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Royal Continental Hotel

Updated Safety and Efficacy Results from the First-in-Human Study of MDNA11 (ABILITY-1), a Next Generation 'Beta-Enhanced Not-Alpha' IL-2 Superkine, Show Single-Agent Activity in Patients with Advanced Solid Tumors

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fondazionemelanoma ONLUS

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

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

Engineered to overcome key limitations of high dose rhIL-2

Superior selectivity with enhanced 'β-only' pharmacology

Improved PK profile

Engineered IL-2 — **Linker** — **Human Albumin**

Abolished α binding

Enhanced β binding

↑ half life

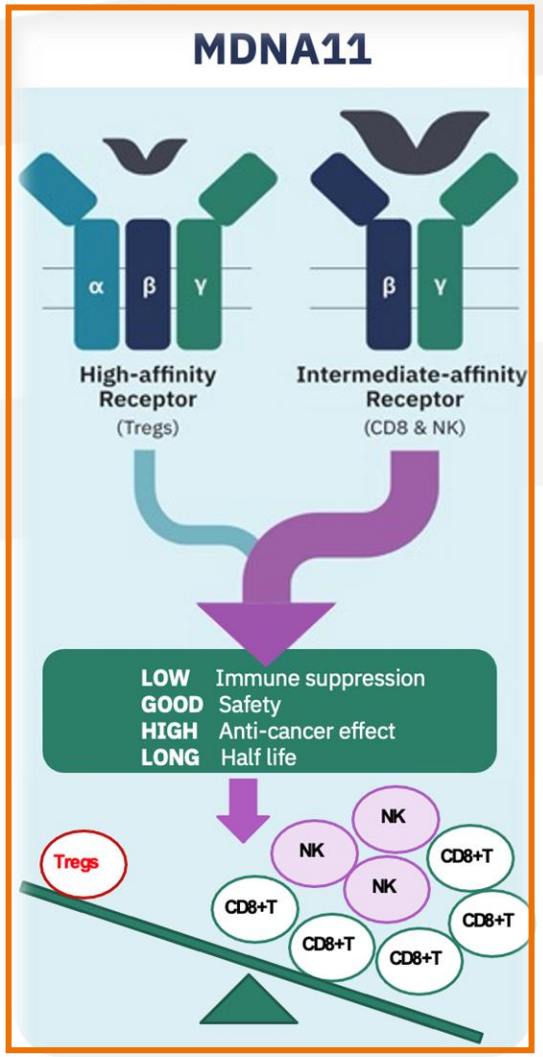
↑ tumor accumulation

Enhanced β-binding + **Non-α binder** + **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



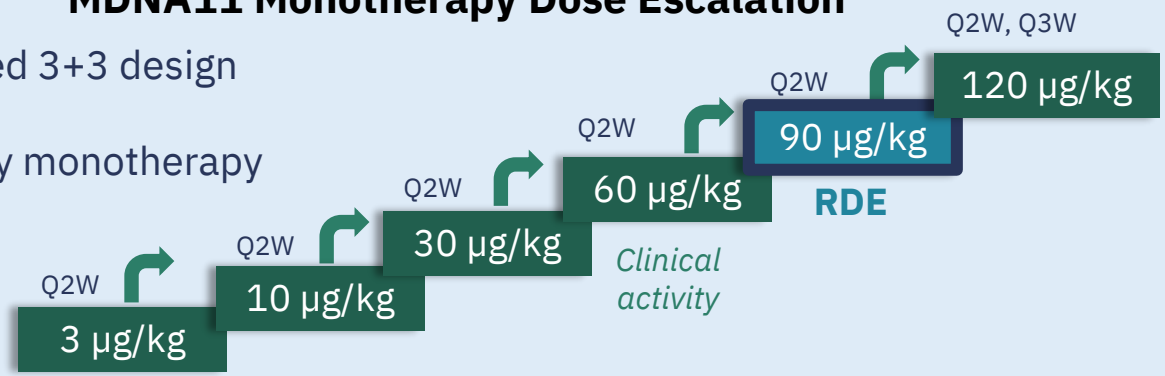
- **MDNA11** demonstrated potent single-agent tumor growth inhibition and additive effect with anti-PD1 in mouse tumor models (Merchant et al., JITC 2022)

ABILITY-1: FIH Trial of MDNA11 in Advanced Solid Tumors

ABILITY-1: **A B**eta-only **IL**-2 **I**mmuno**T**herap**Y** Study (NCT05086692)

MDNA11 Monotherapy Dose Escalation

- Modified 3+3 design
- Identify monotherapy RDE

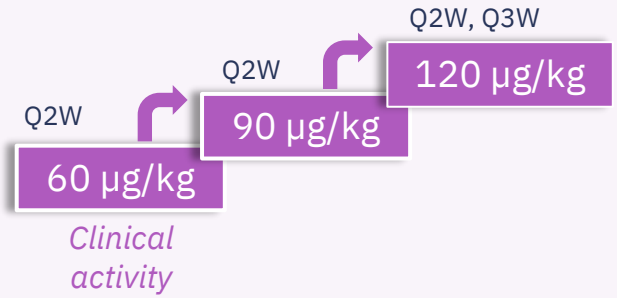


Monotherapy Dose Expansion

- MDNA11 @ **RDE (90 µg/kg Q2W)** in selected CPI resistant solid tumors:
  - Melanoma
  - Non-melanoma skin cancer (cSCC, BCC, MCC)
  - MSI-H/dMMR tumors

MDNA11 + KEYTRUDA® (pembrolizumab; 400 mg; Q6W) Dose Escalation

- Select CPI resistant and CPI-naïve indications
- Identify combination RDE (cRDE)



Combination Dose Expansion

- MDNA11 (cRDE) + pembrolizumab
- Melanoma and other select advanced solid tumors

This study is in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

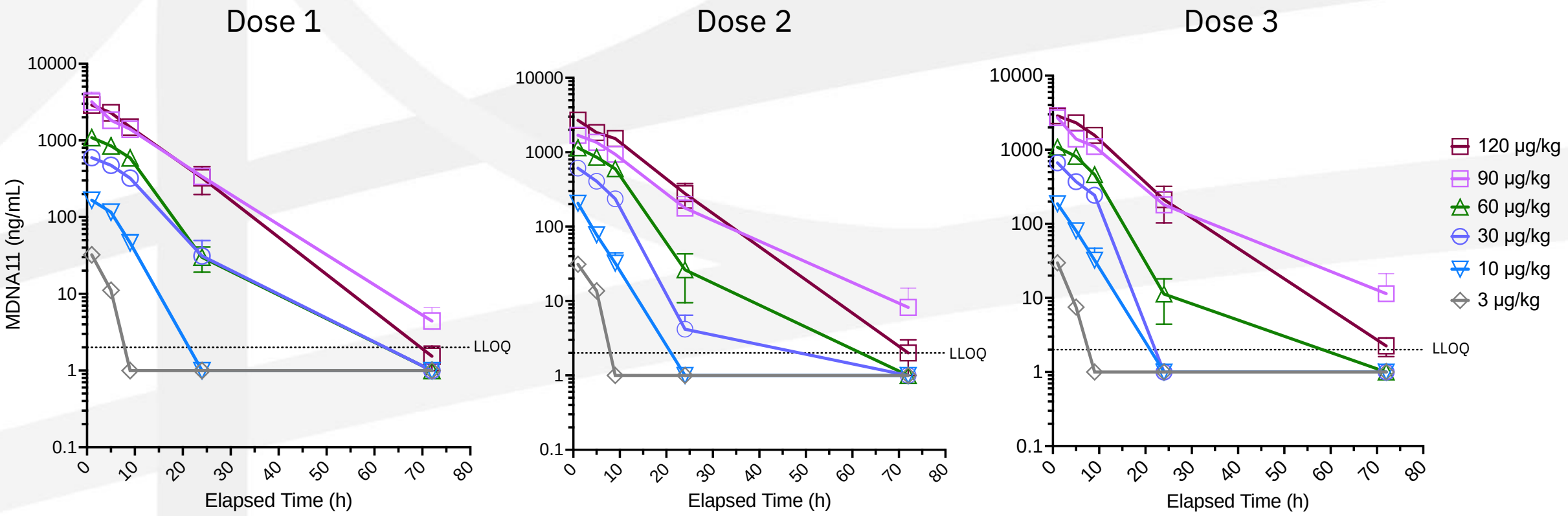
CPI, immune checkpoint inhibitor | RDE, recommended dose for expansion

Baseline Clinical Characteristics

Baseline characteristics	Monotherapy Dose Escalation/Evaluation (N=30)	Monotherapy Dose Expansion (N = 12)	Combination Dose Escalation/Evaluation (N = 16)
Age, median years (range)	63 (27-78)	64 (48-85)	58 (42-70)
Male, N (%)	22 (73.3%)	8 (66.7%)	6 (37.5%)
Baseline ECOG = 0, N (%)	19 (63.3%)	7 (58.3%)	5 (31.3%)
Baseline ECOG = 1, N (%)	11 (36.6%)	5 (41.7%)	11 (68.7%)
Prior Systemic Therapies	**N (%)**	**N (%)**	**N (%)**
Prior Lines of Therapy: 1	7 (23.3%)	6 (50%)	5 (31.3%)
Prior Lines of Therapy: ≥2	23 (76.7%) [range: 2-4]	6 (50%) [range: 2-7]	11 (68.7%) [range: 2-6]
Immunotherapy:	24 (80%)	12 (100%)	10 (62.5%)
Targeted Therapy	13 (43.3%)	5 (41.7%)	9 (56.3%)
Chemotherapy	12 (40%)	4 (33.3%)	14 (87.5%)
Primary Tumor Type	**N (%)**	**N (%)**	**N (%)**
	Melanoma: 16 (53.3 %)	Melanoma: 4 (33.3%)	Endometrial: 3 (18.8%)
	NSCLC: 3 (10%)	MSI-H cancer: 4 (33.3%)	NSCLC: 2 (12.5%)
	PDAC: 3 (10%)	Non-melanoma skin cancers: 4 (33.3%)	SCC (ovarian, anal): 2 (12.5%)
	RCC: 2 (6.6%)		Ovarian cancer: 2 (12.5%)
	Sarcoma: 2 (6.6%)		Pleural mesothelioma: 2 (12.5%)
	Ovarian cancer: 2(6.6%)		TNBC: 1 (6.3%)
	Tonsillar SCC: 1 (3.3%)		Esophageal cancer: 1 (6.3%)
	GEJ adenocarcinoma: 1 (3.3%)		Colon cancer: 1 (6.3%)
			Gastric: 1 (6.3%)
			Testicular: 1 (6.3%)

Dose-Dependent Increase in MDNA11 Exposure

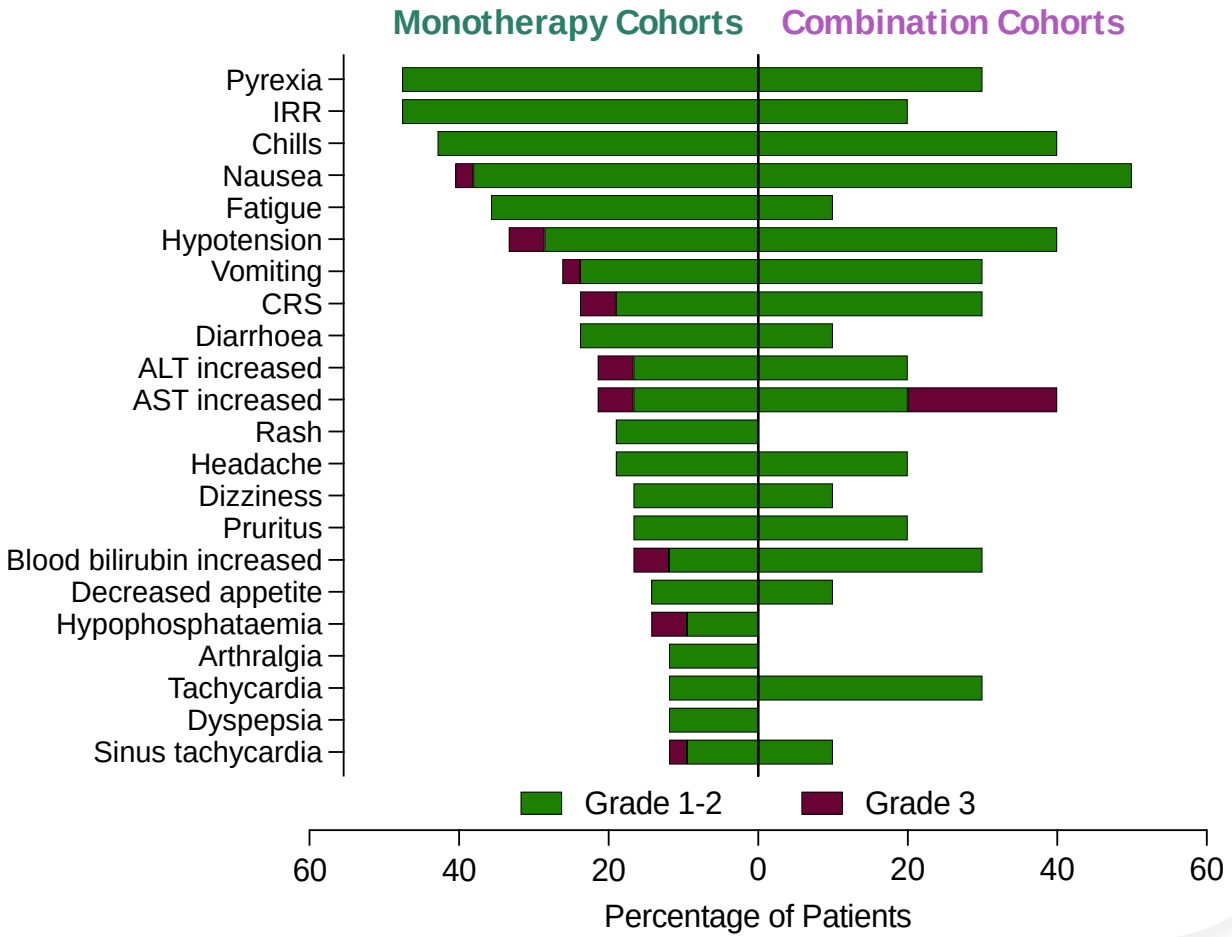
Consistent PK profile following repeat dose administration



LLOQ: lower limit of quantification

Desirable Safety Profile and No Dose Limiting Toxicities (DLTs)

Treatment Related Adverse Events (TRAEs) in ≥ 10% of Patients



Monotherapy Safety Profile

- Majority TRAEs were Grade 1-2 (92.3%) and resolved within 48 hours
- Grade 3 liver function test elevations (ALT/AST) were asymptomatic and transient
- Grade 3 hypotension in patients with adrenal insufficiency
- No non-laboratory grade 4 TRAEs

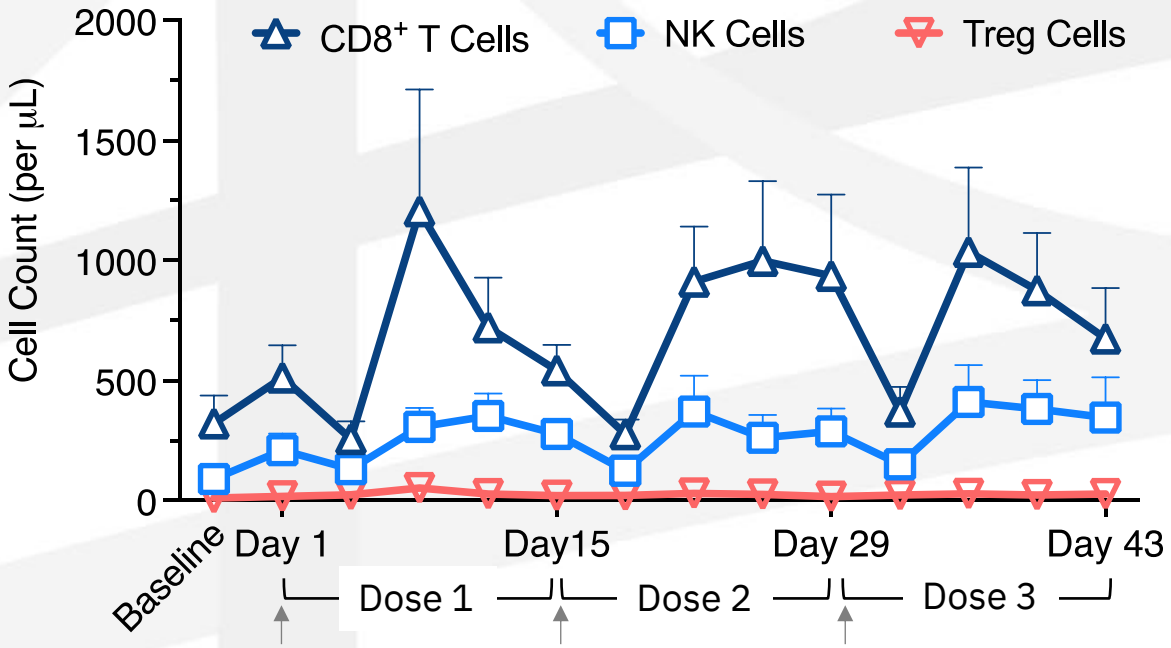
Combination Safety Profile

- Majority TRAEs were Grade 1-2 (93.7%) and resolved within 48 hours
- Grade 3 liver function test elevations were asymptomatic and transient
- No Grade 4 non-lab TRAEs
- **No new safety signals in combination cohorts**

EDC cut-off: November 18, 2024

Single-agent MDNA11 Preferentially Expands Immune Effector Cells

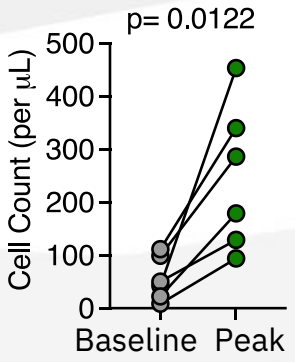
Patients Treated with MDNA11 90 µg/kg Q2W (Monotherapy RDE)



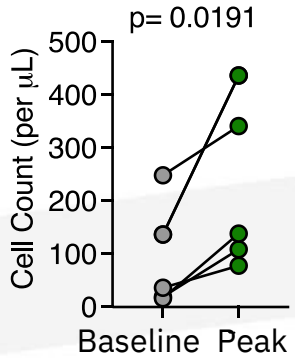
Analysis of PBMCs processed from whole blood; N = 8.

Patients Treated with MDNA11 ≥ 60 µg/kg Q2W

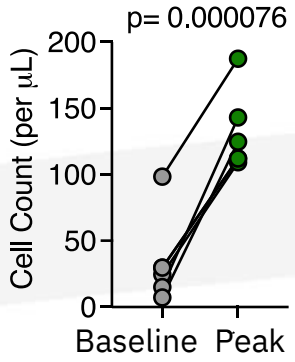
CD25+ (Activation) CD8+ T Cells



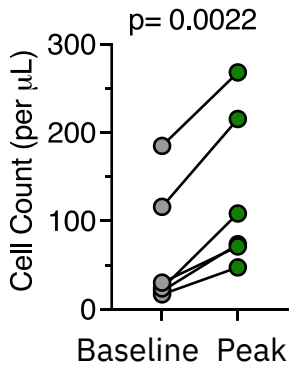
DNAM1+ (Effector) CD8+ T Cells



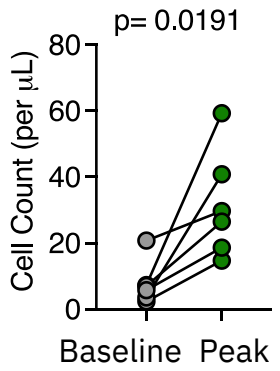
TCF1+ ('Stemness like') CD8+ T Cells



Effector Memory CD8+ T Cells



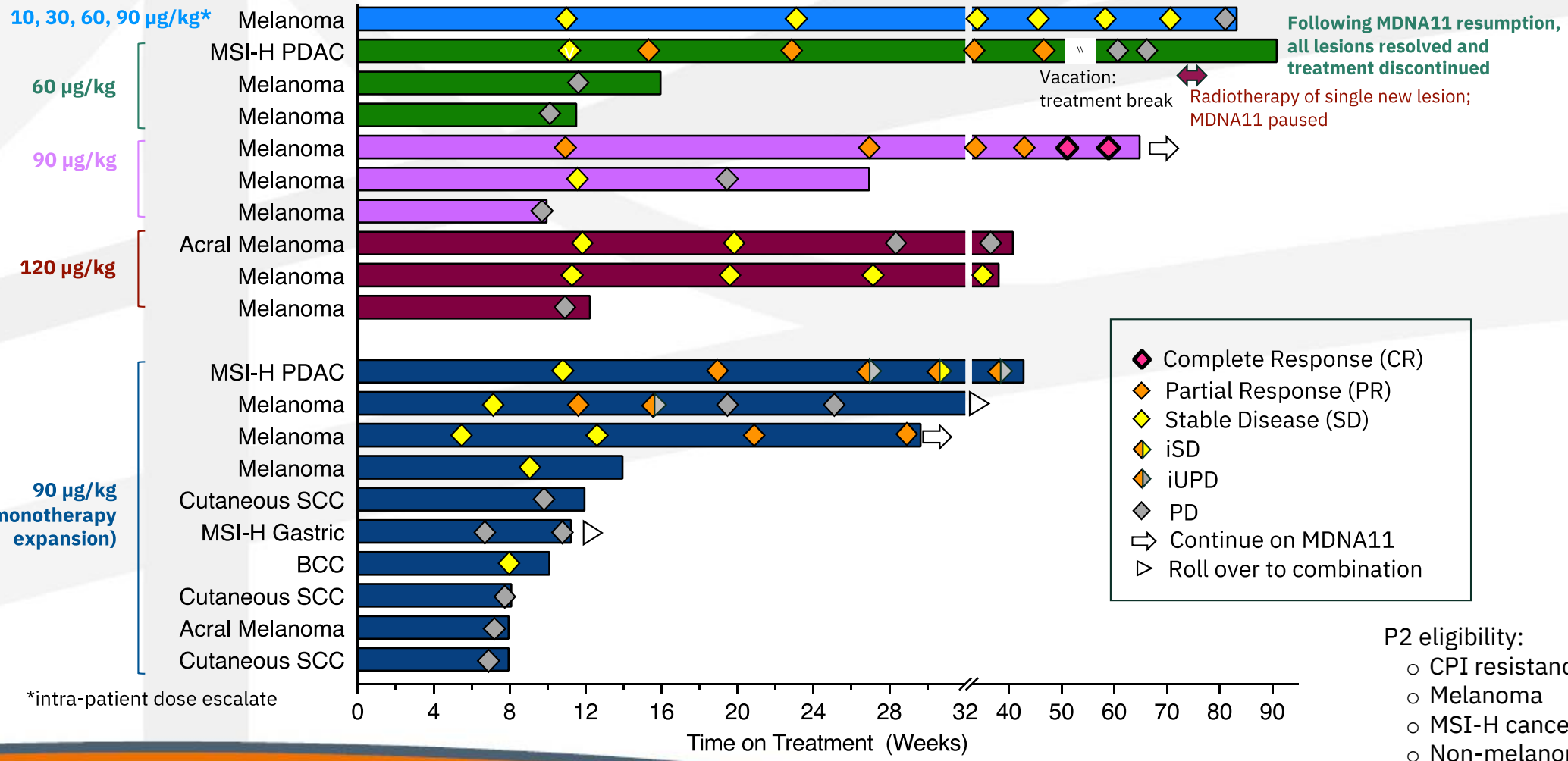
Central Memory CD8+ T Cells



p-values based on paired t-test

Monotherapy: Durable Responses in Higher-Dose (≥ 60 µg/kg) P2 Eligible Patients who Progressed on CPI

Phase 2 eligible patients who received ≥ 60 µg/kg MDNA11



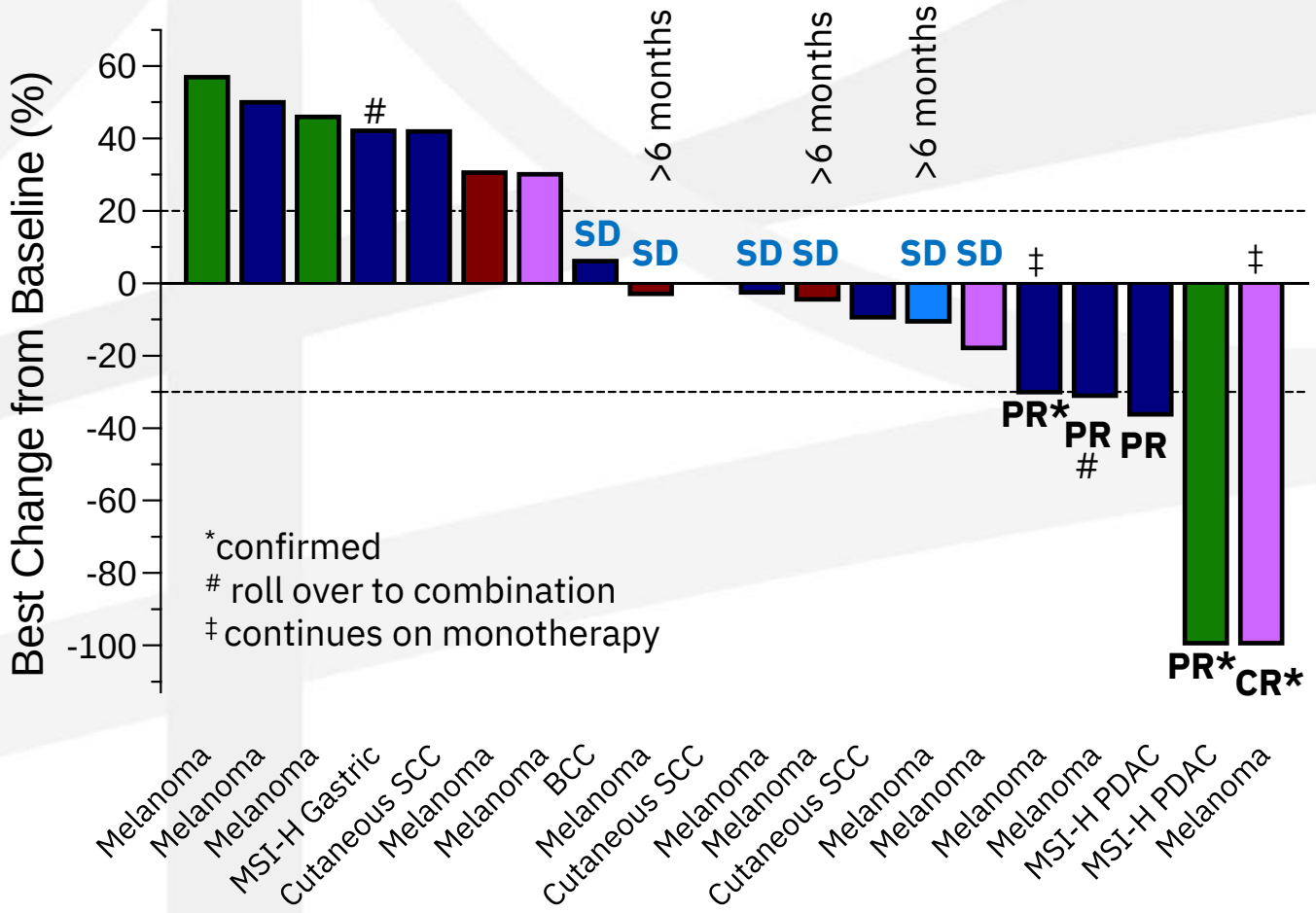
*intra-patient dose escalate

P2 eligibility:

- CPI resistance
- Melanoma
- MSI-H cancer
- Non-melanoma skin cancer

Monotherapy: Objective Response in 5 of 20 Patients (1 CR + 4 PRs)

Best Response in CPI Resistant Patients: Phase 2 Eligible Treated with MDNA11 ≥ 60 µg/kg



Objective Response Rate (ORR):

- 5/20 (25%) [95% CI: 6-44]
  - 1 Complete Response
  - 4 Partial Responses

Clinical Benefit Rate:

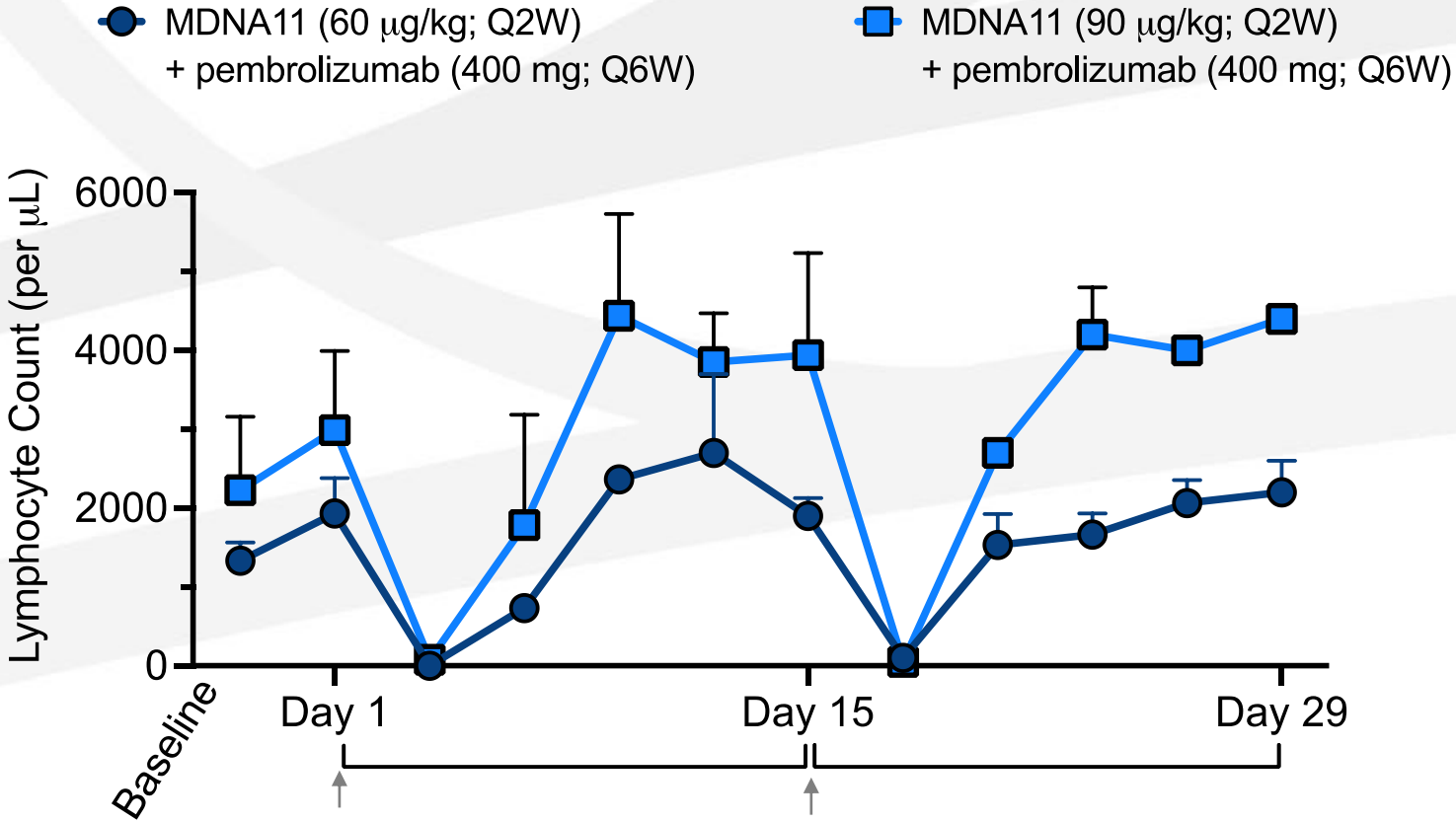
- 8/20 (40%)
  - 1 Complete Response
  - 4 Partial Responses
  - 6 Stable Disease, including 3 for > 6 months

Objective Response in 3 Cutaneous Melanoma (1 CR + 2 PRs)

- Monotherapy expansion (90 µg/kg)
- 120 µg/kg
- 90 µg/kg
- 60 µg/kg
- 10, 30, 60 ,90 µg/kg (intra-patient dose escalation)

Robust Lymphocyte Expansion in Combination Dose Escalation

Dose Dependent Lymphocyte Increase



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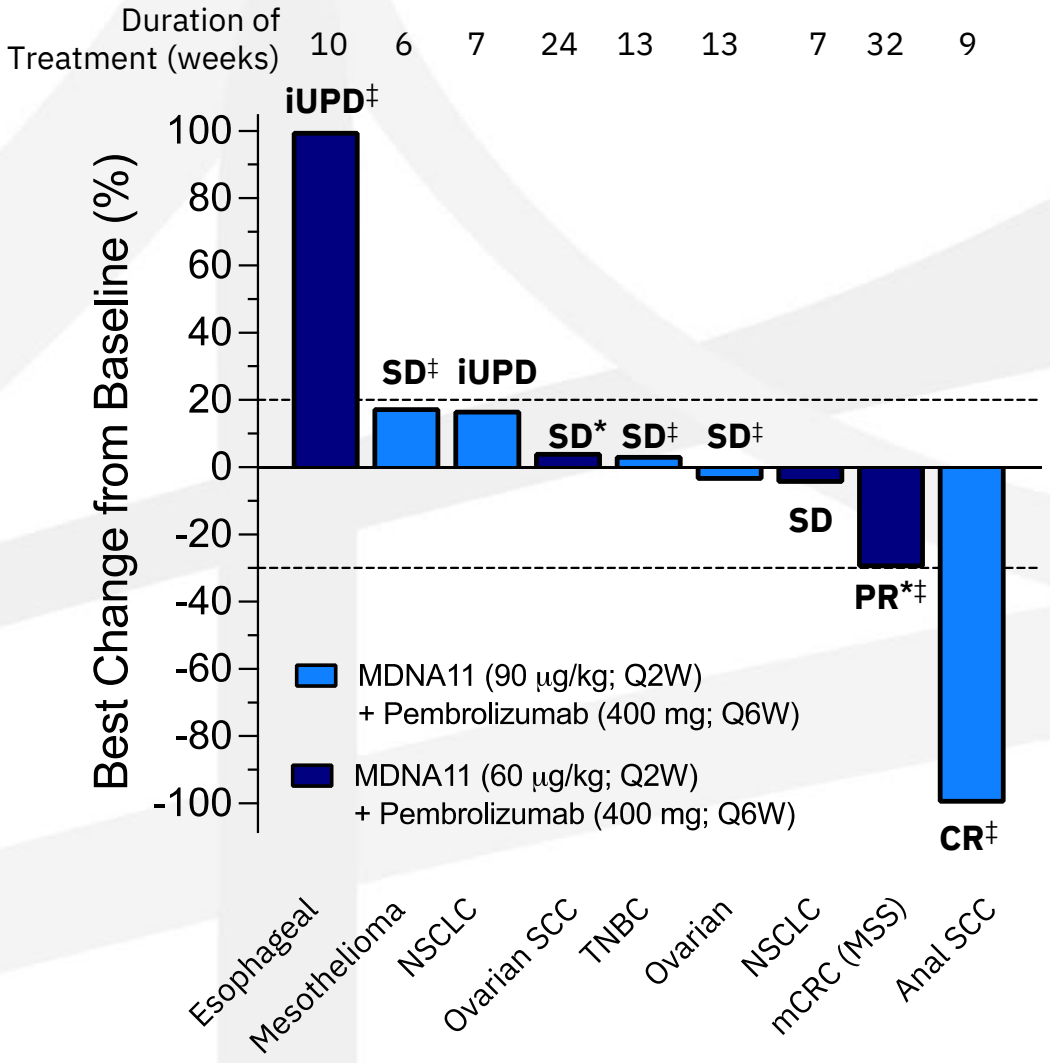
Combination Dose Escalation: Clinical Activity in Heavily Pretreated Patients



*confirmed; ‡ continues treatment

- **Complete Response (CR) in 70 yr M with anal SCC**
  - Progressed on 2 prior lines of treatment (1L capecitabine/mitomycin + radiation; 2L carboplatin/paclitaxel)
  - No prior IO
  - CR achieved on first on study evaluable imaging scan; continues on treatment

- **Confirmed Partial Response (PR) in 52 yr F with MSS mCRC**
  - Progressed on 2 prior lines of chemotherapy (1L folinate/fluorouracil/oxaliplatin; 2L capecitabine)
  - No prior IO
  - Continues on treatment

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EDC cut-off: November 18, 2024

Summary

- **Safety:** MDNA11 has a favorable safety profile in both monotherapy and in combination (no new safety signals) with pembrolizumab with majority (>90%) of TRAEs Grade 1-2 and transient
- **Pharmacodyanamics:** MDNA11 preferentially expands immune effector cells with significant increase in activated ($CD25^+$ and $DNAM^+$), 'stemness-like' ($TCF\text{-}1^+$) and memory $CD8^+$ T cells
- **Efficacy (monotherapy): Durable single-agent activity in heavily pre-treated patients:**
  - **Objective response in 25% (1 CR and 4 PR)** of ICI-resistant P2 eligible patients treated with ≥ 60 µg/kg Q2W MDNA11
  - **ORR 30% (3 of 10)** in ICI-resistant patients in the single-agent dose expansion cohort treated with 90 ug/kg Q2W (RDE)
- **Efficacy (combination with pembrolizumab): objective responses (2 of 9)** observed in ongoing dose escalation with **CR in anal SCC** (historically low IO response) & confirmed **PR in MSS mCRC**
- **Next steps:** completion of Combination Dose Escalation and enrolment to Monotherapy Dose Expansion. Initiation of Combination Dose Expansion cohorts

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