Background: Since standard induction chemotherapy for mCRC is often completely or partially discontinued until first progression in patients responding to 1st-line treatment, maintenance phase opens a window of opportunity to investigate the potential contribution of new drugs. MGN1703 is a synthetic DNA-based immunomodulator acting as TLR-9 agonist which has shown preclinical activity in mCRC and a good safety profile in patients with metastatic solid tumors in a Phase 1 trial. The IMPACT trial was conducted to assess clinical efficacy, safety, and immunological effects of MGN1703 as maintenance therapy vs. placebo.

Methods: IMPACT was an international, multicenter, randomized (2:1) double-blind placebo-controlled phase 2 trial in patients with mCRC, who achieved disease control (CR, PR, SD) after 4.5 to 6 months of 1st-line induction chemotherapy with FOLFOX/XELOX or FOLFIRI +/- bevacizumab. Due to recruitment problems the trial was prematurely closed in May 2012 after randomization of 59 out of 129 planned patients (43 received MGN1703, 16 placebo). We report here the results of the final analysis of the trial.

Results: After a median follow-up of 17.3 months (CI 95% 13.8-21.6) the HR for the primary endpoint PFS on maintenance was 0.56 in favor of MGN1703 (CI 95% 0.29-1.08; p = 0.070). The secondary endpoint PFS calculated from beginning of induction chemotherapy had HR of 0.49 (CI 95%: 0.26-0.94, p = 0.030). Cox regression analysis identified patients with clinical CR or PR to prior induction chemotherapy or with normal CEA values as more likely to benefit with MGN1703 treatment. While on maintenance, three objective responses were observed in the MGN1703 arm and one in the placebo arm. Overall 4 patients are still disease free and receiving MGN1703 (treatment range +11 to +25 months). Survival data are still immature as only 35% of the MGN1703 treated patients died (50% of placebo). The preliminary HR for OS is 0.6 (CI 95%: 0.3-1.5 p = 0.29). Treatment was well tolerated: 32.6% vs. 18.8% of patients (MGN1703 vs. placebo) had any drug-related adverse events (AE) and only 1 patient per arm had a grade 3 drug-related AE (MGN1703: sensory polyneuropathy, placebo: papular exanthema). A pre-planned analysis of immune cell populations by flow cytometry showed a possible predictive effect of activated NKT (CD3+/CD56+/CD69+) cells on treatment with MGN1703 (HR 0.34; CI 95%: 0.14-0.82, p = 0.008). As a sign of biological activity, a significant increase of CD14+CD169+ monocytes was observed in all but one of MGN1703 treated patients while absent in all placebo patients.

Conclusions: MGN1703 compared to placebo showed a prolongation of PFS from start of induction as well as start of maintenance therapy, including 4 patients with sustained PFS still on treatment. Pre-treatment characteristics and immunological biomarkers may prove useful to identify patients who might benefit most from MGN1703 maintenance therapy.