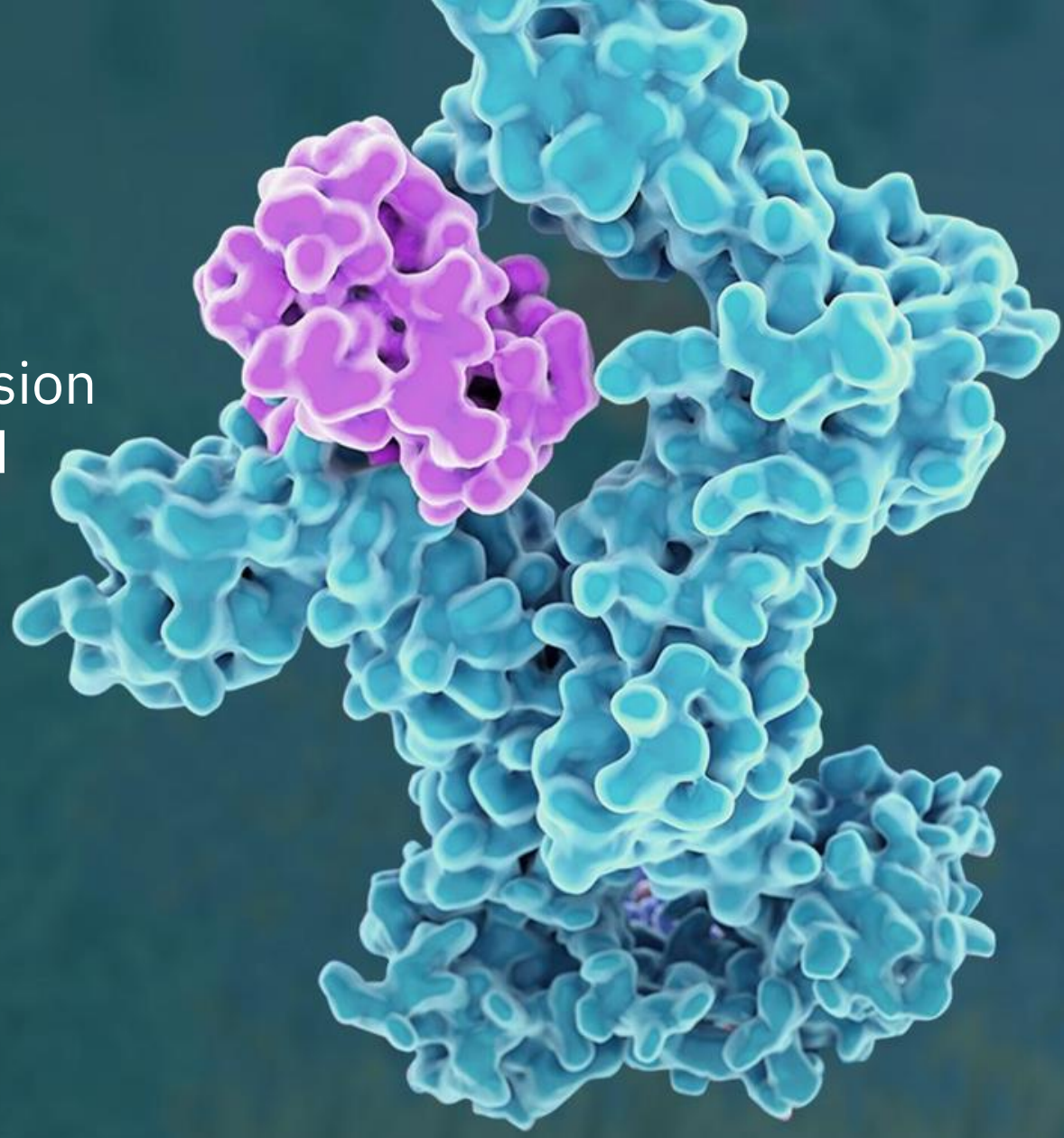
SITC 2024

Results from ABILITY-1 monotherapy dose escalation and ongoing monotherapy expansion with MDNA11, a long-acting ‘beta-enhanced not-alpha’ IL-2 superkine, in patients with advanced solid tumors



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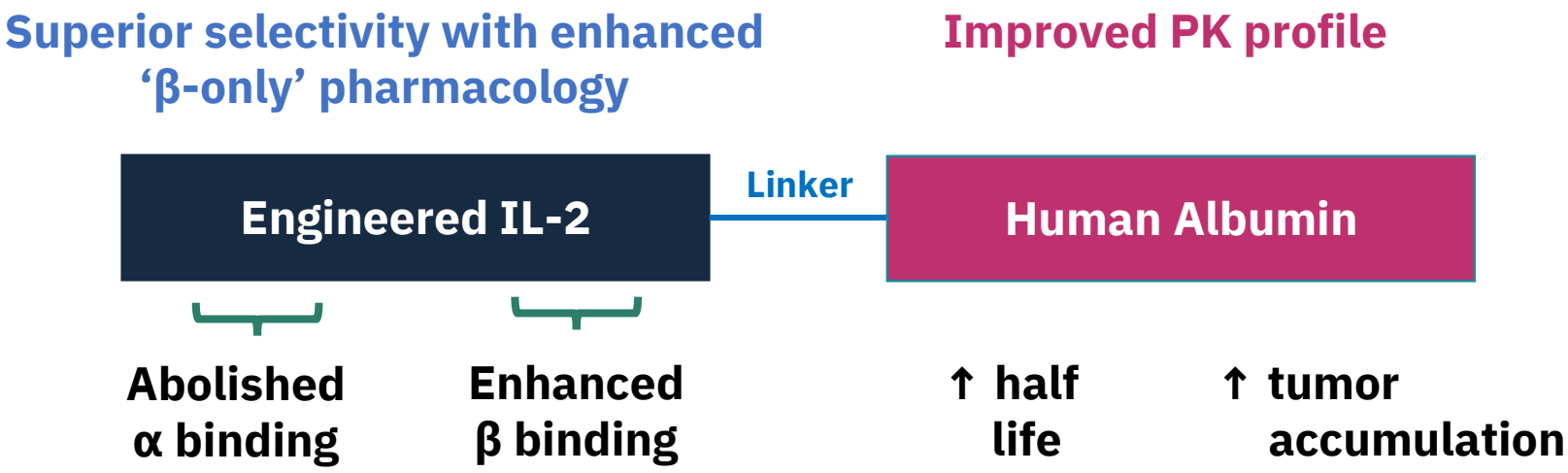
MDNA11: A Long-acting ‘β-enhanced Not-α’ IL-2 Superkine



MDNA11 engineered to overcome key limitations of HD rhIL-2:

- ↑ affinity to IL-2Rβ (CD122) - Potentiate effector immune activation
- Abolish binding to IL-2Rα (CD25) – ↓Treg stimulation & associated toxicities
- Fusion to albumin increases half-life and promotes accumulation in tumors

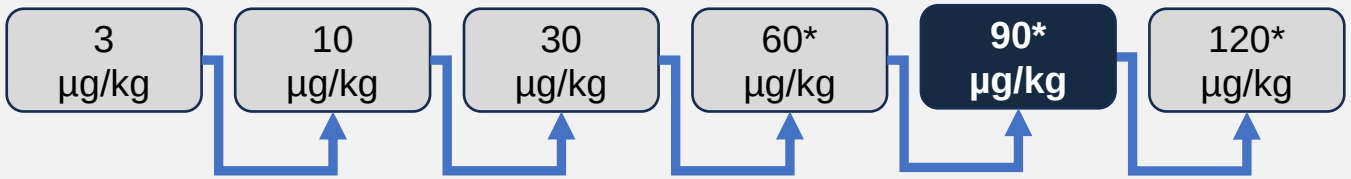
➢ MDNA11 demonstrated potent single-agent tumor growth inhibition and additive effect with anti-PD1 in mouse tumor models (Merchant et al., JITC 2022)

ABILITY-1: First-in-human 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 (IV Q2W)

- Modified 3+3 design
- Identify monotherapy Recommended Dose for Expansion (RDE)



* Step-up dosing (SUD)

Monotherapy Dose Expansion (Phase 2)

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

MDNA11 (Q2W) + Pembrolizumab (Q6W) Dose Escalation

Select PD1/L1 refractory and CPI-naive indications

- Identify combination RDE (cRDE) for MDNA11

Combination Dose Expansion (Phase 2)

- MDNA11(cRDE) + Pembrolizumab (400 mg, Q6W)
- Melanoma and other select advanced solid tumors

Patient Demographics

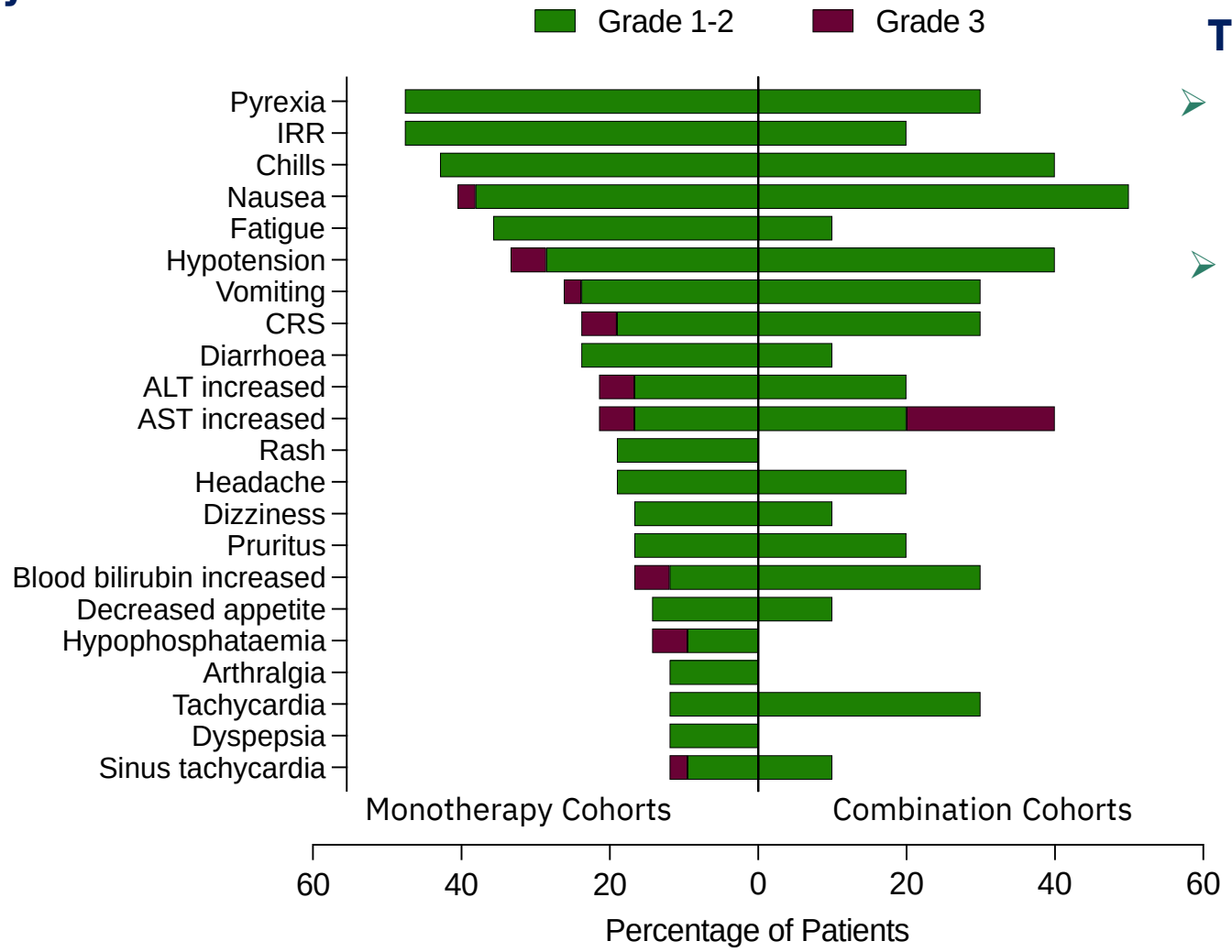
Baseline characteristics	Monotherapy Dose Escalation/Evaluation (N=30)	Monotherapy Dose Expansion (N = 12)	Combination Dose Escalation/Evaluation (N = 10)
Age, median years (range)	63 (27-78)	64 (48-85)	54.5 (42-70)
Male, N (%)	22 (73.3%)	8 (66.7%)	4 (40%)
Baseline ECOG = 0, N (%)	19 (63.3%)	7 (58.3%)	4 (40%)
Baseline ECOG = 1, N (%)	11 (36.6%)	5 (41.7%)	6 (60%)
Prior Systemic Therapies	**N (%)**	**N (%)**	**N (%)**
Prior Lines of Therapy: 1	7 (23.3%)	6 (50%)	4 (40%)
Prior Lines of Therapy: ≥2	23 (76.7%)	6 (50%)	6 (60%)
Immunotherapy: 1	6 (20%)	9 (75%)	3 (30%)
Immunotherapy: ≥2	18 (60%)	3 (25%)	2 (20%)
Targeted Therapy	13 (43.3%)	5 (41.7%)	6 (60%)
Chemotherapy	12 (40%)	4 (33.3%)	8 (80%)
Primary Tumor Type	**N (%)**	**N (%)**	**N (%)**
	Melanoma: 16 (53.3 %)	Melanoma: 4 (33.3%)	NSCLC: 2 (20%)
	NSCLC: 3 (10%)	MSI-H cancer: 4 (33.3%)	SCC (ovarian, anal): 2 (10%)
	PDAC: 3 (10%)	Cutaneous SCC: 2 (16.7%)	Ovarian cancer: 1 (10%)
	RCC: 2 (6.6%)	Non-melanoma skin cancers: 2 (16.7%)	TNBC: 1 (10%)
	Sarcoma: 2 (6.6%)		Esophageal cancer: 1 (10%)
	Ovarian cancer: 2(6.6%)		Colon cancer: 1 (10%)
	Tonsillar SCC: 1 (3.3%)		Pleural mesothelioma: 1 (10%)
	GEJ adenocarcinoma: 1 (3.3%)		Sertoli cell carcinoma: 1 (10%)

TRAEs in ≥ 10% of Patients in MDNA11 Monotherapy and Combination Cohorts

No Dose Limiting Toxicity (DLT) in both monotherapy and combination cohorts

Summary of Monotherapy TRAEs (N = 42)

- Majority (94.4%) of TRAEs were Grade 1-2; majority resolved within 48 hours
- Grade 3 liver function test (LFT) elevations were asymptomatic and transient
- Grade 3 hypotension was observed in patients with baseline adrenal insufficiency
- An isolated single asymptomatic Grade 4 hepatic enzyme increase resolved within 72 hours without intervention



Summary of Combination TRAEs (N = 10)

- Majority (95.5%) of TRAEs were Grade 1-2; majority resolved within 48 hours
- Grade 3 TRAEs (4.5%) were asymptomatic and confined to laboratory abnormalities that resolved within days:
  - 2 events of transient AST increase
  - an isolated event of transient WBC decrease

No new safety signals in combination cohorts

Monotherapy (Escalation/Evaluation & Expansion)

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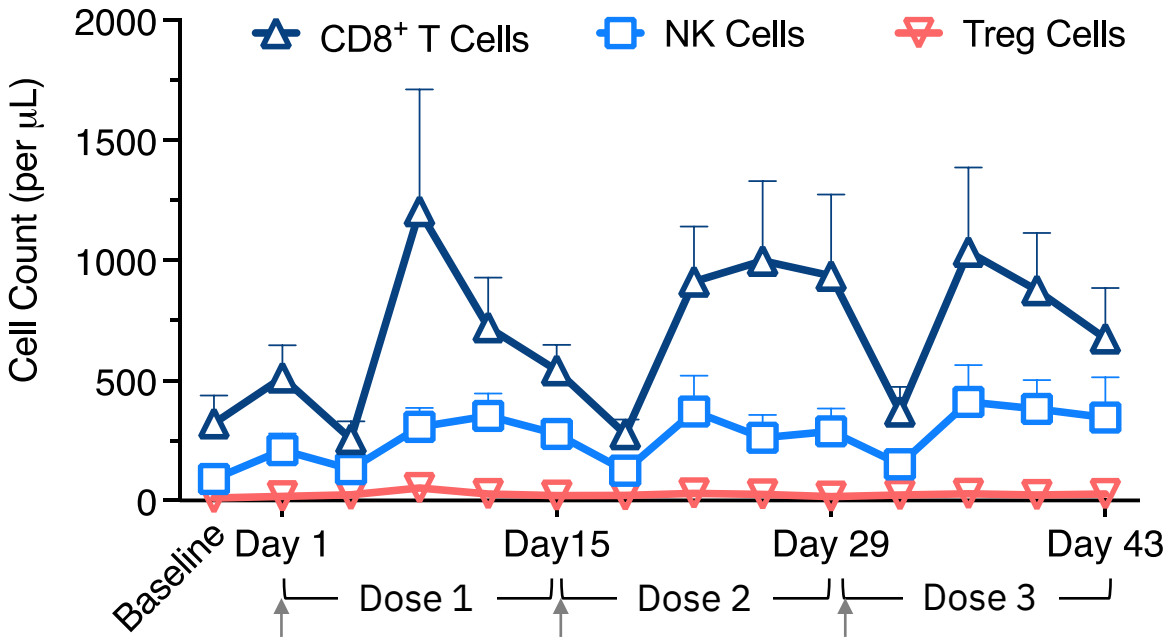
Single-agent MDNA11 Preferentially Expands Immune Effector Cells

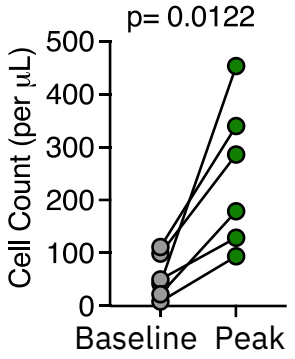
Patients Treated with MDNA11 90 µg/kg Q2W (Recommended Dose for Expansion)



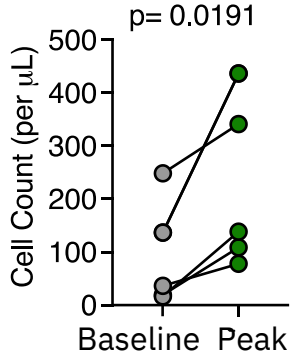
Analysis of PBMC processed from whole blood

Patients Treated with MDNA11 ≥ 60 µg/kg Q2W

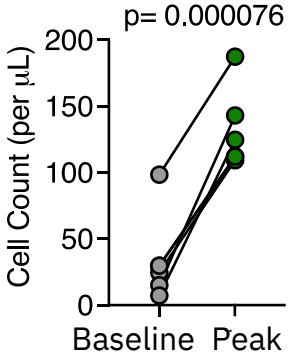
CD25+ (Activation) CD8+ T Cells



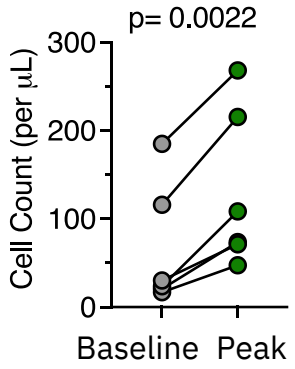
DNAM1+ (Effector) CD8+ T Cells



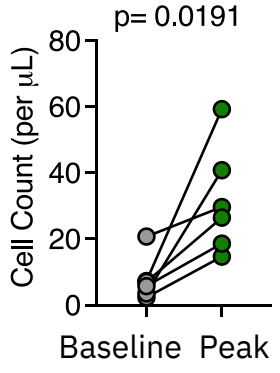
TCF1+ ('Stemness like') CD8+ T Cells



Effector Memory CD8+ T Cells

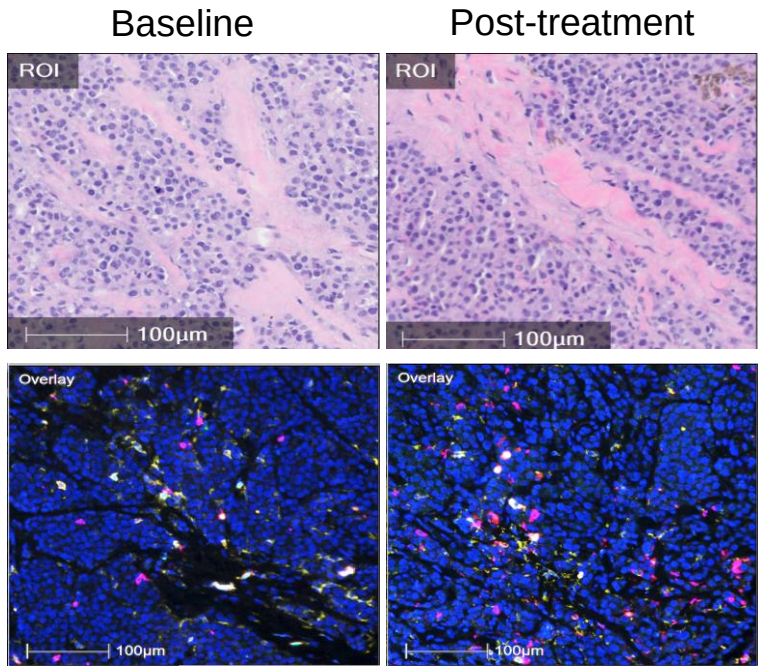


Central Memory CD8+ T Cells

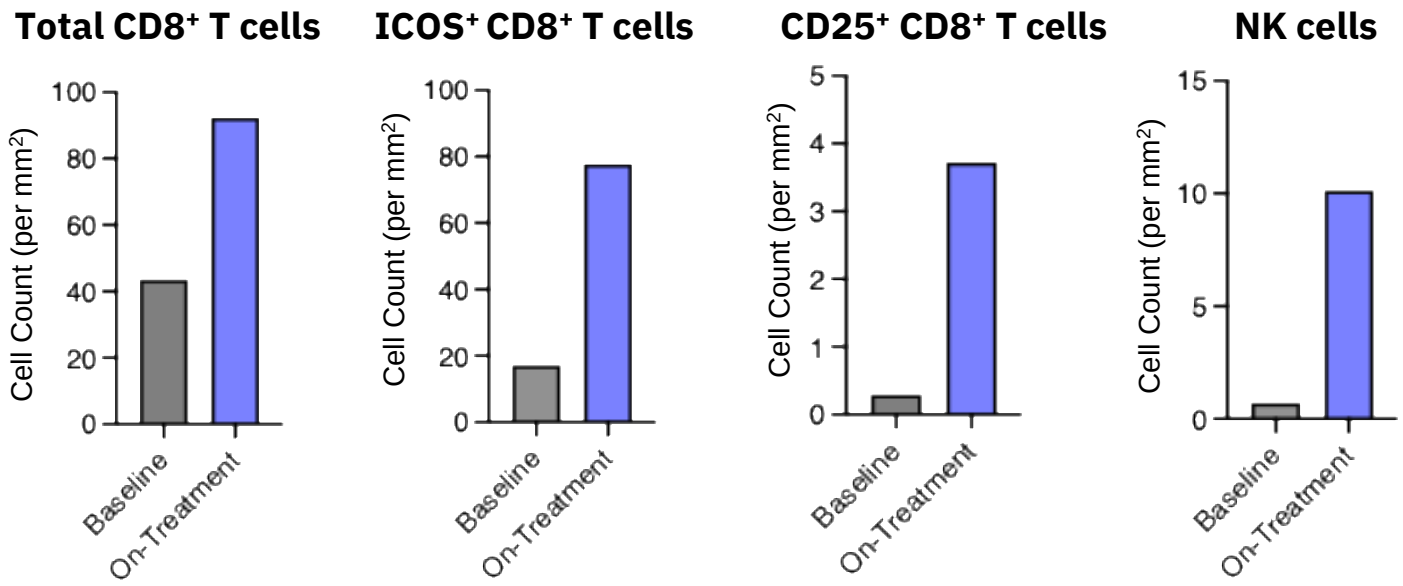


p-values based on paired t-test

Single-agent MDNA11 Increased Tumor Infiltration of Activated CD8⁺ T and NK Cells



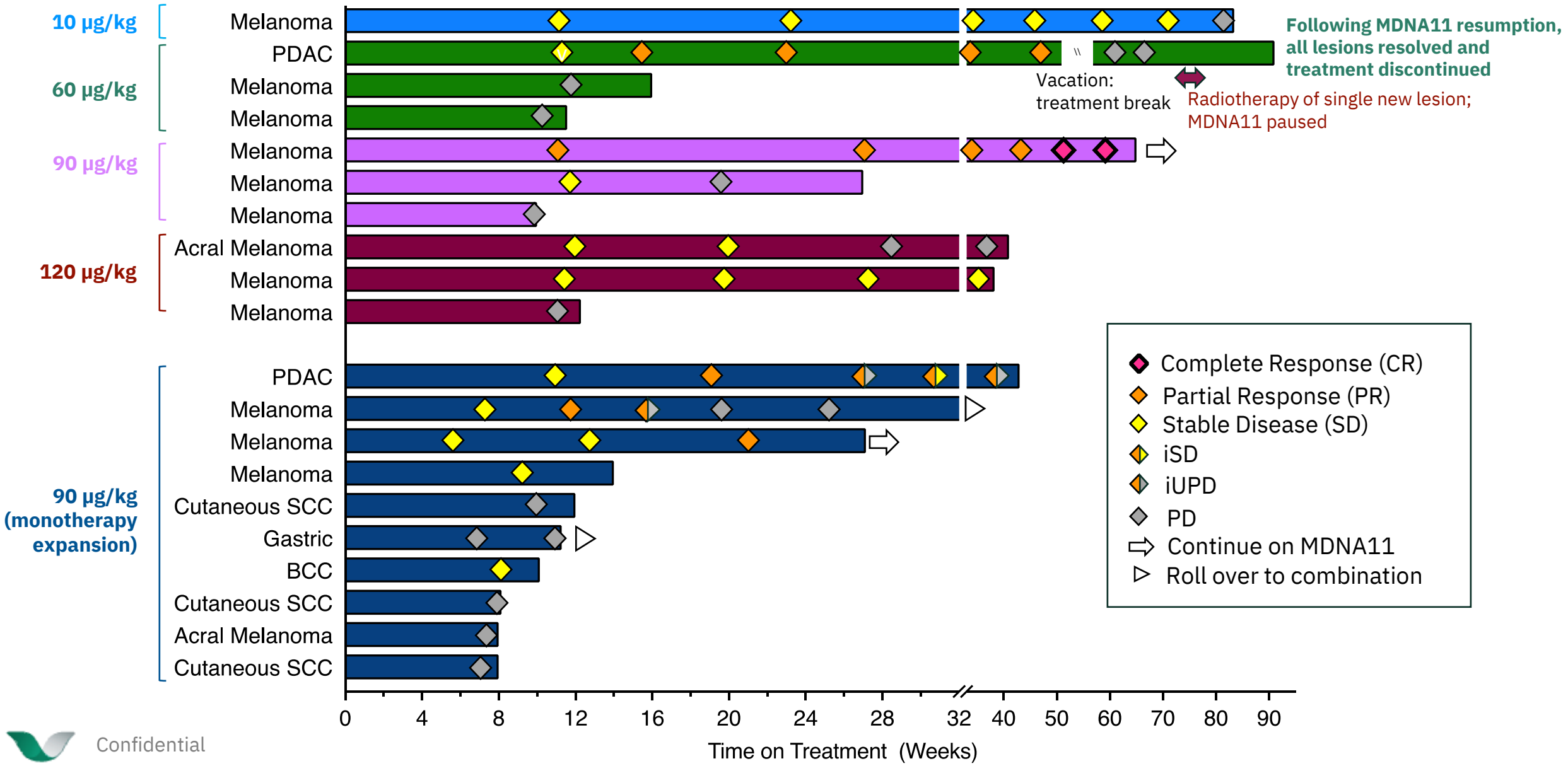
CD8 CD56 CD25 ICOS



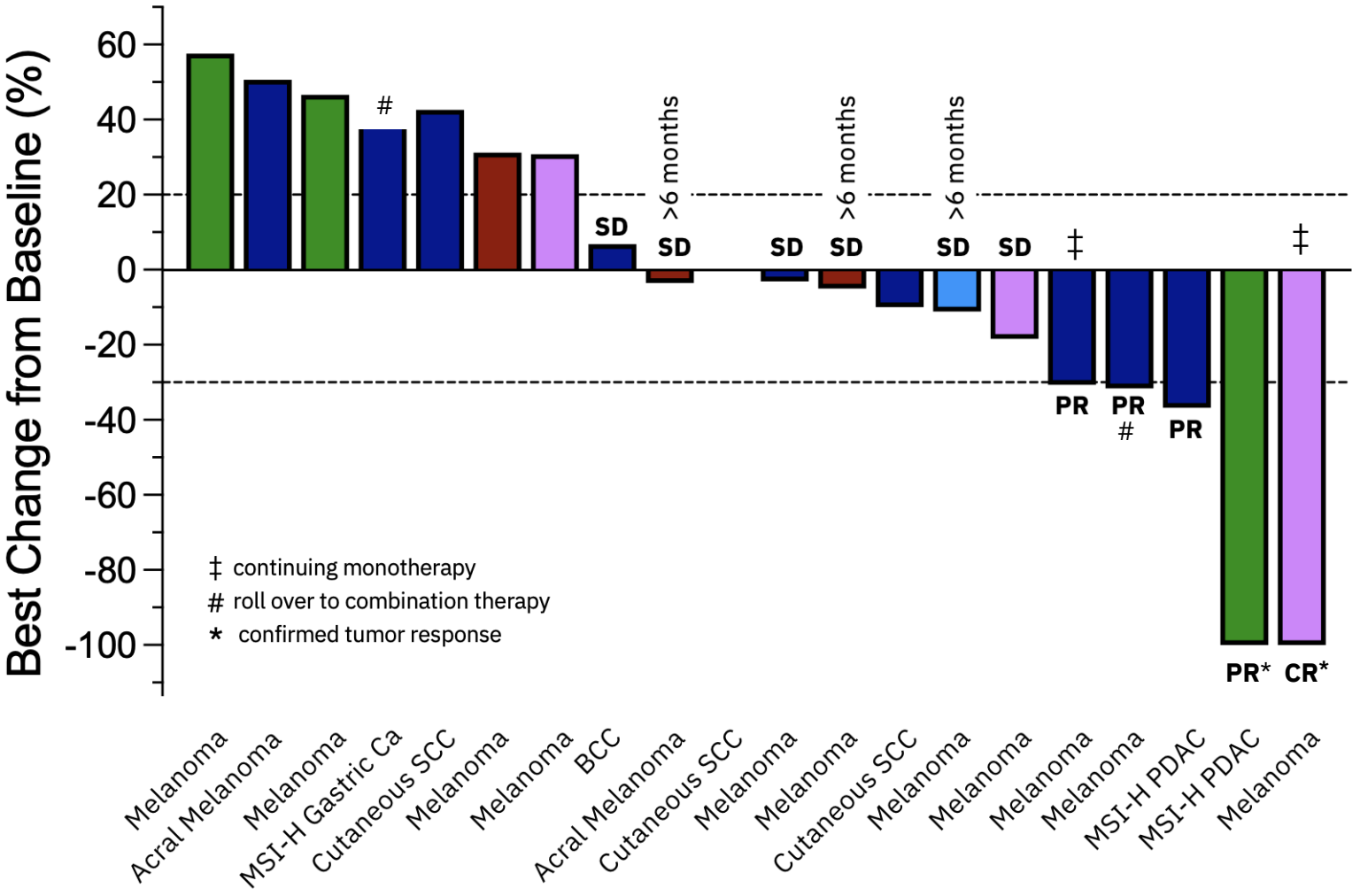
Paired tumor biopsies from a patient treated with single-agent MDNA11 10 µg/kg Q2W. Post-treatment sample collected following 3rd dose

MDNA11 Monotherapy: Duration of Treatment and Anti-Tumor Activity

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



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



MDNA11 Single Agent Activity in Immune Checkpoint Inhibitor Resistant Patients:

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
  - 3 Durable Stable Disease (> 6 months)

Objective response in 3/11 cutaneous melanoma and 2/3 MSI-H tumors

Combination Cohorts

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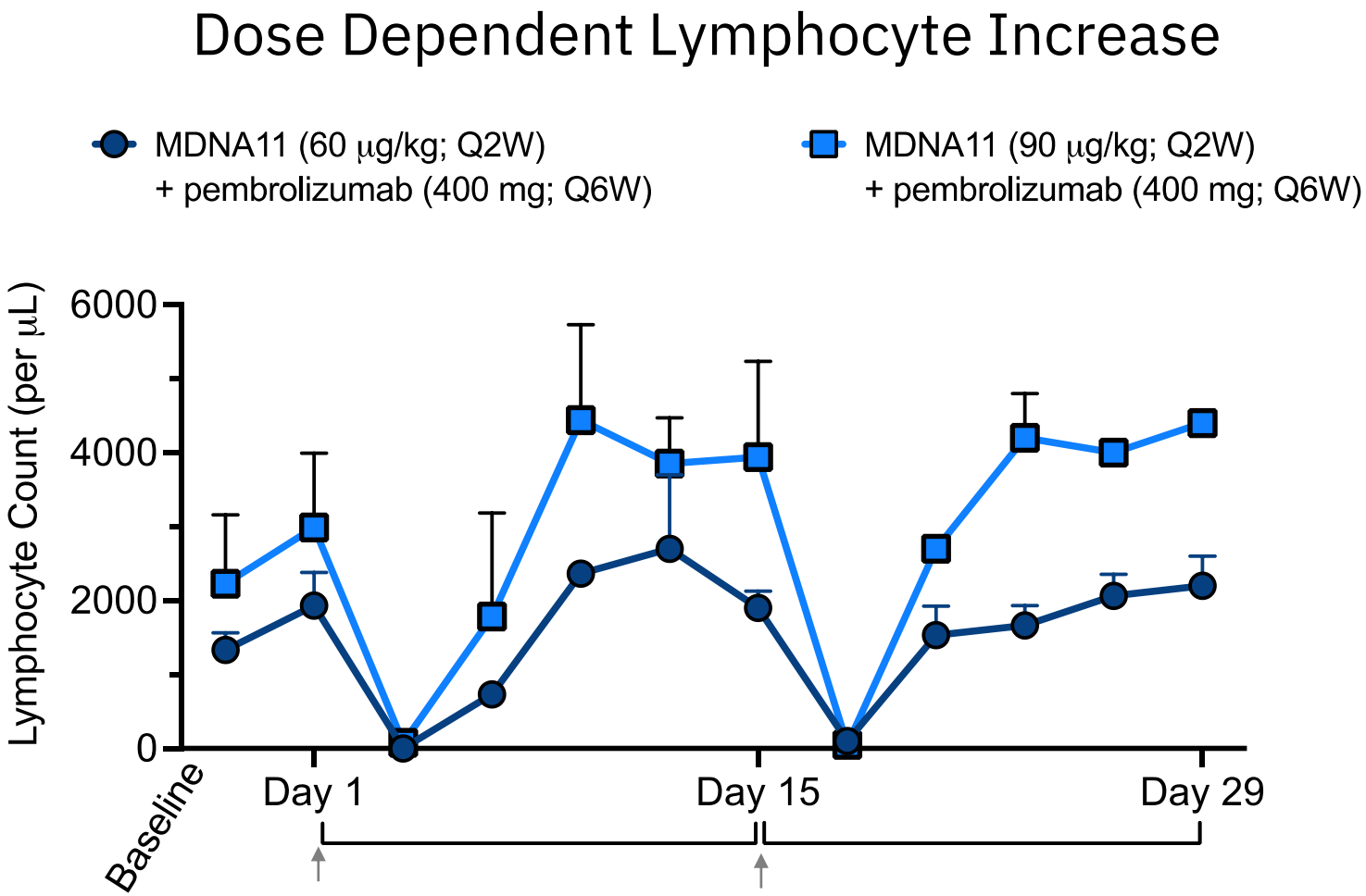
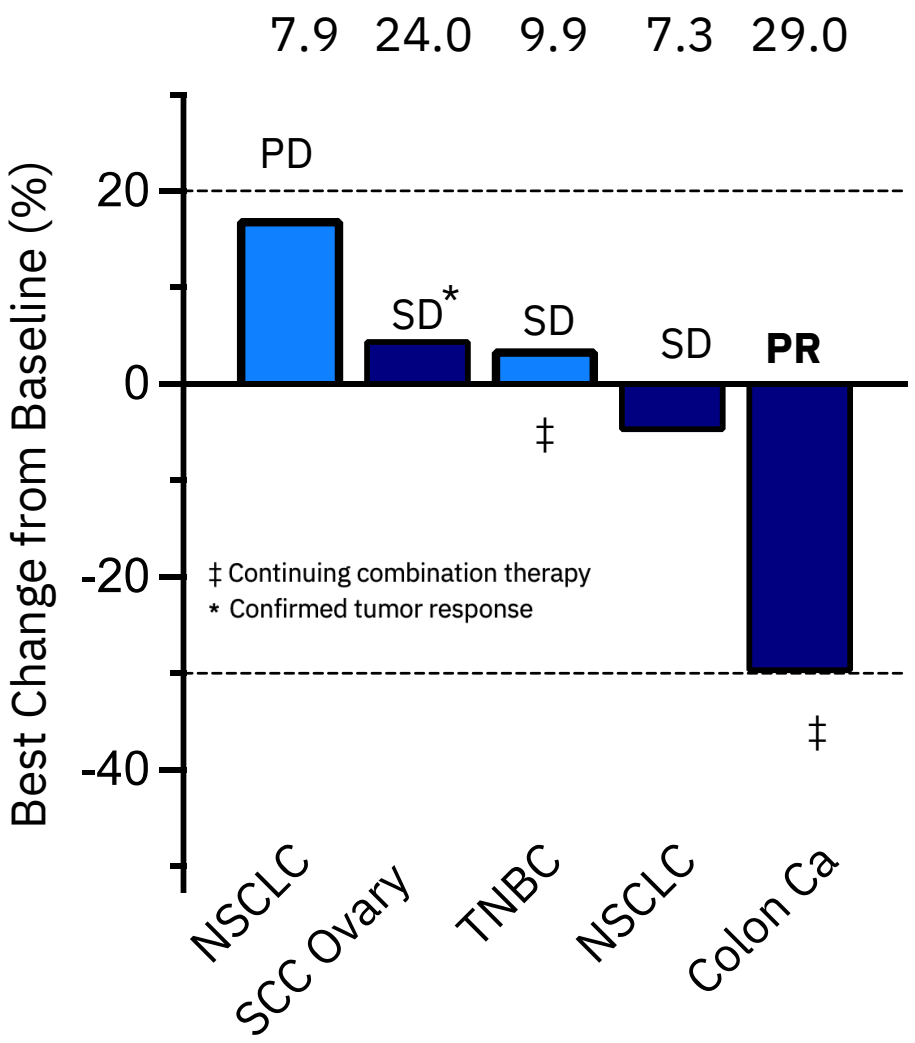
Robust Lymphocyte Expansion in Combination Dose Escalation



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

Combination Dose Escalation Best Tumor Response in Heavily Pretreated Patients



MDNA11 (90 μg/kg; Q2W)
+ Pembrolizumab (400 mg; Q6W)

MDNA11 (60 μg/kg; Q2W)
+ Pembrolizumab (400 mg; Q6W)

Efficacy evaluable patients (as of October 28, 2024); NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma; TNBC, triple negative breast cancer.

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

Summary:

- MDNA11 has a favorable safety profile in both monotherapy and in combination with pembrolizumab with majority (>94%) of TRAEs being Grade 1-2 that resolved within 2 or 3 days
- **Objective response in 3 of 10 ICI resistant patients** in the single-agent dose expansion cohort treated at 90 ug/kg Q2W MDNA11
- Encouraging single agent activity with an **ORR of 25% (1 CR and 4 PR)** in ICI resistant Phase 2 eligible patients treated with ≥ 60 µg/kg Q2W MDNA11
- Among 5 efficacy evaluable patients in MDNA11 + pembrolizumab combination dose escalation, best response of **Partial Response observed in 1 patient** (MSS colon cancer; continue treatment) and Stable Disease in 3 patients
- MDNA11 preferentially expands immune effector cells with significant increase in activated ($CD25^+$ and $DNAM^+$), 'stemness-like' ($TCF\text{-}1^+$) and memory $CD8^+$ T cells
- MDNA11 leads to increased tumor infiltration of $CD8^+$ T cells, activated ($CD25^+$) $CD8^+$ T cells and NK cells

Thank you

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MDNA11 Monotherapy: Duration of Treatment and Anti-Tumor Activity