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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• No Conflicts of Interest to declare
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
IMPACT Study Design

Induction CT 4.5-6 months

Metastatic colorectal cancer patients treated first-line with FOLFOX/XELOX or FOLFIRI +/- Bevacizumab*

* at investigators discretion

Primary endpoint:
Secondary endpoints:

- PFS from randomization (HR 0.50, 129 patients)
- 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)

Start of the trial

Maintenance phase

Randomization 2:1

At least SD

• Experimental arm 60mg MGN1703 twice weekly s.c.

• No maintenance Placebo twice weekly s.c.

First tumor response assessment after 3 months

PD**

PD**

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

- **MGN1703 (n=43)**
  - mPFS: 2.8 months [95% CI: 2.8-4.1]
  - HR = 0.55 [95% CI: 0.3-1.0]
  - Log-rank p=0.04

- **Placebo (n=16)**
  - mPFS: 2.6 months [2.5-2.8]

**Secondary Endpoint:**
PFS from start of induction therapy

- **MGN1703 (n=43)**
  - mPFS: 9.1 months [8.6-10.2]
  - HR = 0.50 [95% CI: 0.31-1.02]
  - Log-rank p=0.02

- **Placebo (n=16)**
  - mPFS: 8.5 months [7.5-8.8]

**Abbreviations:** HR, Hazard ratio; CI, Confidence interval
**Progression Free Survival**
(Independent Radiological Review, IRR)

**Primary Endpoint:**
PFS from start of maintenance

- **MGN1703** (n=43)
  - mPFS: 2.8 months [95% CI: 2.8-5.6]
  - HR = 0.56 [95% CI: 0.29-1.08]
  - Log-rank p=0.07

- **Placebo** (n=16)
  - mPFS: 2.7 months [95% CI: 2.5-2.8]

**Secondary Endpoint:**
PFS from start of induction therapy

- **MGN1703** (n=43)
  - mPFS: 9.2 months [95% CI: 8.7-12.4]
  - HR = 0.49 [95% CI: 0.26-0.94]
  - Log-rank p=0.03

- **Placebo** (n=16)
  - mPFS: 8.6 months [95% CI: 7.9-8.8]

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

- **MGN1703** (n=43)
  - mOS [95% CI]: 22.6 months [14.9-...]

- **Placebo** (n=16)
  - mOS [95% CI]: 15.1 months [10.6-...]

- HR = 0.63 [95% CI: 0.3-1.5]
- Log-rank p=0.29

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

- Patients with normal CEA
  - MGN1703 (n=15) Placebo (n=7)
  - HR = 0.12
  - Log-rank p=0.0026

- Patients with CR/PR after induction therapy
  - MGN1703 (n=29) Placebo (n=14)
  - HR = 0.40
  - Log-rank p=0.0094

- Patients above cut-off for activated NKT cells
  - MGN1703 (n=20) Placebo (n=10)
  - HR = 0.27
  - Log-rank p=0.0073

Abbreviations: HR, Hazard ratio; CI, Confidence interval; IRR, Independent Radiological Review
Response Under Maintenance – Status at Study Closure

<table>
<thead>
<tr>
<th></th>
<th>MGN1703</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response n (%)</td>
<td>3 (7%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Time to response</td>
<td>3, 9, 9 months</td>
<td>3 months</td>
</tr>
<tr>
<td>Duration</td>
<td>All ongoing at study closure (11, 22, 26 months)</td>
<td>6 months</td>
</tr>
</tbody>
</table>

- 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.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Sex</th>
<th>Induction therapy</th>
<th>CEA serum level [*]</th>
<th>aNK T cells [%] [*]</th>
<th>Objective response [RECIST]</th>
<th>Date of randomization **</th>
<th>Time of response to MGN1703</th>
<th>Duration of response to MGN1703</th>
<th>Time on MGN1703</th>
</tr>
</thead>
<tbody>
<tr>
<td>028</td>
<td>56</td>
<td>m</td>
<td>6.5m FOLFOX +Bv</td>
<td>1.7 µg/L</td>
<td>9.3</td>
<td>PR</td>
<td>27.04.11</td>
<td>new PR after 3m</td>
<td>+38m</td>
<td>+41m</td>
</tr>
<tr>
<td>049</td>
<td>54</td>
<td>m</td>
<td>5.0m FOLFIRI +Bv</td>
<td>3.0 µg/L</td>
<td>10.8</td>
<td>PR</td>
<td>16.12.10</td>
<td>new PR after 9m</td>
<td>+36m</td>
<td>+45m</td>
</tr>
<tr>
<td>057</td>
<td>69</td>
<td>f</td>
<td>5.5m FOLFIRI +Bv</td>
<td>8.1 ng/mL</td>
<td>13.7</td>
<td>CR</td>
<td>31.08.11</td>
<td>ongoing CR</td>
<td>-</td>
<td>+37m</td>
</tr>
<tr>
<td>094</td>
<td>69</td>
<td>m</td>
<td>4.0m FOLFIRI +Bv</td>
<td>2.7 ng/mL</td>
<td>5.0</td>
<td>PR</td>
<td>21.03.12</td>
<td>new PR after 9m</td>
<td>8m</td>
<td>17m</td>
</tr>
</tbody>
</table>

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 1\textsuperscript{st} 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).
Responses are assessed locally according to RECIST 1.1 criteria.

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

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.