Maintenance treatment with immunomodulator MGN1703 following induction with standard 1st line therapy prolongs progression-free survival in patients with metastatic colorectal carcinoma (mCRC): results of the phase II/III IMPACT trial.

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for the IMPACT Study Team

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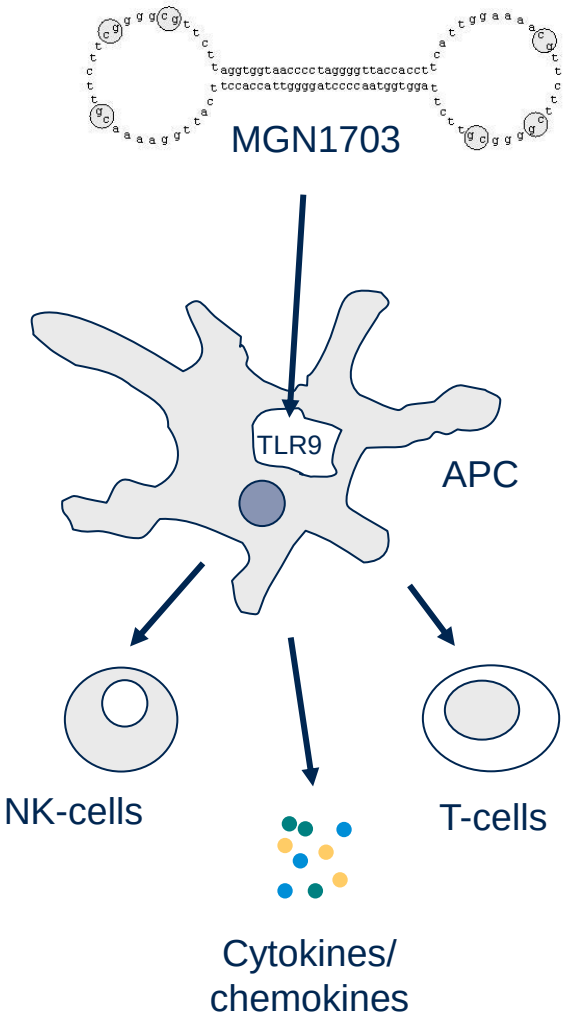
MGN1703: A DNA Immunomodulator

- Non-coding DNA molecule with CG-motifs
- Linear, double-stranded, covalently-closed, dumbbell-shaped immunomodulator
- TLR9 agonist
- Broad activation of innate & adaptive immune system
  - Antigen presenting cells (pDCs, B-cells)
  - Subsequent activation of various pathways (like CTL, NK-cells, ADCC)
- Phase 1 Study with metastatic solid tumor patients (i.e. mCRC, metastatic lung cancer)
  - Good safety profile and first signs of a potential clinical effect



Abbreviations - TLR-9: toll-like receptor 9; APC: antigen presenting cells; pDC: plasmacytoid dendritic cells; NK-Cells: natural killer cells; CTL: cytotoxic T-lymphocytes; ADCC: antibody-dependent cell-mediated cytotoxicity;

AIM AND OBJECTIVES

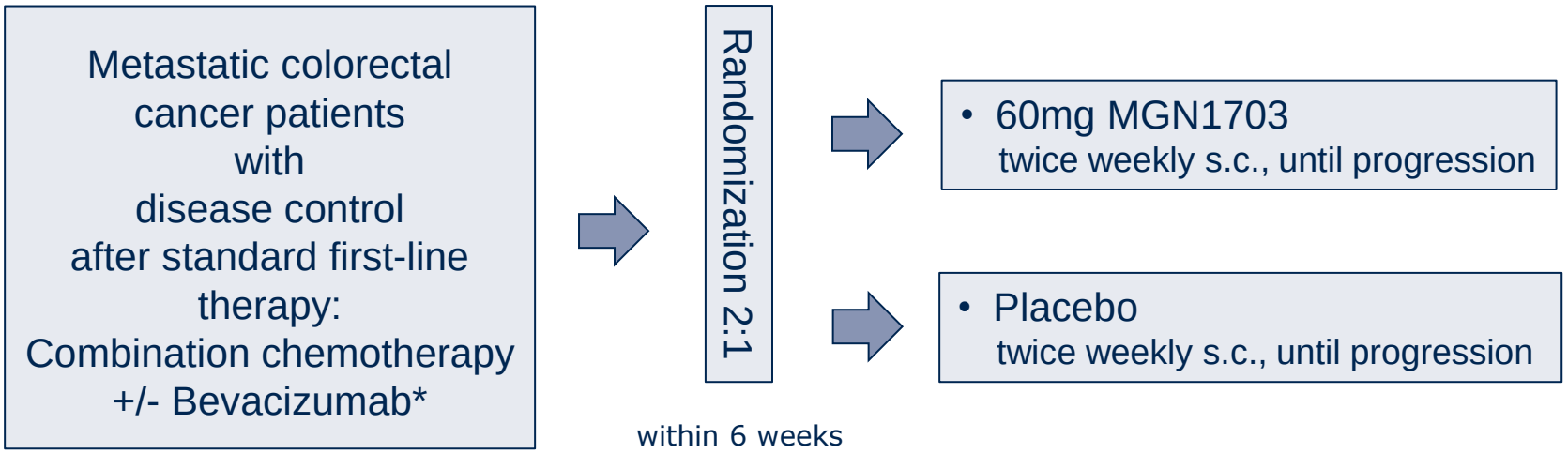
Study rationale - based on mode of action

- MGN1703 activates all components of innate / adaptive immune system
- Requires release of tumor-associated antigens by previous chemotherapy
- Post-therapy interval: recovery of the immune system is common
  - ➔ Evaluation as a post-chemotherapy maintenance treatment

Study aim

- Evaluation of MGN1703 as post-induction maintenance therapy

STUDY DESIGN



* at investigators discretion

Primary endpoint:	• PFS from randomization
Secondary endpoints:	• PFS from induction therapy • Overall survival, Overall response rates • Safety (CTCAE v4.0) • Pharmacodynamics • Biomarker (incl. immunologic response) • QoL (QLQ-C30 and -CR29)

KEY INCLUSION CRITERIA

- Patients older than 18 years of age
- Histologically confirmed metastatic colorectal carcinoma
- First-line therapy (induction treatment):
  - FOLFOX / FOLFIRI / XELOX + /- Bevacizumab
  - treatment duration between 4.5 and 6 months
  - Oxaliplatin / Irinotecan: at least 3 months
- Disease control after first-line therapy
- No history of autoimmune disease or immune deficiency

STATISTICS / GROUP DEFINITION

Sample size calculation

- Double blind, placebo controlled superiority study
- Power of 80%, 2-sided test, alpha = 0.05
- Assumption: Increase of median maintenance PFS from 3 months (placebo) to 6 months (MGN1703) → at 6 months, HR would be 0.5

  → 129 patients required (with 2:1 randomization)

Cohorts for analysis

- Intent-to-treat (ITT) population

  All patients who have been randomized
- "Good risk" sub-group (GRSG)[1,2] population

  Eligible patients with 2 out of 3 factors:

  CEA <30 x ULN, GGT <2 x ULN, AP <2 x ULN

[1]Tournigand et al., J. Clin. Oncol. 22: 229-37, 2004; [2]Chibaudel et al., Ann. Oncol. 20: 1383–1386, 2009

RANDOMIZATION STOP

- Sponsor-driven recruitment stop following an interim analysis after **55 patients**

  (in accordance with authorities and ethics committees):

  - Slow recruitment of patients

    (could not have been accelerated, despite of several initiatives of the sponsor).
  - Subgroup of patients seemed to benefit from the study therapy

    (verum or placebo) and had no signs of tumor progression.

- Recruitment was stopped before unblinding for the primary analysis.
- Data was unblinded by the data management

  (investigators and patients remained blinded).
- Analysis of all 59 patients is ongoing (including those randomized after the cut-off).

PRIMARY ANALYSIS

- Accrual period: **22** months (June 2010 – data cut off April 2012)
- 12 active sites in Germany (33 patients), 6 sites in Austria (17 patients), 3 sites in Russia (4 patients), 1 site in France (1 patient)

Population	MGN1703	Placebo	All
Intent-to-treat (ITT)	40	15	55
"Good risk" sub-group (GRSG)*	32	14	46

Exclusion of "bad risk" and not eligible pts (i.e. secondary tumor, second-line therapy, etc.)

- Median follow-up time (from cut-off) [95% CI]:
  - MGN1703 8.8 [5.7;11.1] months
  - Placebo 9.7 [3.6;10.2] months

PATIENT DEMOGRAPHICS

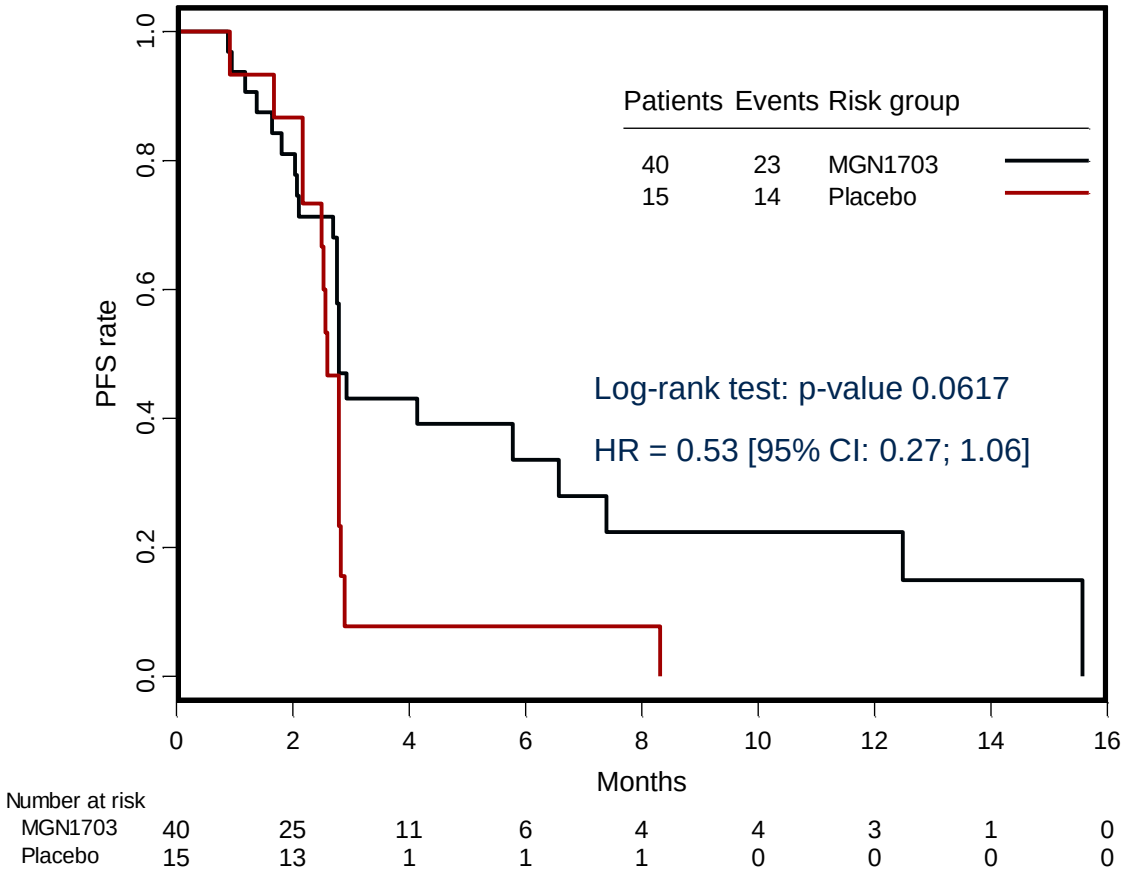
Characteristics [% patients]	MGN1703 N=40	Placebo N=15
Age, median	62.3	64.3
Gender, male / female	50 / 50	47 / 53
PS, 0 / 1	70 / 30	60 / 40
Colon / rectum / both	57.5 / 30 / 12.5	60 / 33.3 / 6.7
Resection / no resection primary	77.5 / 22.5	66.7 / 33.3
Resection / no resection metastases	15 / 85	13.3 / 86.7
Neo- / Adjuvant chemotherapy	7.5 / 17.5	13.3 / 33.3
Lung / liver / peritoneal carcinomatosis	40 / 80 / 17.5	46.7 / 86.7 / 20
LDH, N / > ULN	65 / 35	93.4 / 6.6
AP, N / > ULN	60 / 40	80 / 20
GGT, N / > ULN	42.5 / 57.5	50 / 50
CEA, N / > ULN	40 / 60	46.5 / 53.3
PLT, Albumin, Lymphocytes	similar distribution between both groups	

PRETREATMENT CHARACTERISTICS

Characteristics [% patients]		MGN1703 N=40	Placebo N=15
Induction therapy duration	mean [months]	5.2	5.5
	median [months]	5.4	5.3
	quart. [25%;75%]	[4.6; 5.8]	[4.5; 6.2]
Regimen (in %):			
FOLFOX / XELOX + bevacizumab		37.5	46.7
FOLFIRI / XELIRI + bevacizumab		47.5	46.7
FOLFOX / XELOX alone		15.0	6.7
Best response (according to investigator)			
CR / PR		72%	93%
SD		28%	7%

PRIMARY ENDPOINT: PFS OF MAINTENANCE

Intent-to-treat (ITT) population

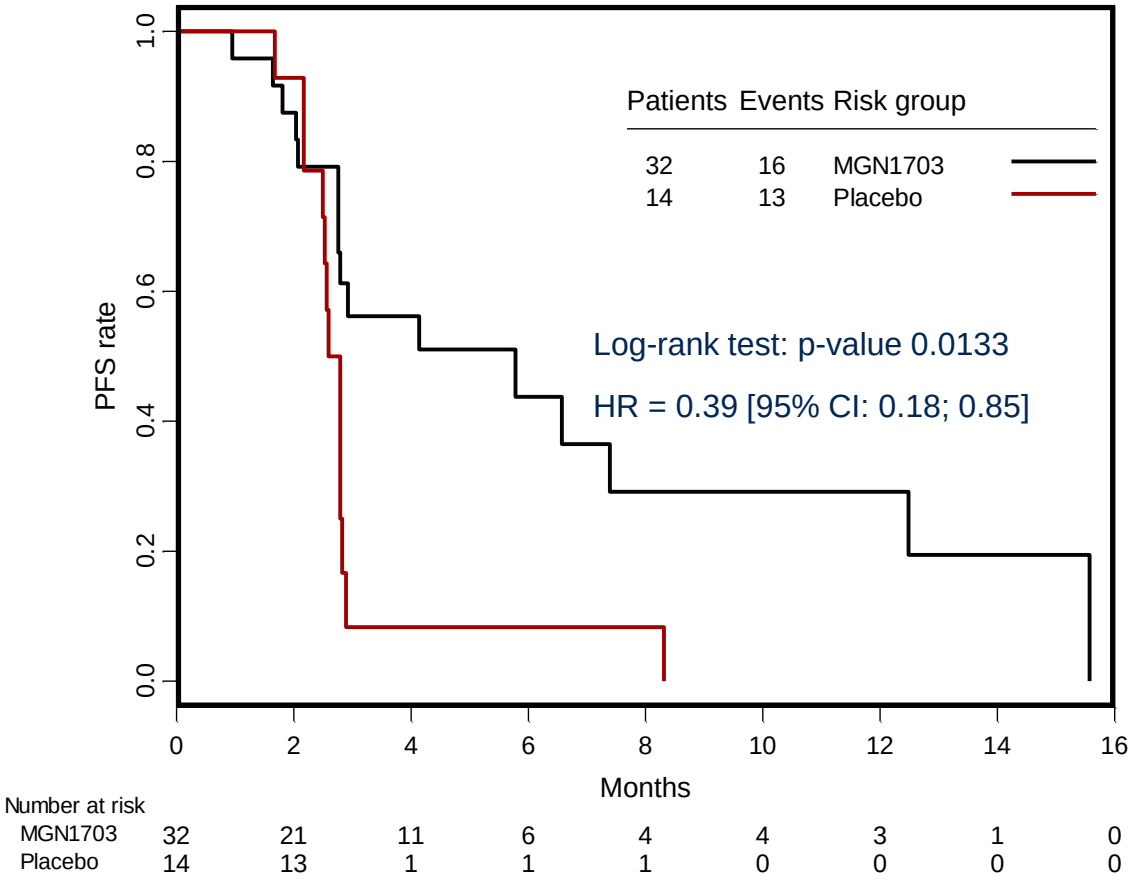


	Months [95% CI]	
PFS	**MGN1703**	**Placebo**
Median PFS	**2.8** [2.8; 6.6]	**2.6** [2.5; 2.8]
25% quartile	2.1 [1.6; 2.8]	2.2 [1.7; 2.6]
75% quartile	7.4 [2.9;15.6]	2.8 [2.6; 2.9]

Abbreviations: HR, Hazard ratio; CI, Confidence interval

PFS OF MAINTENANCE: “GOOD RISK” SUBGROUP

GRSG

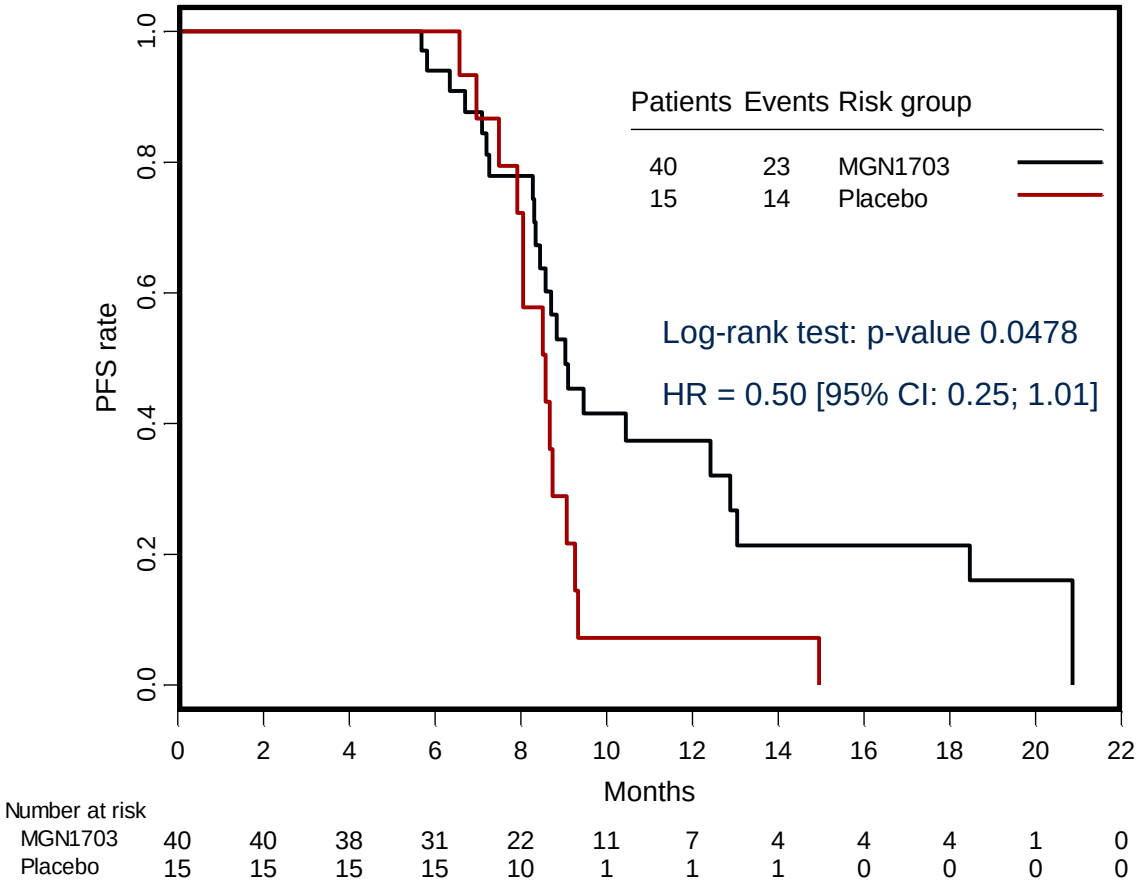


	Months [95% CI]	
PFS	**MGN1703**	**Placebo**
Median PFS	**5.8** [2.8; 12.5]	**2.7** [2.5; 2.8]
25% quartile	2.8 [1.8; 4.1]	2.5 [2.2; 2.8]
75% quartile	12.5 [5.8;15.6]	2.8 [2.6; 2.9]

Abbreviations: HR, Hazard ratio; CI, Confidence interval

PFS FROM INDUCTION START

Intent-to-treat (ITT) population



	Months [95% CI]	
PFS	**MGN1703**	**Placebo**
Median PFS	**9.0** [9.2; 13.1]	**8.6** [8.1; 9.4]
25% quartile	8.3 [7.1; 8.7]	7.9 [7.0; 8.6]
75% quartile	13.0 [9.5; 20.9]	9.1 [8.5; 9.3]

Abbreviations: HR, Hazard ratio; CI, Confidence interval

SAFETY: SUMMARY OF AE

ITT population

	MGN1703	Placebo
No. of patients	40	15
No. of pts with *any* AE	27 (68%)	6 (40%)
No. of pts with drug-related AE	13 (33%)	5 (33%)
No. of AE	110	44
No. of drug-related AE	37 (34%)	18 (41%)
No. of patients with AE with CTC Grade 3 or 4	7 (18%)	2 (13%)
No. of patients with drug-related AE with CTC Grade 3 or 4	1 (3%)	2 (13%)

RESULTS – ADVERSE EVENTS (1/2)

Grade 3 & 4 Toxicities

Event	MGN1703, n=40		Placebo, n=15	
Grade / No. of events (patients)	3	4	3	4
Hypertension	4 (2)	---	---	---
Hypertension worsening	1 (1)	---	----	---
Ileus	1 (1)	2 (2)	---	---
Paralytic ileus	1 (1)	---	---	---
Sepsis	---	1 (1)	---	---
Pain	---	---	1 (1)	---
Sensory polyneuropathy	1 (1)	---	---	---
Papular exanthema	---	---	1 (1)	---
Nausea / Vomiting	1 (1)	---	---	---

RESULTS – ADVERSE EVENTS (2/2)

Adverse events - expected due to the mode of action (examples)

Adverse event	MGN1703, n=40				Placebo, n=15			
Grade / No. of events (patients)	1	2	3	4	1	2	3	4
Fever	5 (3)	1 (1)	---	---	1 (1)	---	---	---
Myalgia	1 (1)	---	---	---	1 (1)	---	---	---
Chills	1 (1)	---	---	---	---	---	---	---
Fatigue	1 (1)	---	---	---	---	---	---	---
Rash	1 (1)	1 (1)	---	---	---	---	---	---
Injection site swelling	1 (1)	---	---	---	---	---	---	---
Injection site urticaria	1 (1)	---	---	---	---	---	---	---
Injection site pruritus	2 (2)	1 (1)	---	---	---	---	---	---

SUMMARY AND CONCLUSIONS

- First randomized clinical trial that prospectively investigated the impact of an immunomodulator as maintenance therapy in mCRC.
- With the limitations of the early termination and therefore limited sample size, the study demonstrates that maintenance therapy with MGN1703 after standard induction chemotherapy is associated with a trend towards improved progression-free survival and is accompanied by low toxicity.
- Findings indicate a potential new approach in management of mCRC patients.
- Confirmatory data are needed , also in comparison to other maintenance strategies. Therefore, a further clinical study is currently in planning.

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