Baseline biomarkers associated with clinical benefit in patients with solid tumours refractory to immune checkpoint inhibitors (ICIs) treated with live biotherapeutic MRx0518 in combination with pembrolizumab

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Introduction

MRx0518 is a novel, gut microbiome-derived, single strain oral Live Biotherapeutic Product (LBP) with potent anti-tumour efficacy in multiple cancer models.

MRx0518 has been shown to induce activation of CD8+ T cells and suppress differentiation of Treg cells *in vitro*, and to increase the CD8/Treg cell ratio in murine models of cancer.

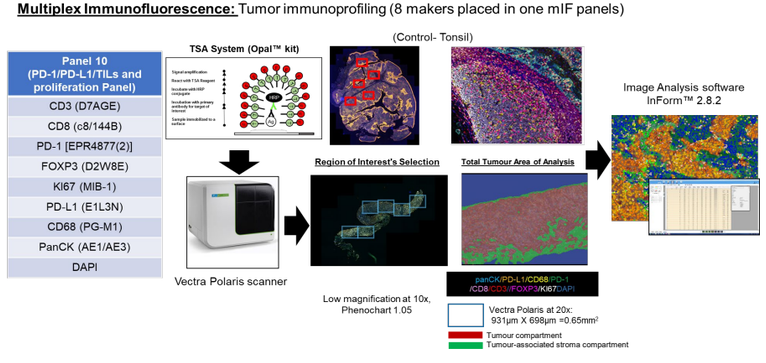
Phase I/II study (NCT03637803), preliminary antitumor activity has been observed in patients refractory to ICIs when MRx0518 is administered in combination with pembrolizumab.

Our aim was to characterize the tumor microenvironment baseline profile in treated patients, using multiplex immunofluorescence and image analysis approaches, and associations with clinical outcomes.

Methods

- Patients received MRx0518 1 capsule PO BID ($1x10^{10}$ to $1x10^{11}$ CFU) and pembrolizumab (200mg Q3W) for up to 2 years or until progression.
- Eligible patients have experienced clinical benefit from a prior ICI before eventually progressing.
- Tumour response was assessed every 9 weeks by RECIST v1.1.
- Responders (R) were classed as patients who experienced complete response (CR), partial response (PR) or stable disease (SD) ≥6 months.
- Baseline FFPE tumour biopsies from 12 patients, (4 responders and 8 non responders) were use for this analysis.

Figure 1. Showing the markers in the panel and the workflow of staining, scanning and analysis.



Results

Table 1. Cell phenotypes distribution in the total tumour (tumour and tumour-associated stroma) area of analysis according to best overall response.

Phenotypes	R (min/max)	PD (min/max)
	Median (cell/mm²)	
Total CK+	907.95 (131.17/5860.41)	1916.46 (17.75/1571.63)
CK+PD-L1+	269.41 (0.70/4676.76)	1703.08 (1.56/1260.22)
CK+KI67+	31.82 (0.70/892.76)	161.52 (0.31/149.77)
Total CD3+	106.88 (5.69/213.80)	45.36 (28.96/289.49)
CD3+CD8+	20.04 (0.00/43.82)	7.28 (2.18/91.32)
CD3+PD-1+	8.58 (0.00/12.52)	2.24 (0.62/62.10)
CD3+PD-L1+	8.58 (0.00/50.71)	0.94 (0.00/104.11)
CD3+KI67+	0.95 (0.00/13.79)	0 (0.31/4.24)
CD3+CD8+KI67+	0.37 (0.00/2.19)	0 (0.00/2.65)
CD3+PD-1+PD-L1+	0.95 (0.00/10.01)	0 (0.00/33.79)
CD3+CD8+PD-1+	0.95 (0.00/7.19)	0.56 (0.00/39.27)
CD3+CD8+PD-L1+	3.81 (0.00/21.59)	0 (0.00/43.83)
CD3+FOXP3+CD8−	12.19 (0.94/37.25)	3.40 (2.49/25.57)
Total CD68+	3.42 (3.91/135.85)	16.83 (0.95/10.05)
CD68+PD-L1+	0.37 (0.00/56.03)	3.35 (0.00/3.65)

Note: CK, pancytokeartin; PR, Partial response; SD, stable disease; PD, Progressive disease; min, minimum; max, maximum.

Figure 2. Representative microphotographs and summary box plots showing CD68+ macrophages cell density in the tumour and tumour-associated stroma of R (A) and PD (B) patients. We observed an increase of CD68+ macrophages in tumour (red arrow) and stroma (green arrows) compartments in PD (B) when compared with R (A).

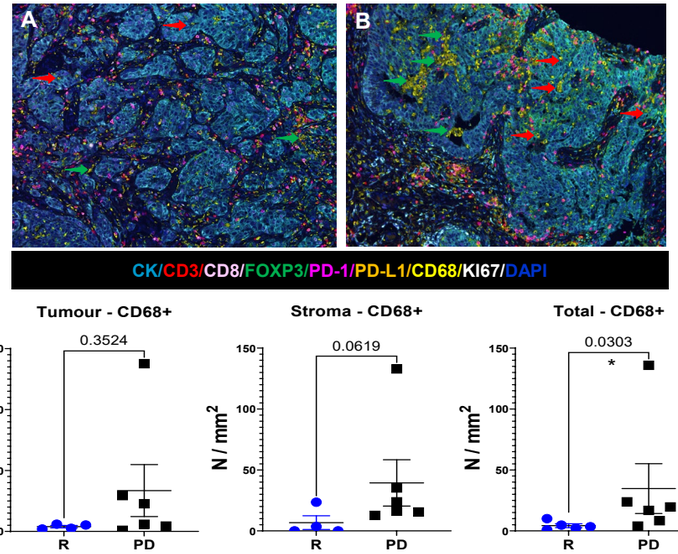
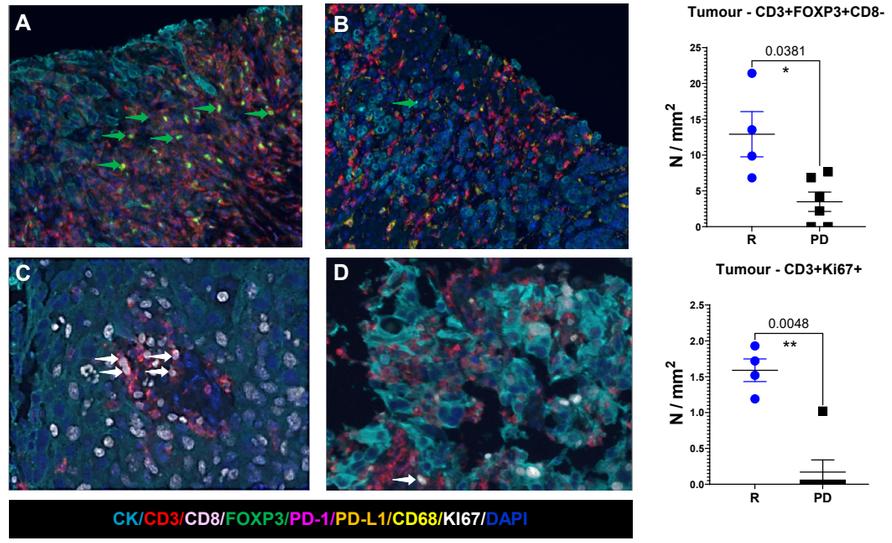


Figure 3. Representative microphotographs and summary box plots showing significant differences in CD3+FOXP3+CD8- regulatory T cells (green arrows) and CD3+KI67+ proliferating T cells (white arrows) in the tumour compartment from R patients (A,C) when compared with PD patients (B,D).



Conclusion

- Understanding mechanisms of resistance to ICIs is key in identifying patients who may respond to subsequent therapies.
- Significantly higher numbers of tumour infiltrating Tregs and proliferating T-cells was observed in responders (R) compared with PD patients.
- Interestingly, higher amounts of macrophages at baseline were observed in PD compared with responder patients.
- With the observations of increased CD8+ T cell activation and reduced induction of Treg cells in the presence of tolerogenic cytokines *in vitro* and in preclinical models, this provides insight for further investigation into the potential for MRx0518 + pembrolizumab to overcome Treg-mediated acquired resistance to ICIs.

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For additional information on clinical studies involving MRx0518 see posters **543P**