Trial in progress: A phase II switch maintenance study of live biotherapeutic MRx0518 and avelumab in patients with unresectable locally advanced or metastatic urothelial carcinoma (UC) who did not progress on first-line platinum-containing chemotherapy.

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Amishi Y Shah[1], Jianjun Gao[1], Arash Rezazadeh Kalebasty[2], Suzanne Cole[3], Rohit Jain[4], Matthew Zibelman[5], Alex Stevenson[6], Gayle Fyvie[6], Nina Gaw[6], Shubham Pant[1].

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]University of California Irvine, Irvine, CA; [3]University of Texas Southwestern Medical Center, Dallas, TX; [4]H Lee Moffitt Cancer Center, Tampa, FL; [5]Fox Chase Cancer Center, Philadelphia, PA;[6]4D pharma plc, Leeds, UK.

Background

The JAVELIN Bladder 100 study (NCT02603432) demonstrated the following results with avelumab as first-line maintenance treatment after completion of chemotherapy at 38 months median follow up:

- Median OS of 23.8 months (95% CI, 19.9 to 28.8) in the avelumab arm vs 15.0 months (95% CI, 13.5 to 18.2) on BSC alone (HR 0.76; 95% CI, 0.631 to 0.915)[1].
- Median PFS of 5.5 months (95% CI, 4.2 to 7.2) vs 2.1 months (95% CI, 1.9 to 3.0) (HR 0.54; 95% CI, 0.457 to 0.645)[1].
- Objective response rate (ORR) of 9.7% (95% CI 6.8-13)[2].

JAVELIN Bladder 100 led to FDA approval of avelumab for maintenance treatment as the standard of care for patients with locally advanced or metastatic UC that have not progressed with first-line platinum-based chemotherapy.

MRx0518

MRx0518 is a novel, human gut microbiome-derived live biotherapeutic consisting of a single, novel strain of *Enterococcus gallinarum*. MRx0518 was selected for development in solid tumor treatment for its strong immunostimulatory activity.

In non-clinical studies, MRx0518 has shown activity as a single agent in multiple syngeneic cancer models, and increases TILs (CD4+ and CD8+ T cells and NK cells) in the tumor microenvironment *in vivo*. *In vitro*, MRx0518 was also able to increase Th1 and Tc1 lymphocyte differentiation.

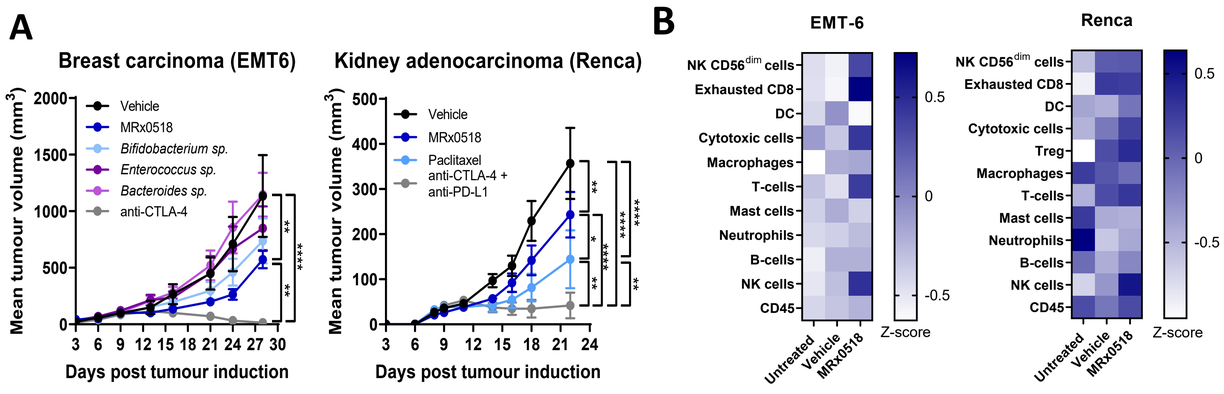


Figure 1. *Inhibition of tumour growth in murine models* ***(A)*** *and quantification of cell subsets utilizing tumour tissues and analysis via NanoString PanCancer IO360™ Gene Expression Profile* ***(B)****. (N=8 mice per group)*

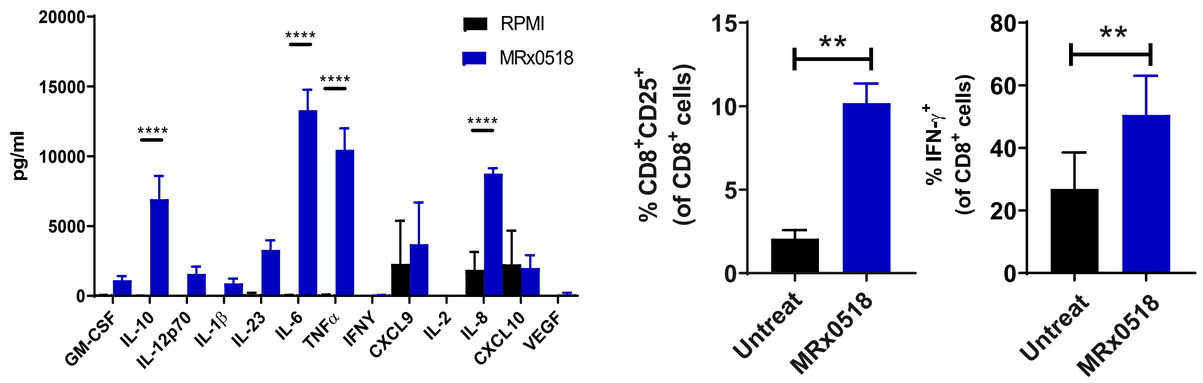


Figure 2. *In vitro immunostimulatory effect inducing the production of pro-inflammatory cytokines and chemokines by MoDCs* ***(A)*** *and the activation (CD25 expression) and IFN-γ production by CD8⁺ T cells* ***(B)****. (N = 10)*

Rationale

Recent data from the JAVELIN Bladder 100 study showed that increased overall survival with avelumab in the setting could be correlated with increased TILs (CD8+ T cells, NK cells and macrophages) at baseline; and increased expression of gene sets related to innate and adaptive immune activation[3,4].

MRx0518 is known to induce changes in TILs, tumor inflammation and immune-related gene expression, justifying a pilot study investigating whether the addition of MRx0518 to avelumab in the maintenance setting of metastatic platinum-treated UC may improve outcomes.

Methods

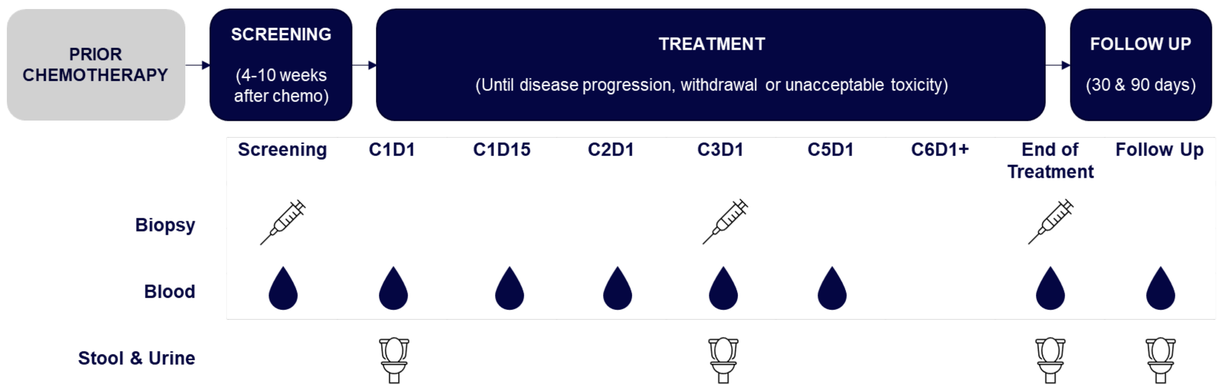
Population

Up to 30 patients will be enrolled across multiple US centers, meeting the following criteria:

- Have unresectable locally advanced or metastatic UC
- Have received 4-6 cycles of platinum-containing chemotherapy
- Have no evidence of disease progression after chemotherapy
- Have at least 1 measurable lesion per RECIST v1.1 after chemotherapy
- ECOG 0-1

Design

The study is a Phase II, single-arm, open-label, switch maintenance design.



Treatment

- 800 mg avelumab IV infusion every 2 weeks in 4 week cycles
- 1 oral capsule ($10x10^{10}$ – $10x10^{11}$ CFU) MRx0518 twice daily

All patients will receive both drugs in combination until disease progression, withdrawal or unacceptable toxicity.

Primary Objectives

- To assess safety of the combination as determined by adverse events
- To assess effect of the combination on PFS (per RECIST v1.1) at 6 months

Secondary Objectives

- PFS, ORR, OS, duration of response, time to response, and disease control rate.

Exploratory Objectives

- Investigation of microbiome and metabolomics in stool and urine
- Investigation of immunological changes in tumor and blood through mandatory, longitudinal sample collections
- Investigation of potentially predictive markers e.g. PD-L1, immune gene signature, CD8, tumor mutational burden

Study Status

The study is open to enrolment, pending first patient dosing.

For further information:
www.clinicaltrials.gov ref. NCT05107427
Contact clinicaltrials@4dpharmaplc.com

Avelumab is provided by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945), as part of an alliance between the healthcare business of Merck KGaA, Darmstadt, Germany and Pfizer.

[1]J Clin Oncol 40, 2022 (suppl 6; abstr 487); [2]Powles, T., et al. (2020) N Engl J Med 383:1218-1230; [3] Ayers M, et al. J Clin Invest. 2017;127:2930–40; [4] Powles, T., et al. (2021) Nat Med 27:2200–2211