Safety and efficacy signals in the complete phase I study of live biotherapeutic MRx0518 in combination with pembrolizumab in patients refractory to immune checkpoint inhibitors (ICIs)

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BACKGROUND AND RATIONALE

The gut microbiome is recognized to be an important modulator of response to anti-cancer treatment and the efficacy of immune checkpoint inhibitors (ICIs) in particular. MRx0518 is a novel, human gut microbiome-derived, single-strain, live biotherapeutic in clinical development for the treatment of solid tumors. Preclinically, MRx0518 monotherapy induced broad immunostimulatory activity and demonstrated anti-tumorigenic effects in a range of murine tumor models. MRx0518 increased CD4+ and CD8+ T cell and NK cell tumor infiltration and decreased Tregs.

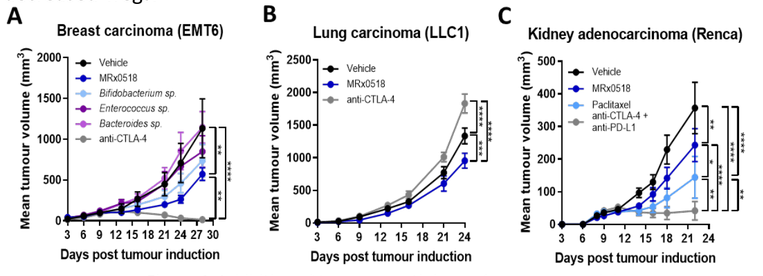

Figure 1: Inhibition of tumor growth in murine cancer models

STUDY DESIGN

The Phase I (Part A) component of this study enrolled 12 heavily pre-treated RCC and NSCLC patients to be treated with 1 capsule of MRx0518 BID ($1x10^{10}$ to $1x10^{11}$ CFU/capsule) and 200mg pembrolizumab Q3W for up to 35 cycles (approx. 2 years) or disease progression. Tumor response was assessed by RECIST v1.1 every 9 weeks.

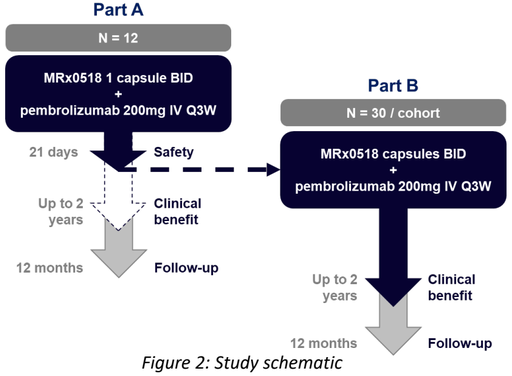

Figure 2: Study schematic

For additional information on the ongoing phase II see poster 376

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

PATIENT CHARACTERISTICS

All patients had advanced malignancies which had developed resistance to checkpoint inhibition as confirmed by:

- Having had at least 2 doses of a prior PD-1 pathway targeting ICI and experiencing a clinical benefit (CR, PR or SD) from it, and
- Having progressed within 12 weeks of the last dose of prior ICI with confirmation by repeat imaging at least 4 weeks later (in the absence of rapid clinical progression)

Demographics	n (%)
Gender	
Male	10 (83%)
Female	2 (17%)
Median age	62
ECOG	
0	2 (17%)
1	10 (83%)

Disease Characteristics	n (%)
Tumor type	
RCC	9 (75%)
NSCLC	3 (25%)
CPS/TPS	
Positive	7 (58%)
Negative	1 (8%)
Unknown	4 (33%)

Prior Therapies	n (%)
Median prior therapies	3
Prior anti-PD-(L)1 therapy	
Nivolumab	10 (83%)
Nivolumab & Pembrolizumab	1 (8%)
Avelumab	1 (8%)
Best response to prior anti-PD-(L)1 therapy	
PR	2 (17%)
SD	10 (83%)

Table 1: Baseline characteristics of enrolled patients

RESULTS - SAFETY

- No treatment related Grade 4/5 or serious adverse events were reported.
- No treatment related adverse events resulted in treatment discontinuation.
- Only one event (Grade 2 dyspepsia) was reported with a possible relationship to MRx0518.
- All events in Table 2 are possibly related to pembrolizumab.

Event	All Grades	Grade 1	Grade 2	Grade 3
Hyponatremia	11	11		
Hypoalbuminemia	6	3	3	
Lipase increased	6	3	1	2
Fatigue	5	4	1	
White blood cell decreased	5	4	1	
Hypercalcemia	4	4		
Neutrophil count decreased	4	4		
Constipation	3	3		
Alkaline phosphatase increased	2	2		
Aspartate aminotransferase increased	2	2		
Hyperkalemia	2	2		
Total	**50**	**42**	**6**	**2**

Table 2: Treatment related adverse events reported in >1 patient by CTCAE grade

RESULTS - EFFICACY

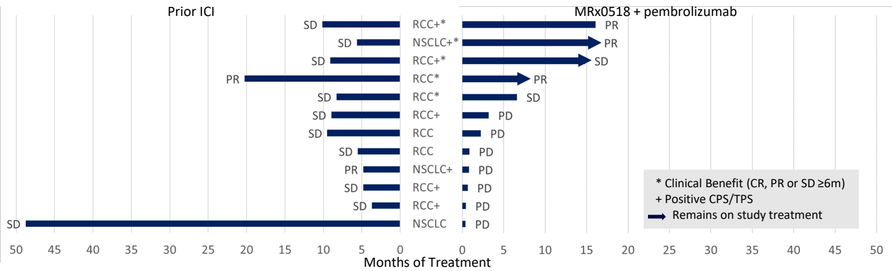

Figure 3: Duration of study treatment and best response compared to prior ICI

- 3 patients experienced a PR on treatment with MRx0518 + pembrolizumab, 2 of which had best response of SD to prior ICI.
- 3 patients, to date, have been treated with MRx0518 + pembrolizumab for longer than their prior ICI (70 vs. 44; 70+ vs. 25; 65 vs. 40 weeks).

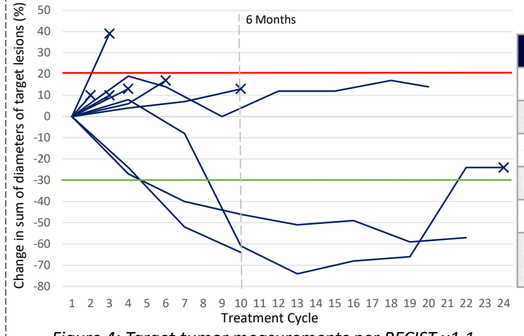

Figure 4: Target tumor measurements per RECIST v1.1

	Total	RCC	NSCLC
N	12	9	3
Continuing on Study	3	2	1
ORR, n (%)	3 (25%)	2 (22%)	1 (33%)
DCR, n (%)	5 (42%)	4 (44%)	1 (33%)
DOR, months		3.4+, 8.1	12.0+
Median PFS, months (95% CI)	2.14 (0.43, NE)		

Table 3: Summary of efficacy parameters

CONCLUSIONS

- MRx0518 and pembrolizumab was well tolerated with no treatment-related SAEs or drug discontinuations and, importantly, no increase of irAEs commonly associated with ICI therapy.
- MRx0518 and pembrolizumab provided clinical benefit to 5 of 12 patients with 3 partial responses and 2 patients with durable stable disease.
- These early results are encouraging, and recruitment is ongoing in the Phase II (Part B) component of the study where up to 120 additional patients will receive the MRx0518 and pembrolizumab combination.