Neoadjuvant MRx0518 treatment is associated with significant gene and metagene signature changes in solid tumours

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Poster: 543P

BACKGROUND

• Accumulated data has demonstrated a direct impact of specific bacteria strains on immune cell subsets activation and polarisation, and ultimately on the efficacy of cancer immunotherapies such immune checkpoint inhibitors (ICIs) and adaptive cytokotic T-cell therapy.

• MRx0518 is a novel, human gut microbiome-derived single strain, live biotherapeutic product in clinical development for the treatment of solid tumours.

• MRx0518 monotherapy demonstrated immunostimulatory activity and anti-tumorigenic effects (Figure 1) in a range of murine tumour models including MMT (breast cancer) and Renca (Renal cancer).

• MRx0518 monotherapy has been shown to increase tumour infiltration by cytotoxic cells, CD8+ T cells and other immune subsets associated with anti-tumour activity, as well as preliminary clinical activity in combination with ICI pembrolizumab in patients refractory to anti-PD-(L)-1 ICI therapy.

• We investigated immune and metagene signature changes in solid tumours associated with MRx0518 neoadjuvant monotherapy.

METHODS

• In Part A of the study 17 patients have completed treatment across a broad range of cancer types including breast (n=8), prostate (n=4), endometrial (n=3), bladder (n=1) and melanomas (n=1).
  • No severe adverse events or grade 3/4 Common Terminology Criteria for Adverse Events reported
  • Independent Data Monitoring Safety Committee review has permitted transition to Part B
  • 31 tumour samples were obtained for paired analysis (15 patients) including 16 pre-treatment (disease biopsies) and 15 post-treatment (surgical specimens)
  • Gene expression profiling (GEP) was performed using the NanoString IQ 360 panel to evaluate both the gene and metagene changes
  • Analysis was correlated with cytokine and chemokine changes present in paired pre- and post-treatment plasma samples

GENOMIC MODULATION

• GEP analysis identified 96 differentially expressed genes (DEGs; p<0.05) between pre- and post-treatment tumour samples. The majority of DEG (n=92) were upregulated after treatment and a small number (n=4) were down-regulated (Figure 2)
  • Pathway analysis was performed (using the roBio software) and both undirected and directed global significance scores (GSS) calculated (Table 1). DEGs pathway analysis showed that treatment with MRx0518 was associated with anti-tumour immune activity including:
    • Antigen Presentation (AXL & CK112)
    • Inhibit Immune Processes (CHUK, RELA, PRARG & HRAS)
    • Interferon Response (IFNLR1 & IFN2R)

RATIONAL & CLINICAL STUDY DESIGN

The MICROBIOME trial is designed to investigate the effects of oral MRx0518 for 2-4 weeks in patients with solid tumours awaiting surgical removal of the tumour

IMMUNE & FUNCTIONAL SIGNATURES

• Analysis of paired tumour samples identified an increase in mast cells, Th1, CD8+ T cells, endothelial cells and inflammatory chemokine metagene signatures following MRx0518 therapy (Figure 3A).

• Effects were particularly pronounced in the breast cancer cohort (n=7), with a significant increase in total and activated dendritic cells (DC), CD8+ T cells, cytotoxic cells and mast cells in the tumour microenvironment.

• Functional metagenome analysis also identified positive changes in prognostic indicators and metagene signatures predictive of immunotherapy response, including the cytotoxicity and lymphoid scores, and tumour infiltration signature (TS), demonstrated to retrospectively predict clinical benefit of anti-PD-(L)-1 ICI therapy efficacy in various cancer types (Figure 3B).

CONCLUSION

• Analysis of paired tumour samples shows oral administration of the single strain live biotherapeutic MRx0518 monotherapy increases expression of genes associated with anti-tumour immune activity.

• Furthermore, metagene changes predictive of immunotherapy response and favourable disease prognosis, such as increased TIS, lymphoid and cytotoxicity scores were observed post-therapy

• These results show evidence of immune activation after MRx0518 therapy, further validation in treatment naive patients is planned.

For additional information on clinical studies involving MRx0518 see poster 1024P

Disclosure: The study is sponsored by Imperial College London & funded by 4D Pharma plc. For more information, contact clinicaltrials@4dpharma.co.uk. M.F. declares no conflicts of interests.

Clinical trial number: NCT03051487

Figure 1. Inhibition of tumour growth in murine models (A) and quantification of cell subsets utilising tumour tissues and analysis via Nanostring PanCancer 105000 Gene Expression Profiling (BE). (n=4 mice per group)

Figure 2: Comparison of the gene expression profiles in paired tumour samples collected pre- and post-treatment with MRx0518. Selected genes with significant (P<0.05) change in expression are highlighted (red indicates increased and blue indicates reduced expression)

Table 1: logistic (diagnostic) sample (CD8+ T cell) pathway

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Unaffected Score</th>
<th>Affected Score</th>
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<tr>
<td>Antigen presentation</td>
<td>1.05</td>
<td>1.00</td>
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<tr>
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<td>1.33</td>
<td>2.18</td>
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Figure 3: Changes in expression of metagene signatures in paired tumour samples. Forest plots show the Log2 mean fold change. 95% confidence intervals, of immune cell type and functional score signatures in pre- vs post-treatment in all paired tumour samples (A) or breast cancer cohort paired tumours (B).三角形/Δ | I indicate significant difference (p<0.05) as assessed by univariate analysis.

METHODS

A Immune Cells Signatures

B Immune Cells Signatures

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