A Phase I/II study of live biotherapeutic MRx0518 in combination with pembrolizumab in patients who have progressed on prior anti-PD-1 therapy

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Background
The Microbiome and Immunotherapy
The gut microbiome has emerged as a new therapeutic target to augment the efficacy of immune checkpoint blockade, and has been shown to influence therapeutic responses in both preclinical models and patient cohorts.1-3

MRx0518
MRx0518 is a gut microbiome-derived, oral live biotherapeutic, identified as inducing a broad immunostimulatory response. Preclinical studies showed that MRx0518 reduced tumour growth in models of kidney, lung and breast cancer. MRx0518 increased CD4 and CD8 T cell and NK cell infiltration into the tumour and decreased Tregs. Uprogulation of tumour TLRS in the tumour microenvironment was observed and linked to the bacterial flagellin moiety, which was shown to strongly induce NFκB signalling, cytokine responses and IFNγ+ CD4 and CD8 T cells.

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 (C, D).

2) Efficacy in preclinical syngeneic tumour models
MRx0518 was tested in a number of different preclinical cancer models Breast carcinoma (EMT6), lung carcinoma (LLC1) and kidney adenocarcinoma (Renca).

From D-14, mice received vehicle (culture medium or PBS) or 2x107 bacteria daily until termination. On D0, mice were engrafted with EMT6 (A), LLC1 (B) or Renca (C) tumour cells subcutaneously. Anti-CTLA-4 (10 mg/kg, IP, Twx2), Paclitaxel (15 mg/kg, IP, QOD) or a combination of anti-CTLA-4 and anti-PD-L1 (10 mg each, IP, BID) were used as controls. Tumour length and width were measured 2-3 times a week.

MRx0518 affects tumour immune cell populations
MRx0518 increased tumour infiltrating CD8+ T cells, natural killer (NK) cells and ratio of CD8+ : CD4+ FoxP3+ Tregs.

3) Mode of action mediated by bacterial surface molecules
Bacterial flagellin is a known TLR5 agonist, and reporter assays identified the immunostimulatory effect of MRx0518 was at least partly mediated by TLRS signalling. Genetic knock out of the flagellin protein (flic) resulted in little to no NFκB (A) or TLRS signalling (B). The effect of purified recombinant MRx0518 flagellin was compared to that of a reference strain and was more potent at lower concentrations (C, D). Genomic analysis identified flic sequence divergence between the MRx0518 strain and reference strain (data not shown). MRx0518 culture supernatant and recombinant MRx0518 flagellin protein induced upregulated expression of inflammatory cytokine IL-8 by intestinal epithelial cells (E).

Clinical study rationale
Checkpoint inhibitor immunotherapies are highly effective in some patients but efficacy is limited to a minority. Furthermore, around 40% of patients who respond to checkpoint blockade therapy become refractory over time.3,4

There is a significant need for therapeutics that increase response to immunotherapy and re-engage the immune system in patients who have responded but then lost efficacy.

MRx0518 has potent immunostimulatory activity, and demonstrated anti-tumour activity in multiple preclinical models. Oral administration of the strain increases tumour infiltration of immune cells known to be critical in response to checkpoint blockade immunotherapy.

Clinical study objectives
Primary
Part A: To assess the safety and tolerability of MRx0518 in combination with pembrolizumab
Part B: To assess the safety and clinical benefit of MRx0518 in combination with pembrolizumab

Secondery
Part B: To evaluate the antitumour effect of study treatment per RECIST 1.1
- Objective Response Rate
- Duration of Response
- Disease Control Rate
- Progression-Free Survival

Exploratory
- Blood biomarkers of immune status and treatment effect
- Tumour biomarkers of immune status and treatment effect
- Faecal and urine microbiota and metabolomics analysis

To evaluate the anti-tumour effect of study treatment per IRECISt
- Overall survival, determined from the start of combination therapy until death due to any cause

Clinical study design
The study, one of the first oncology trials conducted with live biotherapeutics, is a single centre, open label, safety and preliminary efficacy study. The study will enrol patients who have progressed on prior anti-PD-1 therapy and who have a diagnosis of:
- Non-small cell lung cancer
- Renal cell carcinoma
- Bladder cancer
- Melanoma

Clinical study status
The study was activated in January 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 4D Pharma plc. Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA provided pembrolizumab for the study.

For further information:
clinicaltrials4dpharma.com
www.clinicaltrials.gov — NCT03637803