1) MRx0518 has broad immunostimulatory effects on immune cell populations in vitro

Strain MRx0518 was identified for its potent immunostimulatory effect on host immune cells, inducing the production of cytokines/chemokines associated with both innate and adaptive immunity (A, B). MRx0518 treatment also decreased the proportion of Tregs in human PBMCs (C).

2) Efficacy in preclinical syngeneic tumour models

MRx0518 was tested in a number of different preclinical cancer models (A, B, C, D).

From D-14, mice received vehicle (culture medium or PBS) or 2×10⁹ bacteria daily until termination. On D0, mice were engrafted with EMT6 (n=8-9) (A), LLC1 (n=8-9) (B) or Renca (n=12) (C) tumour cells subcutaneously. Anti-CTLA-4 (10 mg/kg, IP, Twix); Paclitaxel (15 mg/kg, IP, Q4D) or a combination of anti-CTLA-4 and anti-PD-L1 (100 µg/kg each, IP, Q8D) were used as controls. Tumour length and width were measured 2-3 times a week.

3) Mode of action mediated by bacterial surface molecules

Bacterial flagellin is a known TLR5 agonist, and reporter assays indicated the immunostimulatory effect of MRx0518 was at least partly mediated by TLR5 signaling.

Genetic knock out of the flagellin protein (FliC) resulted in little to no NF-kB (A) or TLR5 signalling (B). The effect of purified recombinant MRx0518 flagellin was compared to that of a reference strain and was significantly more potent at lower concentrations (C, D). Genomic analysis identified broad fliC sequence divergence between the MRx0518 strain and reference strain (data not shown). MRx0518 culture supernatant and recombinant MRx0518 flagellin protein induced significantly upregulated expression of inflammatory cytokine IL-8 by intestinal epithelial cells (E).

Clinical Study Design

Part A
20 patients - 1 capsule of MRx0518 twice-daily for 2-4 weeks prior to tumour resection

Part B
80 patients - 1 capsule of MRx0518 twice-daily for 2-4 weeks prior to tumour resection

Eligibility
Eligibility is limited to treatment-naïve patients with confirmed solid tumours amenable to primary surgery resection with a comparison of the diagnostic biopsy and surgical excision specimen to assess the biomarker response

Clinical Study Objectives

Primary
- Safety and tolerability of MRx0518
- Efficacy in preclinical syngeneic tumour models
- Mode of action mediated by bacterial surface molecules

Secondary
- Responses in respect of intra-tumoural biomarkers compared to placebo
- Clinical outcomes including overall survival

Exploratory
- Surrogate biomarkers of treatment effect
- Microbiome analysis
- Impact on tumoural T cell populations including CD8+ T cells and CD4+FOXP3+ Tregs

Clinical Study Status

- The study commenced in April 2019
- Subjects are being enrolled into Part A in a staggered fashion
- All subjects are currently tolerating the treatment well
- A safety review will be performed after completion of Part A before moving into Part B

The trial is being sponsored by Imperial College London 4D pharma plc. 4D pharma plc is a collaborator on the trial.

For further information please see: www.clinicaltrials.gov — NCT03934827
Or email clinicaltrials@4dpharmplc.com

References