Pharmacokinetic and Pharmacodynamic Profile of a First-in-Human Study with MDNA11, an Engineered Long-Acting 'Beta-Only' IL-2 Agonist

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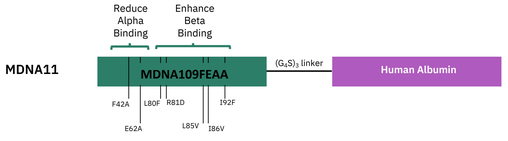
Overview of MDNA11

- An engineered albumin-fusion 'beta-only' IL-2 superkine with superior receptor selectivity and extended pharmacokinetics (PK), designed to enhance activation of CD8⁺ T and NK cells whilst reducing Treg stimulation and toxicities



Differentiated 'Beta-Only' IL-2 Agonist

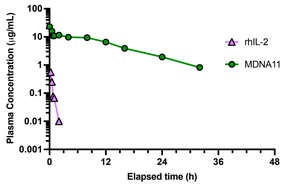
- Enhanced affinity for CD122
  - Potentiate CD8 T and NK cells
- No binding to CD25
  - Reduced capacity to stimulate T_{regs}
  - Improved safety profile

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

Tumor Accumulation of MDNA11 in Mice

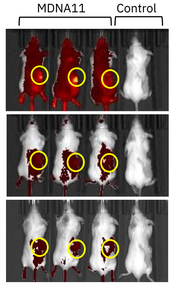
PK Profile in Mice



	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

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

Imaging of CT26 Tumor Bearing Mice



MDNA11 labelled with VivoTag800
IV dose: 1 mg/kg
Tumor size: 150-200 mm³

Trial Design and Objectives

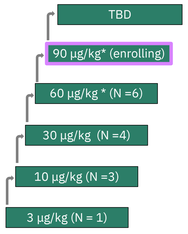
- The ABILITY (A Beta-only IL-2 ImmunoTherapY) study (NCT05086692) evaluates the safety and tolerability of MDNA11 in patients with advanced solid tumors
- The objectives of the dose-escalation phase are to:
  - evaluate safety/tolerability and determine the RP2D of MDNA11
  - study the pharmacokinetic and pharmacodynamic profile of MDNA11
  - assess preliminary tumor response.

Schema of MDNA11 Dose Escalation

MDNA11
Monotherapy Dose Escalation

N ~ 20: Select tumors
IV Infusion, Q2W

- Modified, accelerated 3+3 design
- Intra-patient dose escalation permitted
- Safety and tolerability
- DLT assessment
- Identify RP2D
- Preliminary tumor response



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

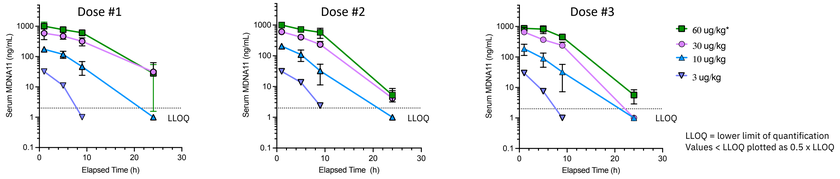
Summary of MDNA11 Safety Data

- The majority (92%) of MDNA11 related adverse events (AEs) are Grade 1-2 and transient, resolving within 1-2 days.
- Majority of AEs are observed after the first dose of MDNA11, with incidence and severity reduced on subsequent dose administrations.
- No Dose-Limiting Toxicities (DLTs) reported in Cohorts 1-4 (3-60 µg/kg)

See Poster (Abstract) #744, Merchant et al for more details

MDNA11 PK Profile in Cancer Patients

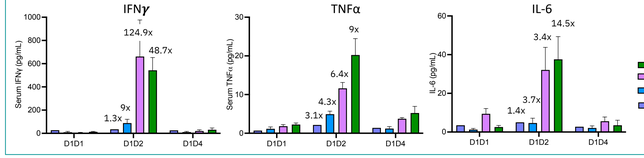
- MDNA11 PK exhibits saturable rapid clearance and a slower parallel linear clearance process
- Dose-dependent increase in exposure (C_{max} and AUC_{last})
- Variability is low between Dose 1-3, suggesting that there is no clinically significant ADA response



LLOQ = lower limit of quantification
Values < LLOQ plotted as 0.5 x LLOQ

	3 µg/kg	10 µg/kg	30 µg/kg	60 µg/kg
Dose 1				
C_{max} (ng/mL)	32.2	174 ± 13.4	611 ± 188	1,019 ± 355
AUC_{last} (h.ng/mL)	103	1,001 ± 189	5,578 ± 2,756	11,629 ± 2,326
Dose 2				
C_{max} (ng/mL)	31.2	206 ± 40.5	604 ± 82.1	999 ± 107
AUC_{last} (h.ng/mL)	138	1,020 ± 317	4,576 ± 1,335	10,646 ± 1,815
Dose 3				
C_{max} (ng/mL)	29.8	188 ± 75	659 ± 259	988
AUC_{last} (h.ng/mL)	89.5	894 ± 405	3,599 ± 840	9,798

Transient Increase in Selected Inflammatory Cytokines

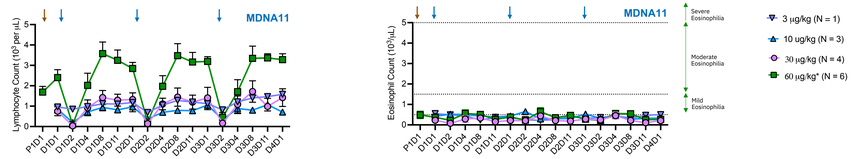


- No change or undetectable levels of IL-1β, IL-2, IL-4, IL-12p70 and IL-13 following MDNA11 administration.

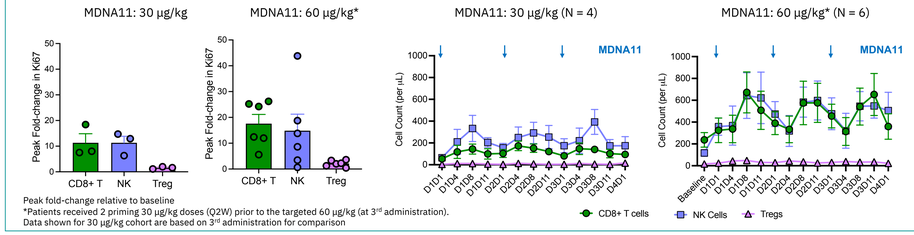
Data following fist dose are shown. Pre-dose (D1D1), 24-hr post dose (D1D2) and 72-hr post dose (D1D4).

Lymphocyte Expansion with Limited Effect on Eosinophils

- Lymphocyte counts sustained above baseline for more than 11 days, indicating a prolonged PD profile
- Eosinophil expansion is associated with increased risk of vascular leak syndrome; not observed with MDNA11

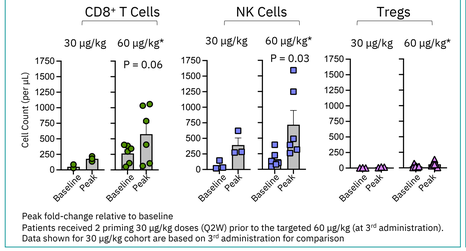


Preferential Proliferation and Expansion of CD8⁺ T and NK Cells Over Tregs



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

Peak Fold-change in Cell Count



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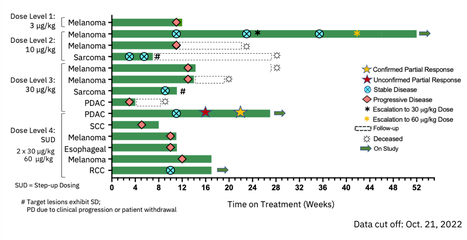
Treatment Duration & Tumor Response



SUD = Step-up Dosing
# Target lesions exhibit SD; PD due to clinical progression or patient withdrawal

Data cut off: Oct. 21, 2022

Conclusions

- Prolonged accumulation of MDNA11 in tumors in mice
- Dose-dependent increase in C_{max} and AUC_{last}
- PK parameters remain consistent following repeat dosing, suggesting no clinically significant ADA response
- Transient increase in selected inflammatory cytokines, consistent with the anticipate pharmacological effect of MDNA11
- Lymphocyte expansion without eosinophilia
- Preferential stimulation of proliferation and expansion of CD8⁺ T and NK cells but not Tregs
- Prolonged PD profile (> 11 days) sustained well beyond MDNA11 exposure
- Tumor control rate of 36% (5 of 14) including 1 confirmed PR (PDAC) and 4 SD (2 sarcomas, melanoma and 1 RCC)