A phase I/II trial of live biotherapeutic MRx0518 in combination with pembrolizumab in patients refractory to immune checkpoint inhibitors

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MRx0518

MRx0518 is single strain Live Biotherapeutic product (LBP), a highly purified, single-strain bacterium of the *Enterococcus* genus, selected for development in the treatment of solid tumours for its strong *in vitro* and *in vivo* immunostimulatory activity.

PRECLINICAL DATA

In vivo studies have shown that MRx0518 can inhibit tumor growth in different syngeneic cancer models, as both a monotherapy and in combination with immune checkpoint inhibitors (ICIs) (**Fig 1A**). MRx0518 has been shown to reduce Treg and increase Th1 and Tc1 lymphocyte differentiation *in vitro* (**Fig 2**), and increase intratumoral CD4+ and CD8+ T cells and NK cells *in vivo* (**Fig 1B**).

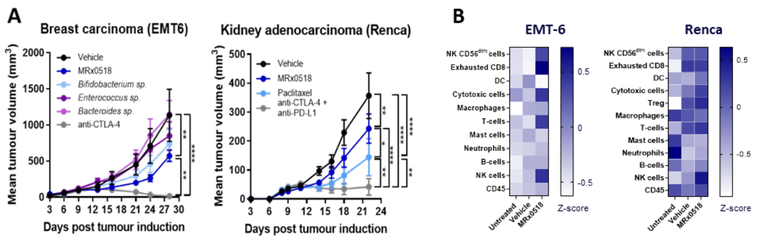

Figure 1. *Inhibition of tumour growth in murine models* ***(A)*** *and quantification of cell subsets using in tumour tissues using the NanoString PanCancer IO360™ Gene Expression Profile (NanoString Technologies, Inc., Seattle, WA)* ***(B)****. (N=8 mice per group)*

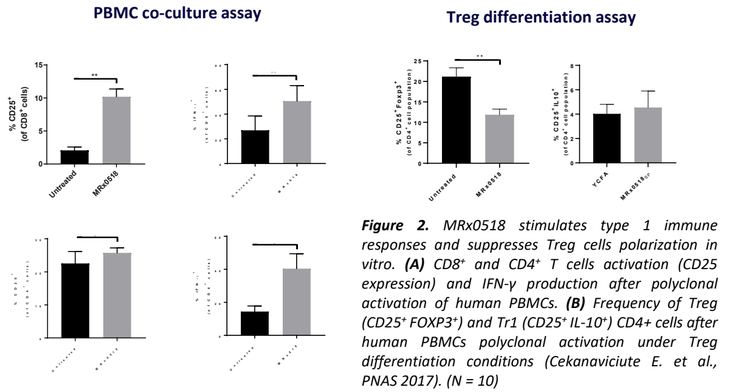

Figure 2. *MRx0518 stimulates type 1 immune responses and suppresses Treg cells polarization in vitro.* ***(A)*** *CD8⁺ and CD4⁺ T cells activation (CD25 expression) and IFN-γ production after polyclonal activation of human PBMCs.* ***(B)*** *Frequency of Treg (CD25⁺ FOXP3⁺) and Tr1 (CD25⁺ IL-10⁺) CD4+ cells after human PBMCs polyclonal activation under Treg differentiation conditions (Cekanaviciute E. et al., PNAS 2017). (N = 10)*

RATIONALE

- Clinical responses to immunotherapies such as anti-PD-1 antibodies can be profound, however responses vary, and many patients experience a decline in efficacy over time - secondary resistance
- Oral LBP MRx0518 may re-engage the antitumor effect of anti-PD-1 therapy after resistance has developed.

OBJECTIVES

PRIMARY

- In Part A, to assess safety and tolerability.
- In Part B, to assess safety and clinical benefit defined as complete response, partial response or stable disease ≥6 months.

SECONDARY

- To assess antitumor effect per RECIST v1.1 including objective response rate (ORR), duration of response (DOR), disease control rate (DCR) and progression free survival (PFS).

EXPLORATORY

- To assess changes in immune status and biomarkers of treatment effect.
- To assess effect on the microbiota and metabolite profile.
- To assess antitumor effect per iRECIST including ORR, DOR, DCR and PFS.
- To assess overall survival.

STUDY DESIGN

A phase I/II, open-label, safety and preliminary efficacy study of MRx0518 in combination with pembrolizumab in patients with advanced malignancies who have progressed on PD-1/PD-L1 inhibitors.

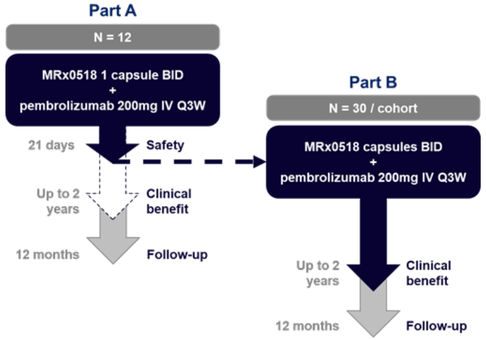

Figure 3*: Study schematic*

ELIGIBILITY CRITERIA

- Eligible patients will have advanced and/or metastatic or recurrent solid tumors including renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), bladder cancer, triple-negative breast cancer, head and neck squamous cell carcinoma or microsatellite instability-high/mismatch repair deficient tumours.
- Eligible patients are refractory to immune checkpoint inhibitors (ICIs). This is defined as having had an initial benefit from PD-1 pathway targeting ICIs but developing disease progression confirmed by two radiological scans ≥4 weeks apart, in the absence of rapid clinical progression, and within 12 weeks of last dose of ICI.
- Eligible patients have failed to respond to standard therapy or have no appropriate therapy options known to provide clinical benefit.

STUDY EVALUATIONS

Tumour response is assessed every 9 weeks per RECIST v1.1. After first evidence of progression, patients may continue with treatment and are assessed by iRECIST.

Tumor tissue will be evaluated at baseline for PD-L1 expression. Tumor and peripheral blood will be evaluated longitudinally for biomarkers of response and immune response activation.

Stool and urine samples will be evaluated to assess the effect of the treatment on the microbiota and metabolite profile.

Safety and tolerability will be evaluated through the collection of adverse events, ECOG performance status, physical examinations, vital signs, blood chemistry and hematology and thyroid function tests.

STUDY STATUS

- Part A of the study is complete. 9 RCC and 3 NSCLC patients were evaluated for safety of the combination therapy.
- The Cycle 1 data was assessed by the Safety Review Committee and it was determined appropriate to proceed to Part B as no dose-limiting toxicities were reported.
- Part B is now recruiting up to 120 additional patients at 5 US centers.
- Ongoing study read-outs will determine future clinical development of the combination.

For additional information on the completed phase I see poster 283

The study is sponsored by 4D pharma plc. For more information, contact clinicaltrials@4dpharmaplc.com

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA provided pembrolizumab for the study

www.clinicaltrials.gov NCT03637803