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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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Background: MDNA11 is a long-acting, albumin-fused IL-2 super-agonist that features 'beta-enhanced not-alpha' receptor selectivity, designed to preferentially stimulate key immune effector cells ($CD8^+$ T and NK cells) required for an effective anti-cancer response. The ABILITY-1 study evaluates the safety, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy of MDNA11, as monotherapy and in combination with pembrolizumab, in patients with advanced solid tumors.

Materials and Methods: Monotherapy dose escalation followed an accelerated 3+3 design with 6 dose levels (3-120 mg/kg, Q2W, IV) and enrolled 23 patients. An additional 6 patients were enrolled at the preliminary recommended dose for expansion (pRDE; 90 mg/kg Q2W) and 1 at 120 mg/kg as part of further evaluation. Of these, 22 (73%) had received at least one prior line of immunotherapy. Enrolment in monotherapy phase 2 dose expansion cohort at the pRDE is ongoing. Eligibility includes patients with non-melanoma skin cancers and MSI-H/dMMR tumors (both with 1º or 2º resistance to checkpoint inhibitor, CPI) and melanoma (2º resistance to CPI). Combination dose escalation with MDNA11 (Q2W) and pembrolizumab (400 mg; Q6W) is enrolling.

Results: Monotherapy dose escalation was completed with no protocol-defined DLTs and the maximum tolerated dose was not reached. The most common indication was cutanenous melanoma (14 of 30). Treatment-related adverse events (TRAEs) were predominantly grade 1-2 (~94%) that included infusion-related reactions, pyrexia, nausea, chills and fatigue, resolving within 72 hours. PK analysis showed dose-dependent increase in MDNA11 serum levels with accompanying expansion of lymphocytes without eosinophilia. PD analysis showed sustained increase in peripheral $CD8^+$ T and NK cells while Tregs remained relatively unchanged. $CD8^+$ T cells also showed increased expression of activation, 'stemness' and memory markers. Analysis of paired tumor biopsies showed increased infiltration of activated $CD8^+$ T and NK cells post-treatment. Twelve patients (of which 3 are cutaneous melanoma) have been enrolled in monotherapy dose expansion and showed a similar safety profile as dose escalation. Of 20 monotherapy efficacy evaluable patients treated to date with ≥ 60 mg/kg MDNA11 in the phase 2 eligible population (10 in dose escalation/evaluation and 10 in dose expansion), objective response was achieved in 5 patients (25% ORR): 1 complete response (CR) and 2 partial responses (PR) in cutaneous melanoma patients and 2 partial responses (PR) in patients with MSI-H pancreatic ductal adenocarcinoma (PDAC). Stable disease (SD) was observed in 7 patients, including 3 with duration > 24 weeks. In combination dose escalation, no DLT was observed at MDNA11 doses of 60 mg/kg (N=3) or 90 mg/kg (N=3). Enrolment in the 120 mg/kg dose level is currently underway. All 3 efficacy evaluable patients in the MDNA11 60 mg/kg

cohort showed a best response of SD, including 2 with tumor shrinkage (NSCLC and colon cancer) of which 1 is continuing on study with a deepening tumor response nearing the –30% threshold.

Conclusions: MDNA11 has a favorable safety profile in monotherapy and in combination with pembrolizumab and demonstrates encouraging single-agent activity in CPI resistant MSI-H PDAC and cutaneous melanoma patients. Enrolment to monotherapy expansion and the combination phase of the trial is ongoing.