ESMO SYMPOSIUM ON IMMUNO-ONCOLOGY

Long-term maintenance therapy with the TLR-9 agonist MGN1703 in a subgroup of metastatic colorectal cancer patients from the IMPACT study

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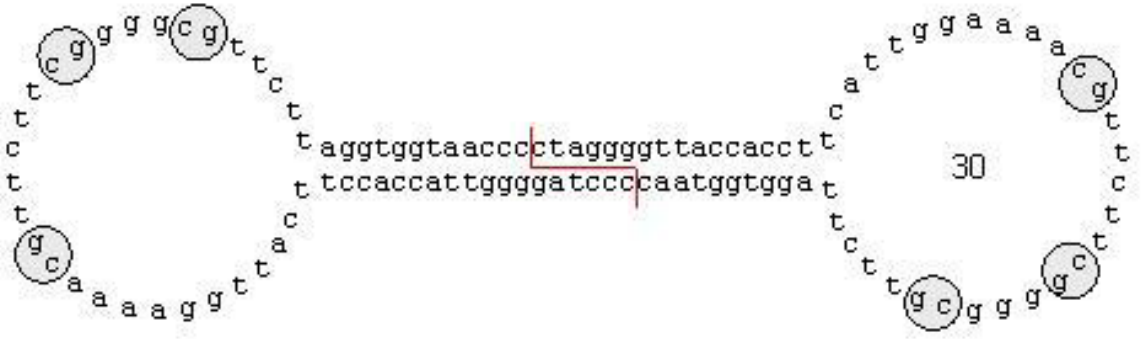
Disclosure Slide

- No Conflicts of Interest to declare

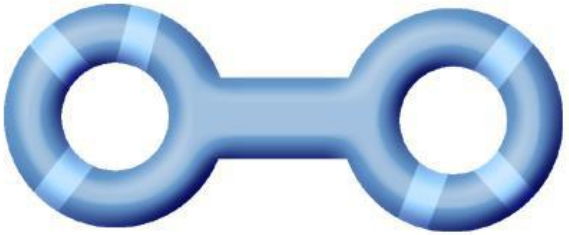
dSLIM® family: double Stem Loop ImmunoModulator



MGN1703

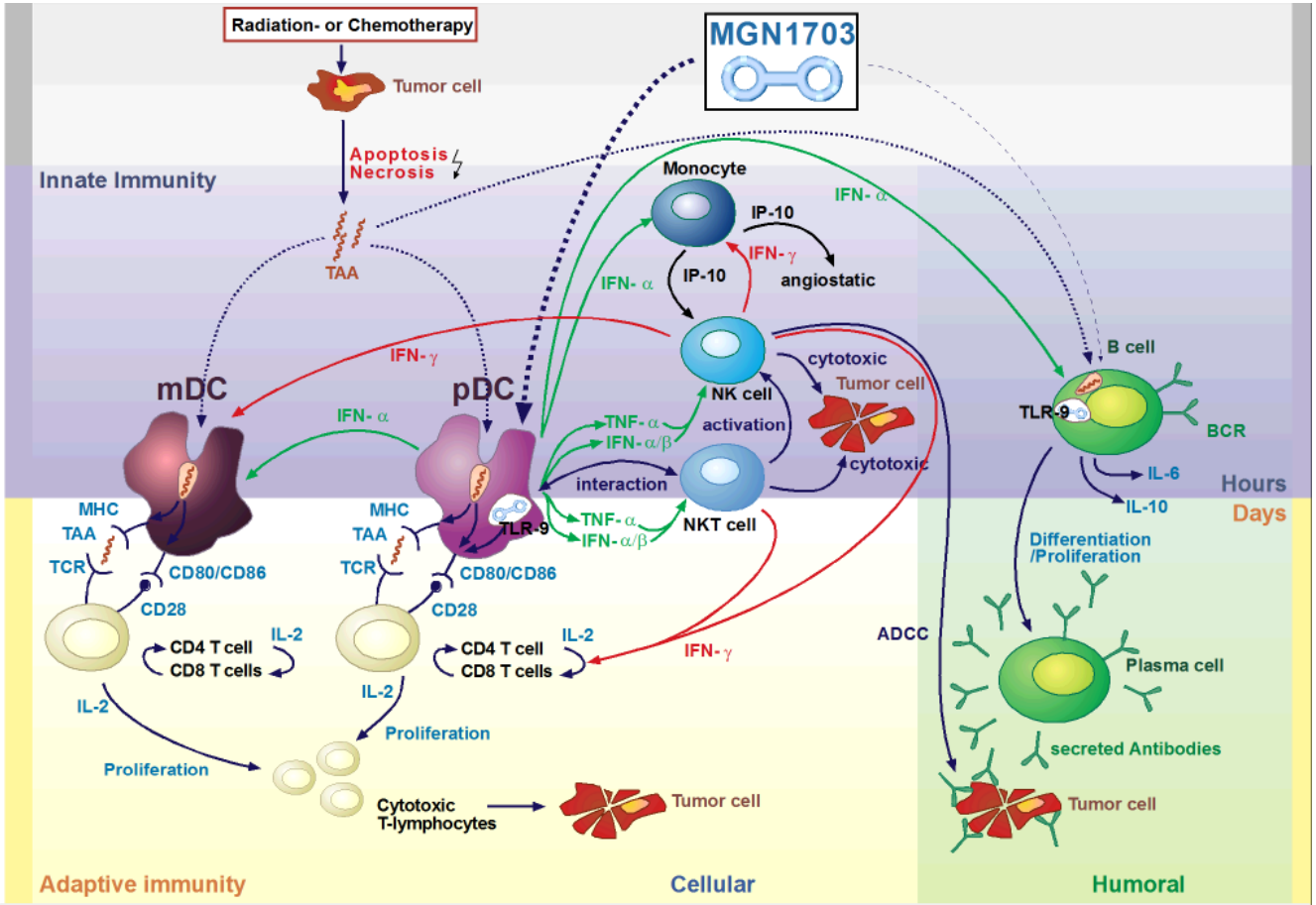
Properties

- no open ends - protection against degradation
- contains only natural DNA components, no chemical modifications
- high stability
- broad activation of the immune system
- proof of efficacy in phase II
- only minimal side effects
- no dose-limiting toxicity
- high dosing over long periods of time



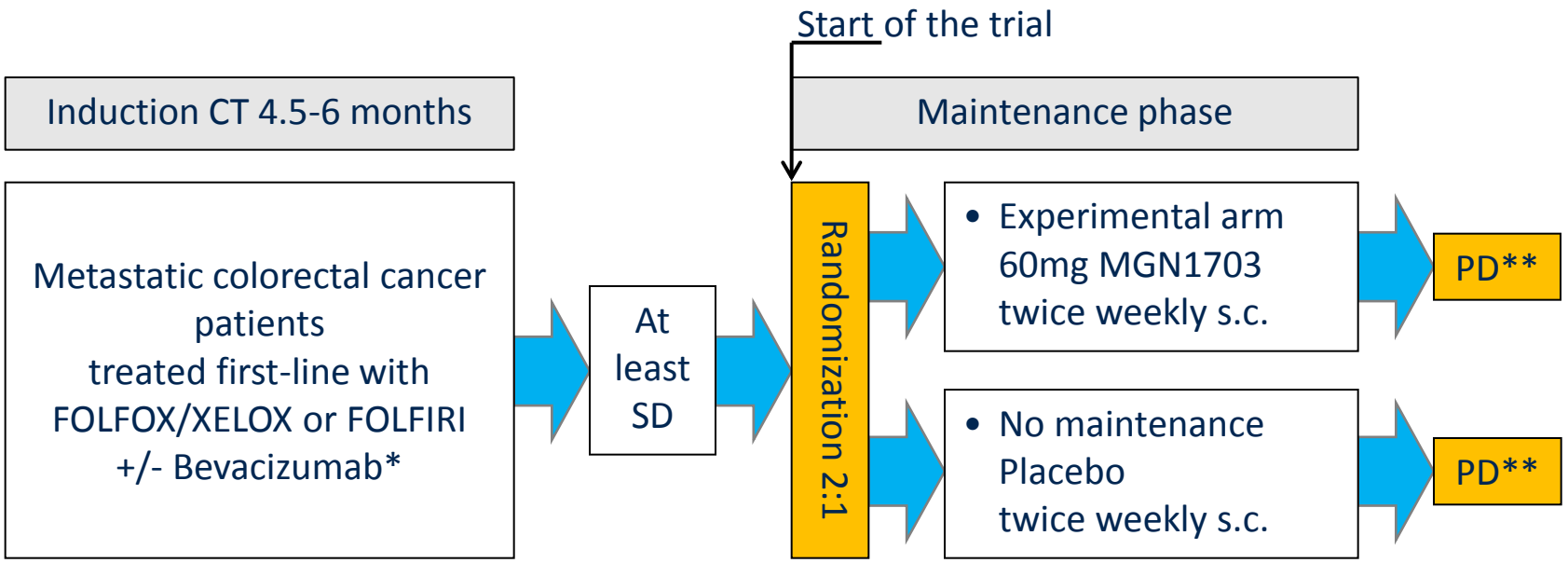
MGN1703: Established Biological Mode of Action

TLR-9 agonist with broad activation of innate and adaptive immune defenses



TAA: tumor associated antigens | pDC: plasmacytoid dendritic cells | mDC: myeloid dendritic cells | NK cell: natural killer cell | NKT cell: natural killer T cell
ADCC: antibody-dependent cell-mediated cytotoxicity | MHC: Major histocompatibility complex
TLR-9: Toll-like receptor 9 | TCR: T cell receptor | BCR: B cell receptor

IMPACT Study Design



** at investigators discretion*

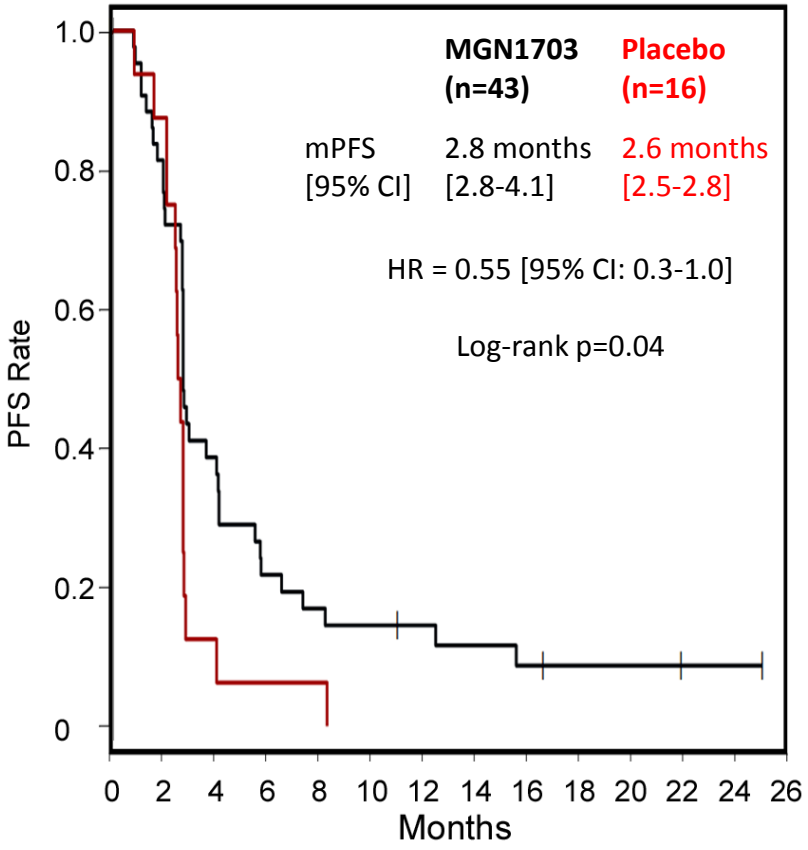
Primary endpoint:
- PFS from randomization (HR 0.50, 129 patients)

Secondary endpoints:
- PFS from start of induction therapy
- Overall survival, OS from start of induction therapy
- Overall response rates
- Safety (CTCAE v4.0)
- Biomarkers (incl. immunological response)
- QoL (QLQ-C30 and -CR29)

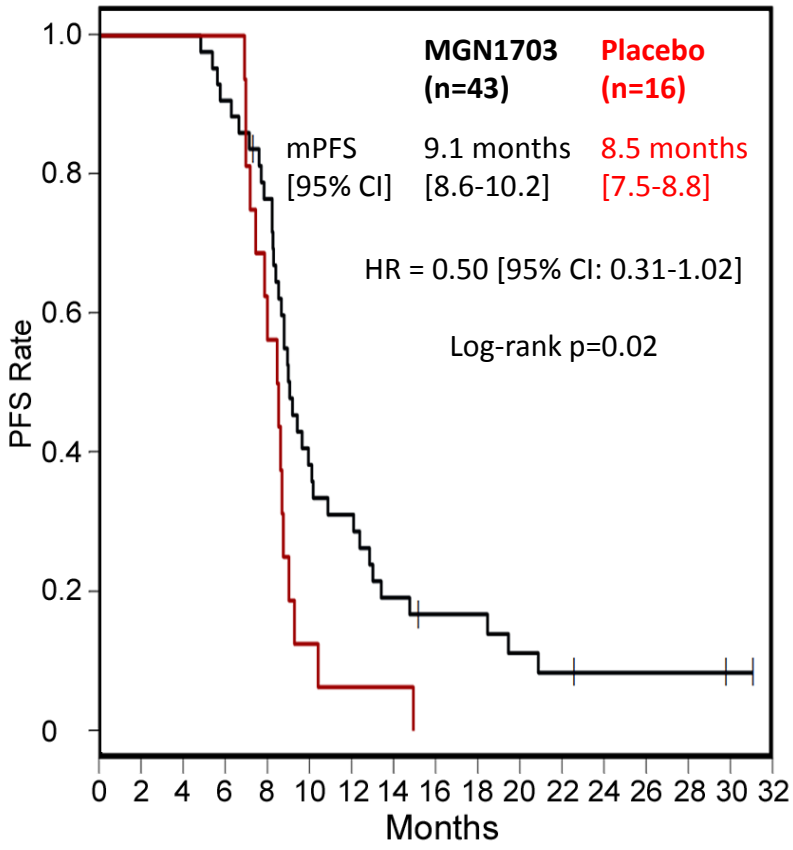
Study finally was stopped due to slow recruitment in May 2012 after 59 patients were enrolled

Progression Free Survival (Local Assessment, LA)

Primary Endpoint: PFS from start of maintenance



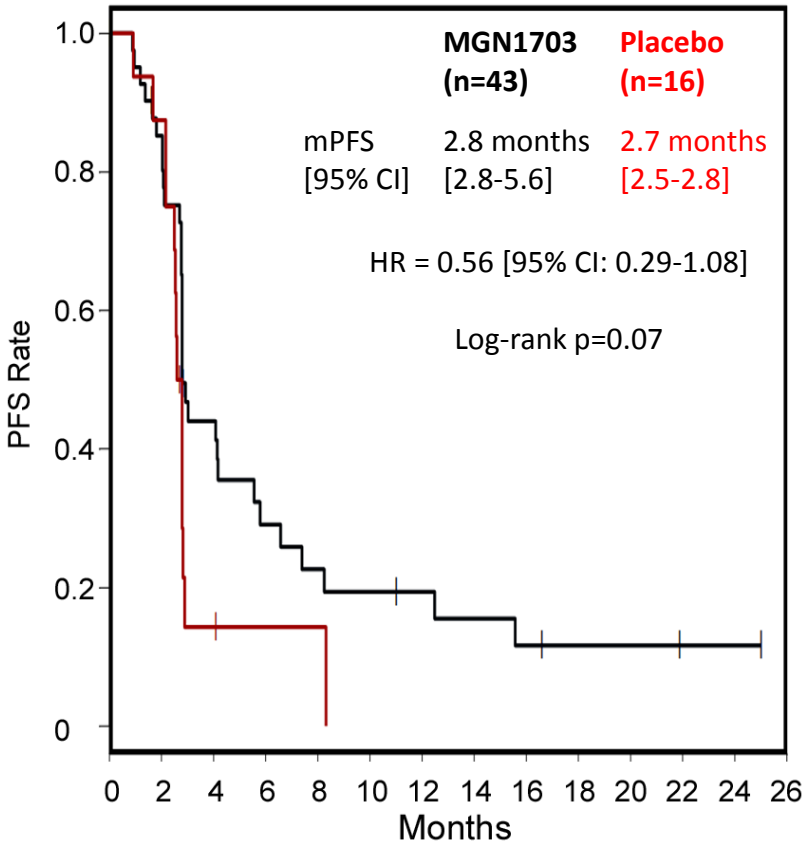
Secondary Endpoint: PFS from start of induction therapy



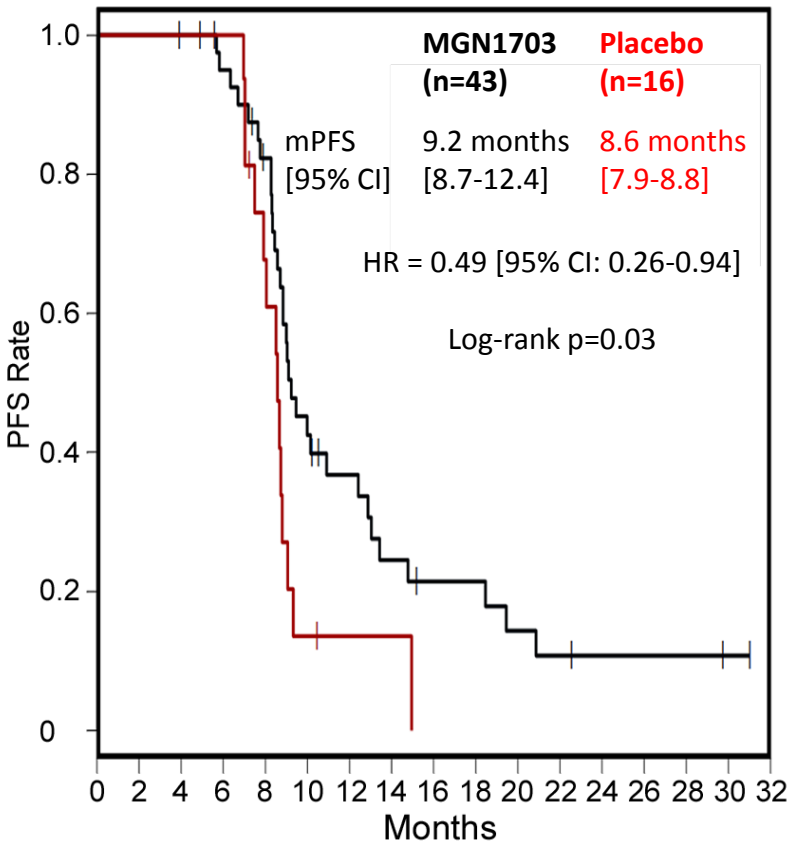
Abbreviations: HR, Hazard ratio; CI, Confidence interval

Progression Free Survival (Independent Radiological Review, IRR)

Primary Endpoint: PFS from start of maintenance



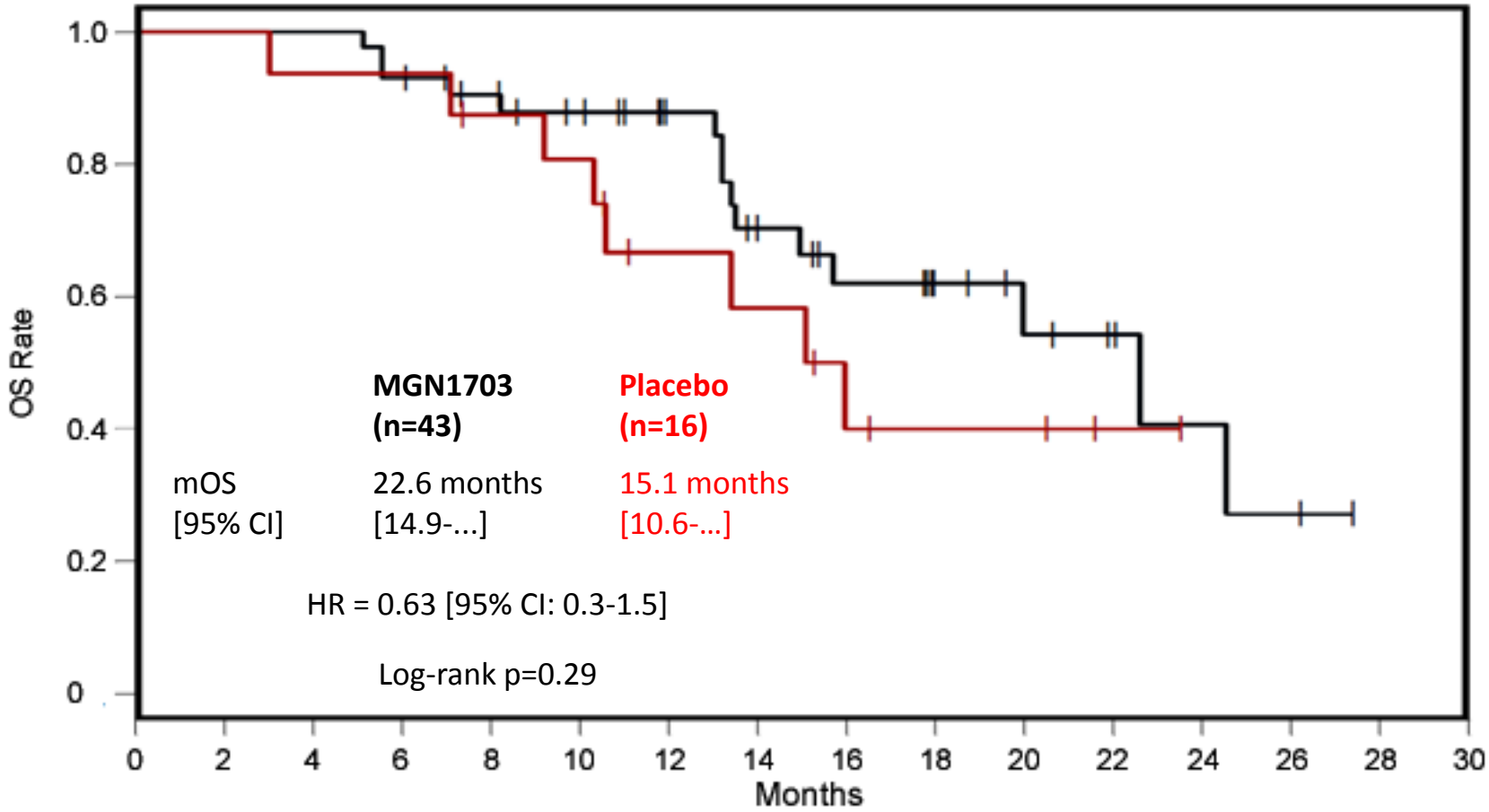
Secondary Endpoint: PFS from start of induction therapy



Abbreviations: HR, Hazard ratio; CI, Confidence interval

Secondary Endpoint: OS from Randomization

Results at final analysis were not mature as more than 50% of patients were censored



Abbreviations: HR, Hazard ratio; CI, Confidence interval

Predictive Pre-Treatment Marker for MGN1703 Benefit

- Exploratory uni- and multivariate Cox regression and ROC analyses on baseline characteristics

Clinical parameter

- Identification of a potentially predictive effect of baseline CEA and objective response to induction chemotherapy (PFS, IRR):
  - Patients with normal CEA (HR of 0.12; p=0.0026)
  - Patients with CR/PR after induction chemotherapy (HR of 0.40; p=0.0094)

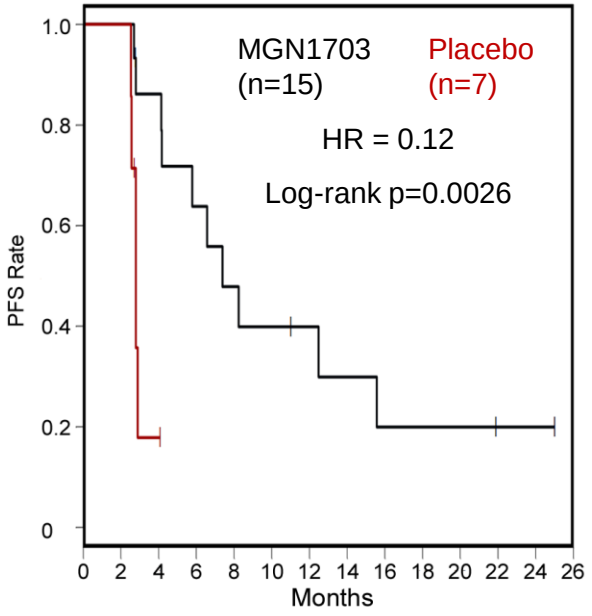
Immunological parameter

- Immune marker analysis confirmed broad activation of innate immune system during MGN1703 treatment
- Identification of potentially predictive value of activated NKT cells at baseline
  - Patients with activated NKT cells (HR of 0.27; p=0.0073) using a cut-off value for activated NKT cells of 3.08%

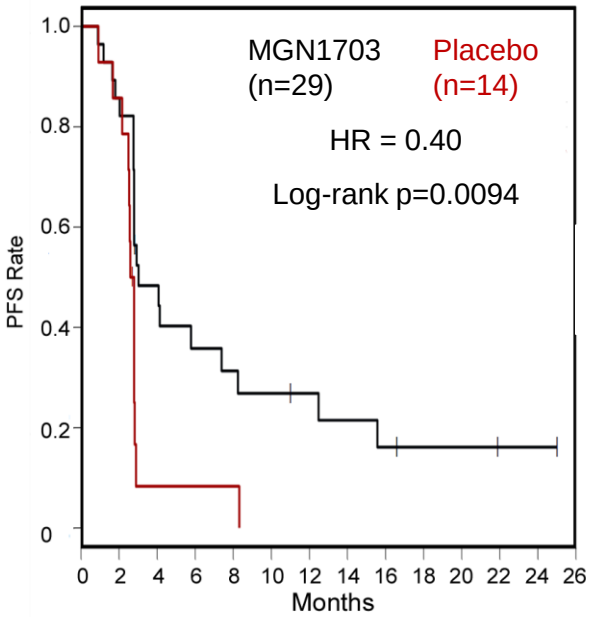
Predictive Marker – Baseline CEA Level, Objective Response, aktivated NKT Cells

- Potential predictive factors for PFS on maintenance from treatment start according to IRR

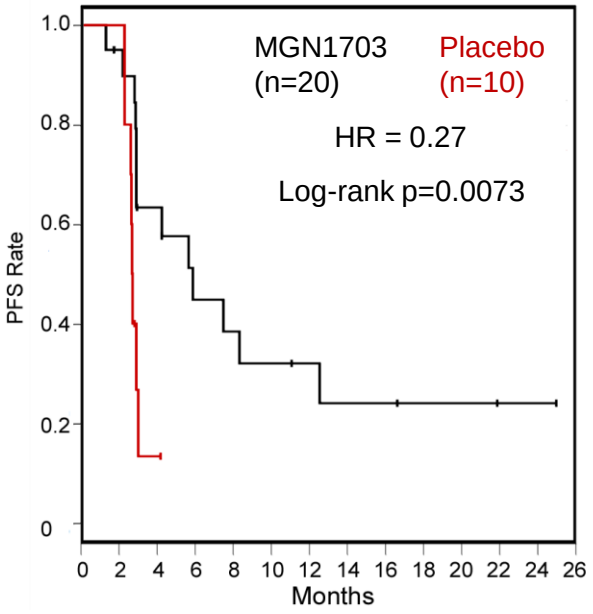
Patients with normal CEA



Patients with CR/PR after induction therapy



Patients above cut-off for activated NKT cells



Abbreviations: HR, Hazard ratio; CI, Confidence interval; IRR, Independent Radiological Review

Response Under Maintenance – Status at Study Closure

	MGN1703	Placebo
Response n (%)	3 (7%)	1 (6%)
Time to response	3, 9, 9 months	3 months
Duration	All ongoing at study closure (11, 22, 26 months)	6 months

- Mean duration of maintenance therapy was 5.3 months for MGN1703 and 3.5 months for placebo at study closure.
- In 2 of 3 responders from the MGN1703 arm the response was observed as late as 9 months after treatment start – making a carry-over effect from induction chemotherapy unlikely.
- 4 patients in the MGN1703 arm were still free of progressive disease at time of study closure and continued therapy in an extension protocol.
- These include the 3 patients with response and 1 patient who was randomized being already in CR after induction chemotherapy.

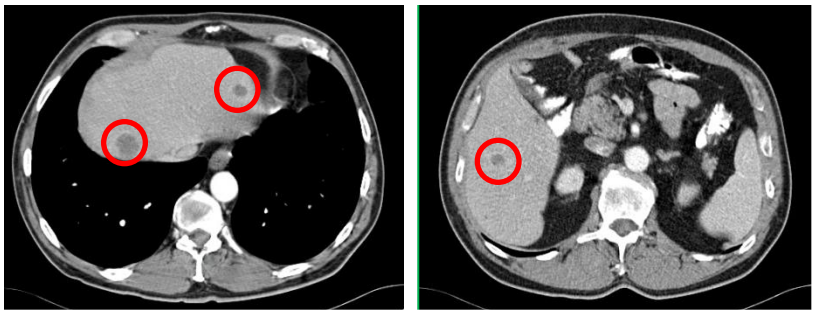
Long-term Follow Up of Selected Patients in the MGN1703 arm (Sept.2014)

Long-term response of patients treated with MGN1703 in an extension phase 2 protocol: Patient characteristics and clinical parameters.

Patient no.	Age	Sex	Induction therapy	CEA serum level *	aNKT cells [%] *	Objective response [RECIST] *	Date of randomi-zation **	Time of response to MGN1703	Duration of response to MGN1703	Time on MGN1703
028	56	m	6.5m FOLFOX +Bv	1.7 µg/L	9.3	PR	27.04.11	new PR after 3m	+38m	+41m
049	54	m	5.0m FOLFIRI +Bv	3,0 µg/L	10.8	PR	16.12.10	new PR after 9m	+36m	+45m
057	69	f	5.5m FOLFIRI +Bv	8.1 ng/mL	13.7	CR	31.08.11	ongoing CR	-	+37m
094	69	m	4.0m FOLFIRI +Bv	2.7 ng/mL	5.0	PR	21.03.12	new PR after 9m	8m	17m

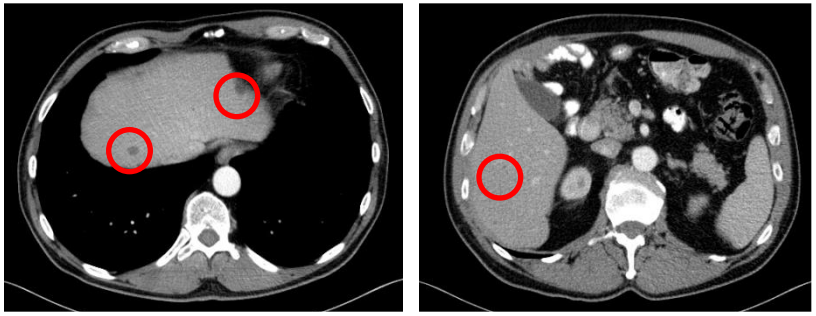
Abbreviations: m = months, PR = partial response, CR = complete response; *after induction chemotherapy; **first injection

Long-term Follow Up: Patient 049



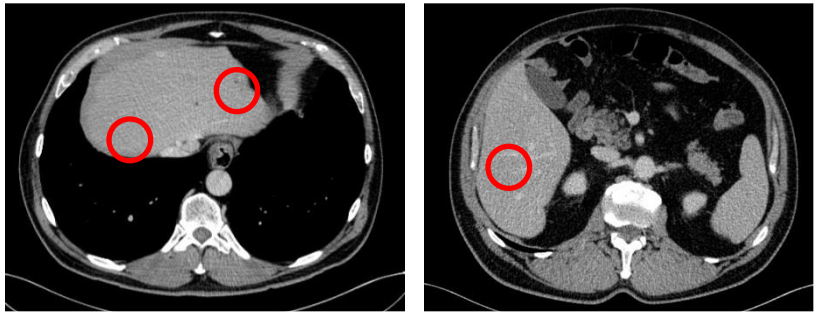
At initial diagnosis (04/2010)

- Colon carcinoma with multiple liver metastases
- Reference lesions: S8 (26 x 23 mm), S2 (13 x 10 mm), S5/6 (15 x 10 mm)



After induction chemotherapy (12/2010)

- 9 courses of FOLFIRI + Bevacizumab
- Response to induction CT: PR*



During MGN1703 maintenance (since 12/2010)

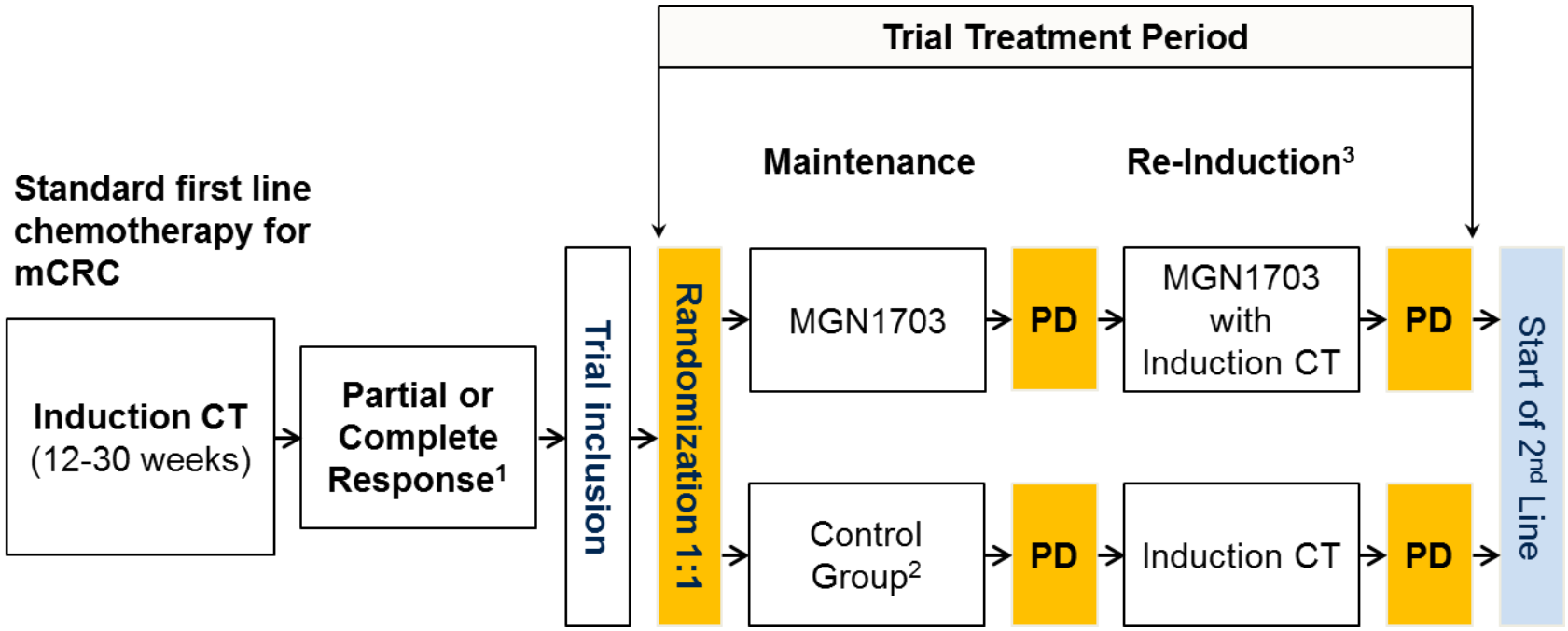
- New PR* after 9 months
- Still ongoing (36 months)
- Good medical condition, mild lokal skin reactions, no further toxicities

*PR confirmed by 2 independent radiologists

Summary and Conclusions

- IMPACT study provided first evidence of the efficacy of TLR-9 agonist MGN1703 as maintenance treatment after 1st line induction CT in mCRC patients.
- Primary endpoint "PFS on maintenance" was met and treatment was well tolerated with no auto-immune toxicity observed.
- Three independently reviewed RECIST responses to MGN1703 maintenance therapy were observed, two occurring as late as 9 months after randomization.
- As of September 2014 three patients are still receiving MGN1703 treatment without PD in excess of three years (37-45 months); two objective responses are ongoing over 36 months.
- Potential predictive factors have been identified and are employed to target the patients most likely to benefit from MGN1703 in the confirmatory IMPALA study (started recruitment in September 2014).

Design of the Phase 3 IMPALA Study with MGN1703



[1] Responses are assessed locally according to RECIST 1.1 criteria.

[2] Control Group may either continue induction CT, halt some of the agents or interrupt all therapies.

[3] Re-introduction of prior therapy mandated whenever feasible in all patients of the MGN1703 arm and in those of the control group who reduced treatment intensity during maintenance.