocyte Expansion

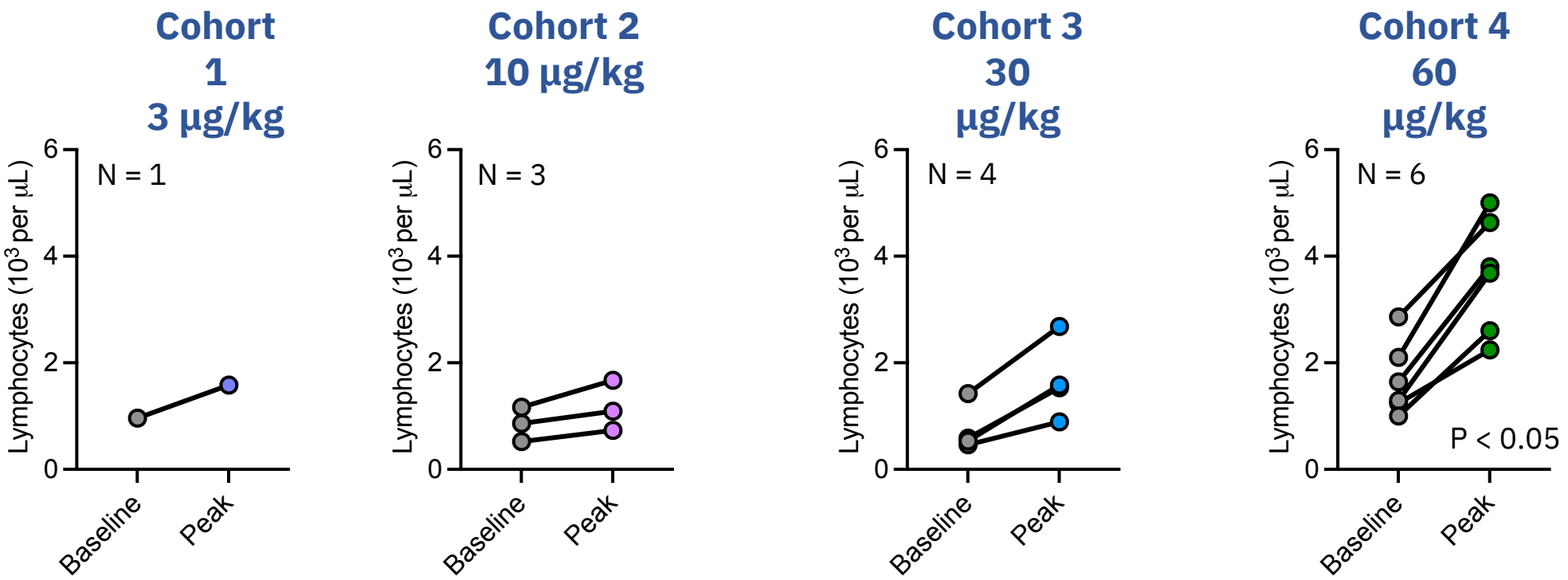
- Lymphocyte counts elevated above baseline for > 11 d consistent with prolonged PD effect
- No significant eosinophil expansion (associated with increased risk of vascular leak syndrome)



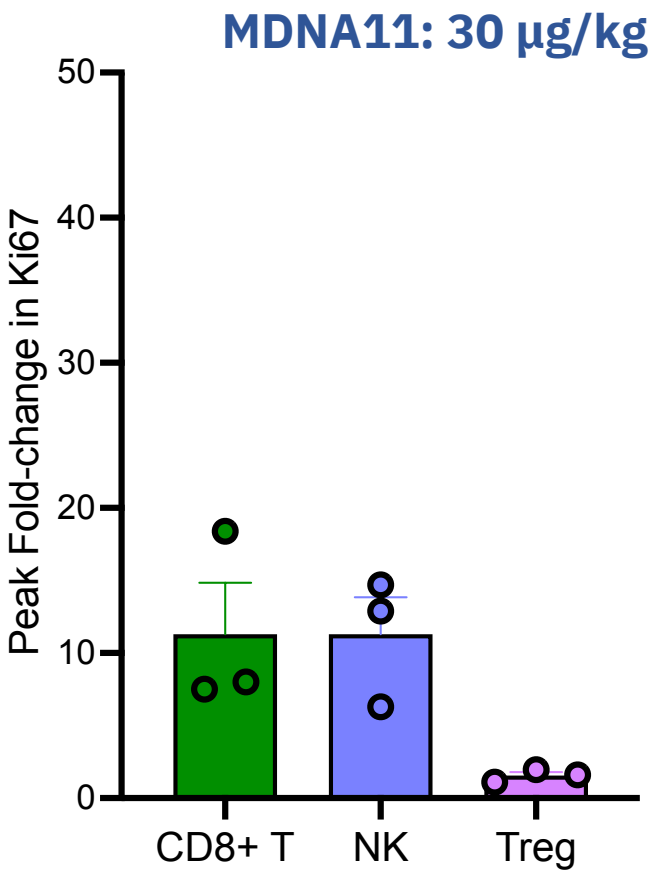
*Patients received 2 priming doses (30 µg/kg; Q2W) prior to target dose of 60 µg/kg (Q2W). Only data following target dose administration are shown

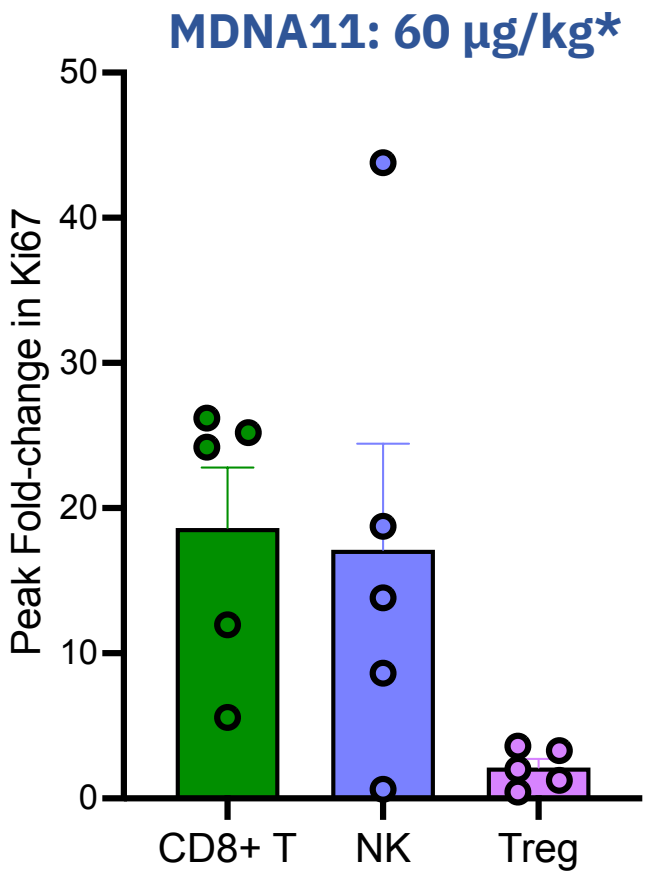
MDNA11's Ability To Induce Lymphocyte Cell Expansion Is Dose-dependent And Consistent Across Patients

- Effect of escalating doses of MDNA11 on individual patient absolute lymphocyte count



MDNA11 Preferentially Stimulates CD8+ T & NK Cell Proliferation, Validating The Molecular Design



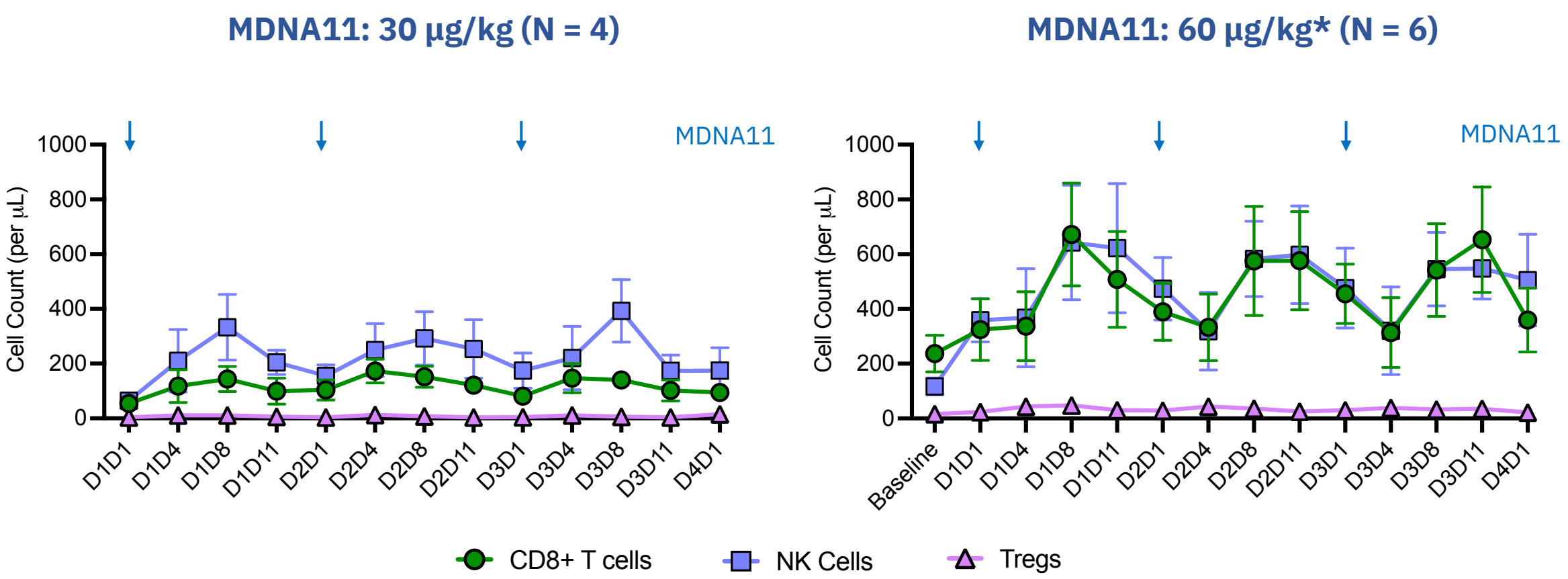


- **Findings consistent with MDNA11's MoA of selective binding to CD122 (i.e. β-only IL-2)**

Peak fold-change relative to baseline. Proliferation assessed based on Ki67 expression

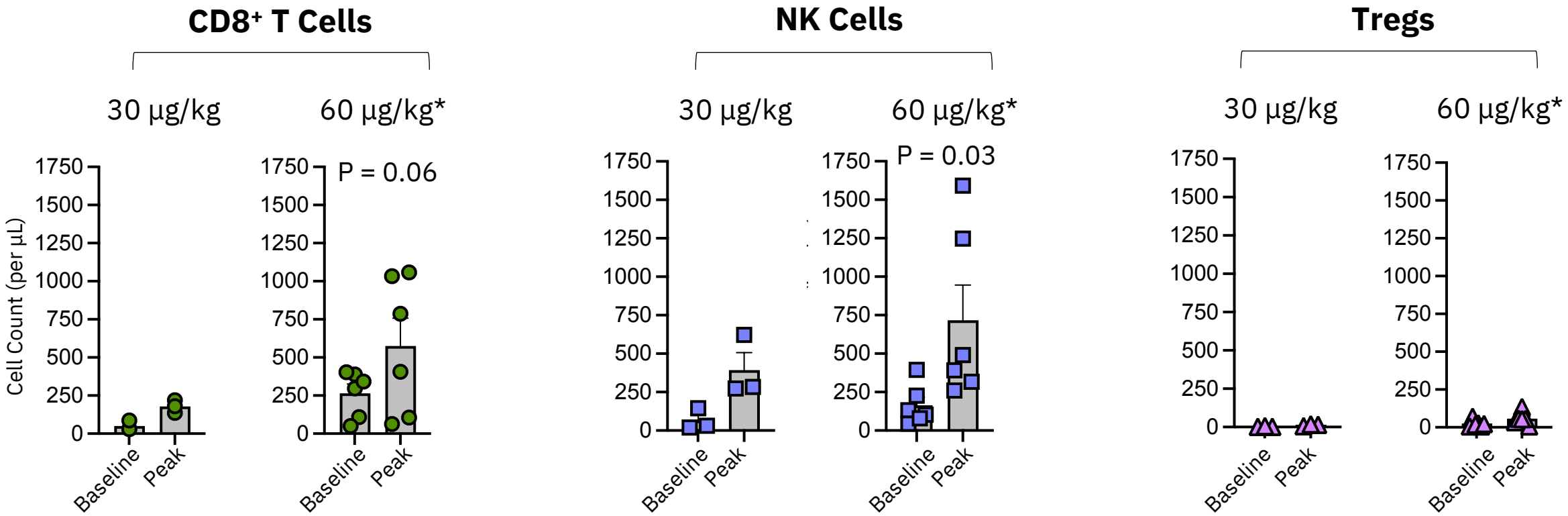
*Patients received 2 priming 30 µg/kg doses (Q2W) prior to target dose of 60 µg/kg. Data for 30 µg/kg cohort are based on 3rd administration for comparison.

MDNA11's Ability To Induce Preferential CD8+ T And NK Cell Expansion Is Maintained Over Multiple Treatment Cycles



* Patients dosed with 2 priming doses of 30 µg/kg (Q2W) prior to the 60 µg/kg target dose (Q2W). Data following priming doses not shown.

MDNA11 Induces Dose-dependent Expansion Of CD8+ T Cells And NK Cells But Not Tregs



Peak fold-change relative to baseline
Patients received 2 priming 30 µg/kg doses (Q2W) prior to the targeted 60 µg/kg (at 3rd administration).
Data shown for 30 µg/kg cohort are based on 3rd administration for comparison

MDNA11 Single Agent Safety Profile Across All Cohorts

Preferred Term	Cohort 1 (3 µg/kg) N = 1	Cohort 2 (10 µg/kg) N = 3	Cohort 3 (30 µg/kg) N = 4	Cohort 4 (60 µg/kg) N = 6	Total N = 14
All Grades (> 20%)					
Infusion related reaction##	1 (100%)	2 (66.6%)	3 (75%)	5 (83.3%)	11 (78.6%)
Nausea		2 (66.6%)		5 (83.3%)	8 (57.1%)
Pyrexia		1 (33.3%)	2 (50%)	4 (66.6%)	7 (50%)
Fatigue		2 (66.6%)	2 (50%)	1 (16.6%)	5 (35.7%)
Diarrhea		1 (33.3%)	1 (25%)	2 (33.3%)	4 (28.6%)
Chills		1 (33.3%)	1 (25%)	1 (16.6%)	3 (21.4%)
Headache			1 (25%)	2 (33.3%)	3 (21.4%)
Grade 3-4 (> 5%)					
Alanine aminotransferase increase				1 (16.6%)*	1 (7.1%)
Blood bilirubin increase				1 (16.6%)*	1 (7.1%)
Hypotension			1 (25%)#		1 (7.1%)
Lymphocyte count decrease		1 (33.3%)$	1 (25%)$		2 (14.2%)

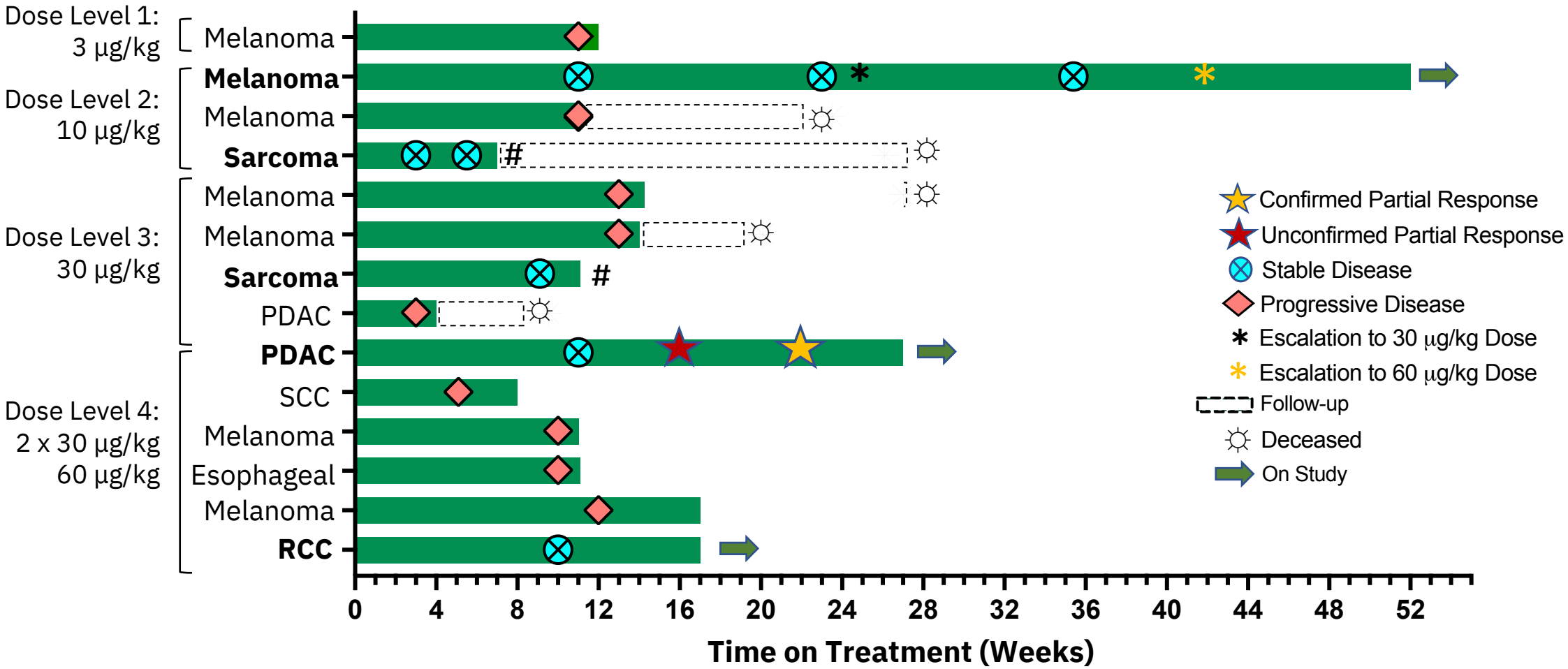
* Transient elevations resolving within 3-4 d; # Patient with adrenal insufficiency; $ Transient expected lymphopenia immediately after MDNA11 administration; ## Infusion related reaction mostly comprised fever, tachycardia and chills

Data cut off: Oct 19, 2022

- **Majority of AEs were Grade 1-2 (92%) and transient, resolving within 1-2 days**
- MTD / RP2D not established yet – dose escalation continues

MDNA11 Single Agent Dose Escalation: Time On Treatment

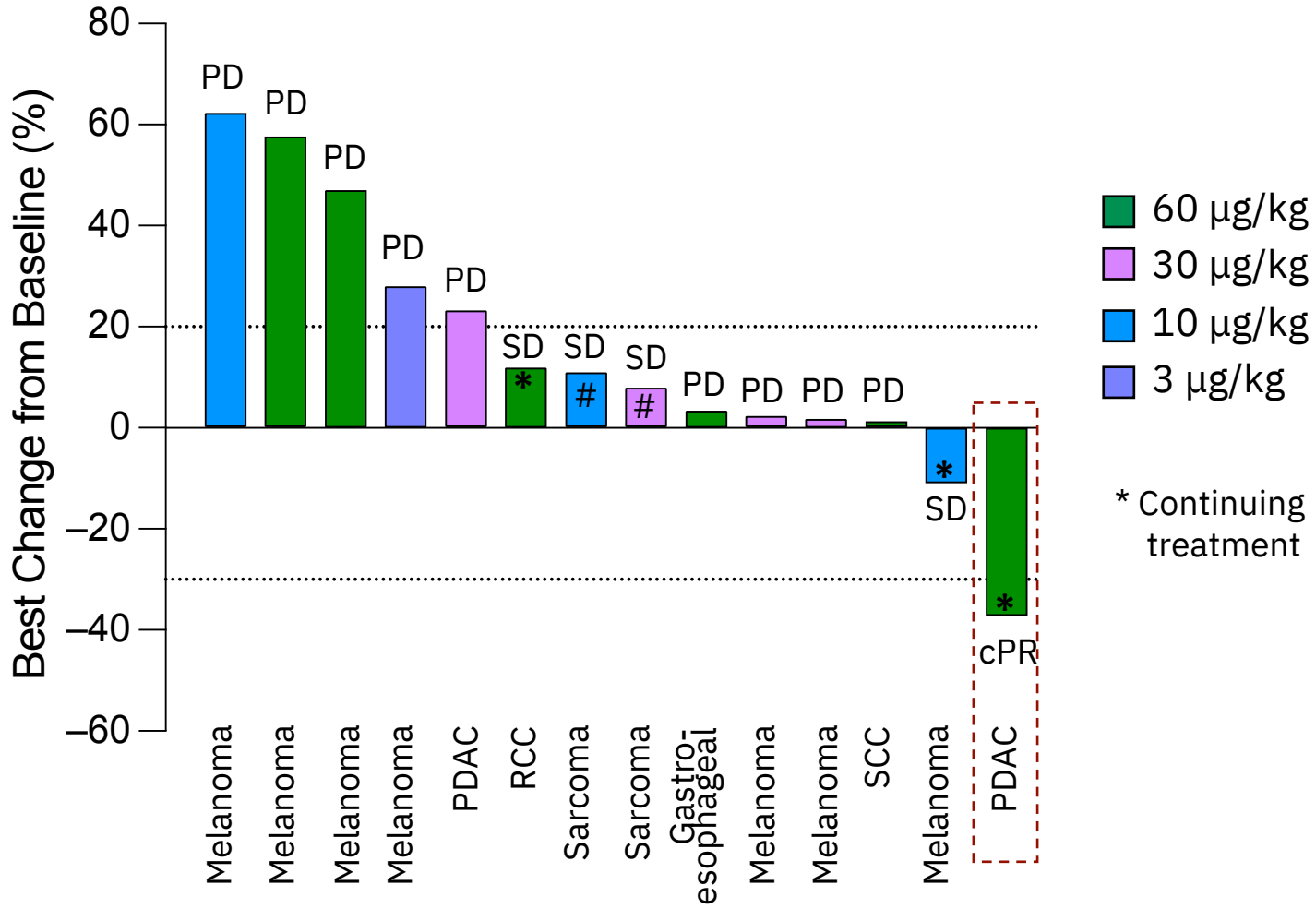
- Evidence of clinical activity & disease control in 5 of 14 evaluable patients (incl. 1 confirmed PR in PDAC) in context of ongoing dose escalation and pre-treated advanced solid tumors



Target lesions exhibit SD; PD due to clinical progression or patient withdrawal

Data cut off: Oct 21, 2022

Single Agent Activity In Dose Escalation: Best % Change From Baseline In Target Lesions (RECIST V1.1)



Target lesions exhibit SD; PD due to clinical progression or patient withdrawal

- **Confirmed partial response with single agent MDNA11 in cohort 4:**
  - Patient with pancreatic ductal adenocarcinoma
  - Surgical resection (Whipple's procedure) June 2021
  - Adjuvant FOLFIRINOX (adjuvant): discontinued due to progression
  - Abraxane (nabpaclitaxel) & gemcitabine: discontinued due to toxicity
  - Pembrolizumab: Discontinued due to progression
  - **Continues on single agent MDNA11**

Conclusions: Single Agent MDNA11

- **Long-acting, next-generation IL-2 with selective & enhanced affinity for the IL-2βR** present on CD8+ T cells and NK cells **and albumin fusion resulting in durable accumulation in tumors**
- **Exhibits dose-proportional PK profile** in patients with advanced tumors
- **Induces sustained, dose-dependent expansion of circulating CD8+ T and NK cells**, without Treg induction, consistent with target engagement and its molecular design
- **Manageable safety profile**: majority (92%) of treatment-related AEs are transient grade 1-2
- **Initial evidence of single agent clinical activity during dose escalation across multiple, treatment-refractory, advanced solid tumor types** and dose levels with a current tumor control rate of 36% (5/14) including a partial response and prolonged stable disease
- Findings support the ongoing dose escalation and further evaluation of MDNA11 as a single agent and in combination with CPI in patients with a range of advanced solid tumors

Acknowledgements

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- We would also like to thank the investigators and all clinical and support trial staff at each of the study sites for their investment of time and effort into the trial

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