Background MDNA11 is an engineered beta-only IL-2 albumin fusion protein with enhanced affinity and signalling via IL2-Rβg (CD122/CD132) and no binding to IL-2Rα (CD25). Consequently, MDNA11 preferentially stimulates immune effector cells to elicit effective tumour regression both, as monotherapy and in combination with immune checkpoint inhibitors in mouse syngeneic cancer models.1 The ABILITY (A Beta-only IL-2 ImmunoTherapY) trial is a first-in-human phase 1/2 study evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamic (PD) effects, and preliminary clinical activity of MDNA11 as monotherapy and in combination with an immune checkpoint inhibitor in patients with advanced solid tumors (NCT05086692).

Methods The ABILITY study comprises a dose-escalation monotherapy phase in a modified 3+3 Q2W design followed by monotherapy and combination expansion at the recommended phase 2 dose (RP2D) in specific-tumor cohorts. Key eligibility criteria are locally advanced or metastatic unresectable solid tumors with no more than 4 prior lines of therapy and measurable disease per RECIST v1.1. Dose levels (DL) 1-3 were administered at a fixed dose of 3, 10 or 30 ug/kg, respectively. A step-up dosing (SUD) strategy was implemented starting at DL4 in which patients received 2 priming doses of 30 ug/kg followed by a target dose of either 60 ug/kg (DL-4) or 90 ug/kg at DL-5 (enrolment initiated).

Results PK analysis showed dose-dependent increase in exposure as anticipated, with no evidence of anti-drug antibodies (ADA) based on consistent PK profile following each of 3 repeat dose administrations. Lymphocyte counts increased with each repeat dose administration and to date, there is no evidence of eosinophilia, associated with vascular leak syndrome (VLS) commonly observed with high dose IL-2. Immune profiling showed several-fold increases in Ki67 expression by peripheral CD8+ T and NK cell without stimulation of immune suppressive Tregs. Accordingly, CD8+ T and NK cell counts increased with each repeat dose (Q2W) of MDNA11 without eliciting any significant increase in Treg number. Increase in activation markers were also noted on CD8+ T cells without elicitation of similar markers on Tregs. Transient increase in some cytokines was observed. Analysis of paired biopsies is underway to examine local changes in the tumor micro-environment.

Conclusions Cumulative PD readouts to date are consistent with the anticipated pharmacological effect of MDNA11 demonstrating dose dependent activation of various biomarkers on effector cells without concomitant stimulation of immune suppression. Updated PK, PD and ADA data will be presented as dose escalation continues.

Acknowledgements We thank the patients participating in the ABILITY study.

REFERENCE

Ethics Approval The study was approved by each institution’s Ethic Board.