Safety and Emerging Evidence of Immune Modulation of the Live Biotherapeutic MRx0518 in the Neoadjuvant Setting for Patients Awaiting Surgical Removal of Solid Tumours

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PRECLINICAL DATA

- The gut microbiome has emerged as a promising therapeutic target for the immune mediated treatment of solid cancers
- MRx0518 is a novel, gut microbiome-derived, oral Live Biotherapeutic (LBP)
  - Highly purified single strain of the *Enterococcus genus*
- Pre-clinical models have shown **potent** anti-tumorigenic efficacy including murine models of breast (*EMT6*) and kidney (*Renca*) cancer (**Figure 1**)

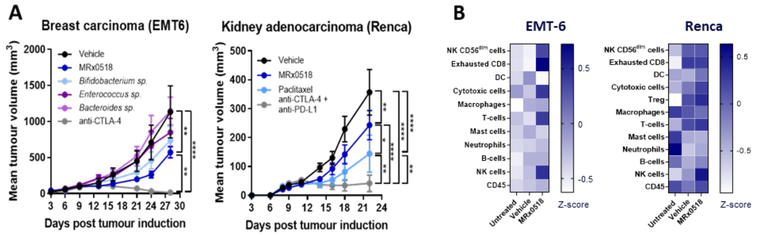


Figure 1. *Inhibition of tumour growth in murine models* ***(A)*** *and quantification of cell subsets utilizing tumour tissues and analysis via NanoString PanCancer IO360™ Gene Expression Profile* ***(B)****. (N=8 mice per group)*

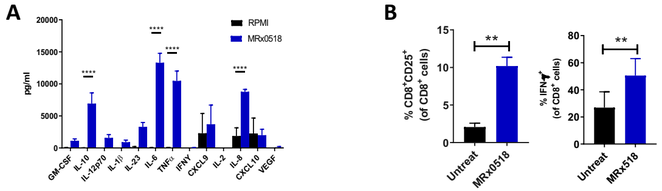
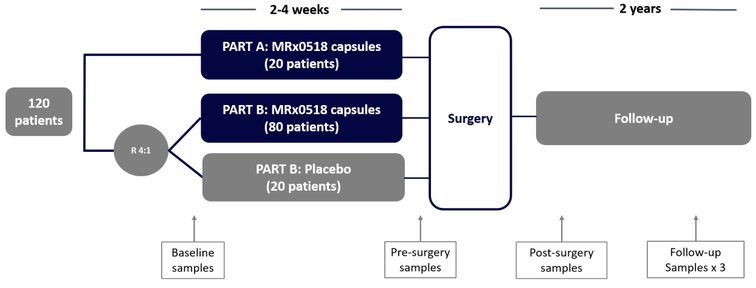


Figure 2. *In vitro immunostimulatory effect inducing the production of pro-inflammatory cytokines and chemokines by MoDCs* ***(A)*** *and the activation (CD25 expression) and IFN-γ production by CD8⁺ T cells* ***(B)*** *. (N = 10)*

RATIONALE & CLINICAL STUDY DESIGN



Part A: *1 capsule of MRx0518 (1x10[10]- 1x10[11]CFU) twice daily for 2-4 weeks prior to tumour resection*

Part B: *1 capsule of MRx0518 or placebo twice daily for 2-4 weeks prior to tumour resection*

OBJECTIVES

PRIMARY:

- Assess safety & tolerability of MRx0518 monotherapy in treatment naïve subjects

SECONDARY:

- Investigate surrogate biomarkers of efficacy of MRx0518 in a range of solid tumours to provide data for future studies
- Assess changes in tumoral and circulating T-cell populations induced by MRx0518
- Examine long term survival in patients receiving MRx0518 prior to cancer surgery

EXPLORATORY:

- Identify histological & genomic alterations in **paired** pre-treatment (diagnostic biopsy) and post treatment (surgical specimen) samples (*analysis with NanoString Pan Cancer IO 360™ Gene Expression panel*)
- Assess the effects of MRx0518 on the microbiome

GENOMIC MODULATION

- Genomic analysis has identified significant expression changes in 98 genes ($p<0.05$) in paired samples
- To identify the biological pathways significantly impacted by MRx0518 treatment, direct and indirect global significance scores (GSS) were generated using nSolver™ (**Table 1**).
- The significance scores show the activation of immunological relevant pathways, such as the Antigen Presentation, Costimulatory Signaling and Cytokine and Chemokines Signaling pathways

Table 1: Surgical vs Diagnostic Samples GSS (top 10 pathways)

Pathway	Undirected Scores	Directed Scores
Angiogenesis	2.003	1.688
Antigen Presentation	1.909	1.706
Apoptosis	1.376	-0.256
Autophagy	1.338	0.721
Cell Proliferation	1.889	1.016
Costimulatory Signaling	1.804	1.522
Cytokine and Chemokine Signalling	2.045	1.875
Cytotoxicity	1.315	0.877
DNA Damage Repair	1.374	0.386
Epigenetic Regulation	1.091	0.304

SAFETY DATA

Table 2: *Adverse effects (CTCAE⁺ grade 1 or 2) reported with an incidence of ≥2 occurrences*

Adverse Event (CTCAE⁺ grade 1 or 2)	Frequency	Proportion potentially related to MRx0518*
Nausea	3	33%
Dyspepsia	3	100%
Diarrhoea	2	100%
Back Pain (Including sciatica pain)	2	0%
Flu-like symptoms	2	0%
Sinusitis	2	0%
Fatigue	2	0%

* Proportion of adverse events with causality recorded by trial investigators as possible/probable/definite relationship to MRx0518

⁺ Common terminology Criteria for Adverse Events (CTCAE) version 5

- At date of censoring 17 patients have received MRx0518
  - **No** Serious Adverse Events or treatment discontinuations
  - **No** grade 3 or 4 toxicities reported
- Other reported toxicities are shown in **table 2**

IMMUNE MODULATION

- Following MRx0518 therapy, a relative increase in cytotoxic cells, CD8+ T cells and immune subsets associated with anti-tumour activity was observed in the paired tumour samples, echoing preclinical findings (**Figure 3A-B**)
- Furthermore, upregulation of key anti-tumoural cytokines, such as IL-12 and CXCL10, were demonstrated in post-treatment plasma samples (**Figure 3C**)

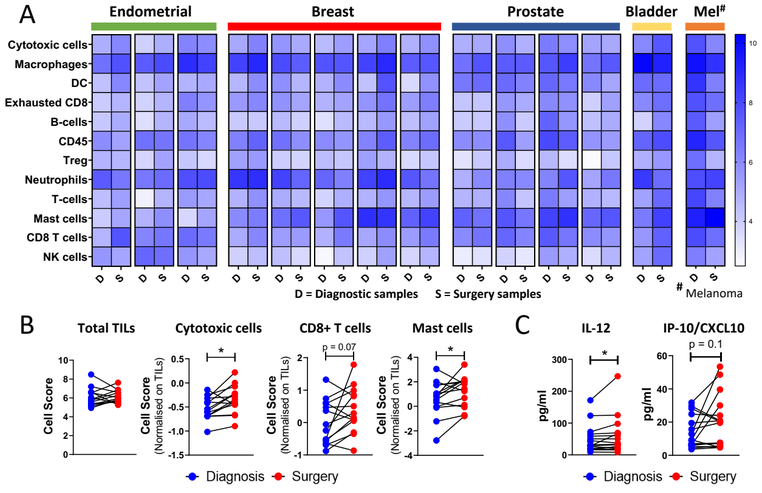


Figure 3. *Relative frequency of immune subsets in diagnostic and surgery tumour samples was evaluated using the NanoString IO360™ platform and nSolver™* ***(A-B),*** *systemic cytokine concentration were evaluated in plasma (Luminex) (**C**). P values were calculated using paired t-test in Prism GraphPad version 6. (* = p<0.05)*

STUDY STATUS

- **Part A** of this study has recruited 17 patients *(censoring date 10/10/2020)*
  - No dose limiting toxicities or other safety signals identified
  - Awaiting review by Independent Data Monitoring Committee before proceeding to Part B
- **Part B** will focus on investigating efficacy in a further 100 treatment naïve patients with a placebo-controlled arm

For additional information on clinical studies involving MRx0518 see posters **283** & **376**

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

Clinical trials number: **NCT03934827**

ACKNOWLEDGEMENTS: We would like to thank the team at *Propath UK* for their help in sample analysis and bioinformatics