

Safety and Pharmacology of the EpCAM/CD3-bispecific BiTE Antibody MT110 in Patients with Metastatic Colorectal, Gastric or Lung Cancer

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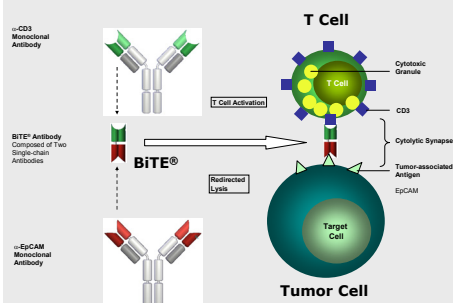
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Background

MT110 is a bispecific T cell engaging antibody construct (BiTE®) binding to epithelial cell adhesion molecule (EpCAM), which is expressed on most solid cancers of epithelial origin, and to CD3 on T cells.

MT110 has shown high anti-tumor activity in various preclinical models including a human colorectal cancer (CRC) xenograft. Clinical proof of concept for BiTE antibodies has been demonstrated with blinatumomab (CD19xCD3) in patients (pts) with B cell lymphoma (Bargou R et al. (2008) Science 321:974).

Figure 1. Generation of MT110 and mode of action



By transiently bridging T cells and cancer cells, MT110 is capable to mount a polyclonal T cell response that is not limited by T cell receptor specificity, presence of MHC class I, generation and presentation of peptide antigen, or the need for T cell co-stimulation.

Methods

STUDY DESIGN

Primary objectives: To assess safety and tolerability
Secondary objectives: To assess pharmacokinetics (PK), pharmacodynamics (PD) and anti-tumor activity of MT110

Patients: With locally advanced, recurrent or metastatic solid tumors known to frequently express EpCAM
- Adenocarcinoma of the lung
- Small cell lung cancer
- Gastric cancer
- Colorectal cancer

Other key eligibility criteria:

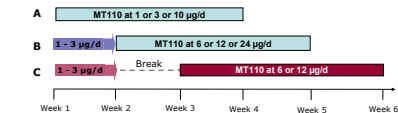
- Standard therapeutic options are exhausted or declined
- At least one course of previous chemotherapy
- ECOG performance status ≤ 2
- Ability to understand the patient information/informed consent form
- No evidence of CNS metastases on baseline CT or MRI scan or other history of CNS pathology
- Neutrophil count < 1,500/mm³ (= 1.5 x 10⁹/l)
- Platelet count < 100,000/mm³ (= 100 x 10⁹/l)
- WBC < 3 x 10⁹/l; hemoglobin < 9.0 g/dl
- No abnormal renal or hepatic function
- No O₂ saturation of < 92% (under room air condition)
- No concurrent anti-neoplastic therapy, except palliative radiotherapy
- No presence of human anti-murine antibodies (HAMA)

MT110 TREATMENT AND DOSE ESCALATION

MT110: Continuous intravenous infusion from day 1-28
Repeated cycles until disease progression with 2 to 4 weeks treatment break if SD or better after first cycle

Dose cohorts: MT110 at 1/ 3/ 6/ 10/ 12/ 24 (currently ongoing) µg per day; further dose escalation in cohorts B/C planned
3+3 design depending on occurrence of DLTs
Decision on dose escalation after completion of the first cycle of each patient in the respective cohort

Treatment performed with schedule A, B or C:



DLT criteria: Any grade 3 or 4 related adverse event (AE) that persists longer than pre-defined despite adequate patient management

Concomitant medication: Prior to MT110 infusion or dose escalation corticosteroid, antihistamine, and antiacid
Further supportive medication permitted

ASSESSMENTS

Safety: Continuous assessment of safety parameters AE reporting according to CTCAE version 3.0
Laboratory parameters at least twice daily on days 1 and 2, once daily on days 3 and 5 in weeks 1 and 2, and twice weekly afterwards

Anti-tumor activity: Assessment after each treatment cycle (according to RECIST version 1.0 in case of measurable lesions)

PK/PD: Samples for analysis of PK, cytokines, lymphocytes subpopulations, circulating tumor cells and immunogenetics are collected at pre-defined time points
EpCAM expression is analyzed in paraffin-embedded tumor tissue

Results

PATIENTS AND MT110 TREATMENT

- The data presented in this poster are as of Sept. 10, 2009; the study is ongoing
- 22 patients have started MT110 therapy, this interim analysis includes:
 - Demographic data of 20 patients
 - Safety and pharmacodynamic data of 20 patients

Table 1. Patient demographics per dose cohort

Characteristic	MT110 dose cohorts						Total
	A1: 1 µg/d	A2: 3 µg/d	A3: 10 µg/d	B1: 3/6 µg/d	B2: 3/12 µg/d	C1: 3/break/12 µg/d	
Median age (years, range)	64	56	54	62	65	75	63 (44-85)
Gender male (n; %)	4	2	1	4	3	0	12 (67.0%)
Diagnosis							
CRC (n; %)	5	2	1	2	3	1	14 (70.0%)
Gastric (n; %)	1	1	0	1	0	0	3 (15.0%)
NSCLC (n; %)	0	0	1	0	1	0	2 (10.0%)
SCLC (n; %)	0	0	0	1	0	0	1 (5.0%)
Prior lines of chemo (n; %)							
≥3	5	2	1	2	3	1	14 (70.0%)
<3	1	1	1	2	1	0	6 (30.0%)
Prior radiation (n; %)	1	2	0	2	1	0	6 (30.0%)
Prior surgery (n; %)	6	2	1	4	4	1	18 (90.0%)
Liver metastases (n; %)	3	2	0	3	4	1	13 (65.0%)
ECOG 0/1/2	1/5/0	2/0/1	1/1/0	2/2/0	1/3/0	0/0/1	7/11/2
Abnormal liver parameters at baseline	3	3	1	2	3	1	13 (65.0%)

SAFETY & TOLERABILITY

Adverse Events Summary

- Out of 20 patients, 17 were able to complete at least one cycle of 4 weeks MT110 intravenous infusion
- The observed clinical AEs were related to the underlying disease in almost all cases
- Non-hematological clinical adverse events related to MT110 consisted of mild pyrexia and fatigue in few patients; pyrexia was not associated with a first infusion reaction
- Laboratory changes that were related to MT110 occurred primarily in the first week of infusion or after dose escalation, were of short duration and resolved during the course of infusion in most cases. Changes in liver parameters were transient and asymptomatic, and were not accompanied by pathological findings within the liver as assessed by diagnostic imaging, or by impaired synthesis parameters of the liver

Table 2. Incidence of AEs regardless of relationship occurring in ≥3 patients

CLINICAL ADVERSE EVENTS	Total, N=18			
	Grade 1/2		Grade 3/4	
Abdominal pain	5 (25.0%)	0 (0.0%)		
Pyrexia	8 (40.0%)	1 (5.0%)		
Vomiting	6 (30.0%)	0 (0.0%)		
Nasopharyngitis	5 (25.0%)	0 (0.0%)		
Cough	4 (20.0%)	0 (0.0%)		
Diarrhoea	4 (20.0%)	0 (0.0%)		
Oedema peripheral	4 (20.0%)	0 (0.0%)		
Fatigue	3 (15.0%)	0 (0.0%)		
LABORATORY CHANGES				
Lymphocyte count decreased/lymphopenia	2 (10.0%)	14 (70.0%)		
Haemoglobin decreased	2 (10%)	1 (5%)		
Gamma-glutamyltransferase increased	3 (15.0%)	13 (65.0%)		
Aminotransferases increased	2 (10.0%)	9 (50.0%)		
Blood glucose increased/Hyperglycaemia	6 (30.0%)	4 (20.0%)		
Blood amylase increased	2 (10.0%)	3 (15.0%)		
Lipase increased	1 (5.0%)	5 (25.0%)		
C-reactive protein increased	4 (20.0%)	0 (0.0%)		
Blood alkaline phosphatase increased	2 (10.0%)	1 (5.0%)		
Blood bilirubin increased	4 (20.0%)	0 (0.0%)		
Hypocalcaemia	3 (15%)	0 (0.0%)		
Blood lactate dehydrogenase increased	3 (15.0%)	1 (5.0%)		

Table 3. Incidence of adverse events related to MT110 occurring in >1 patient

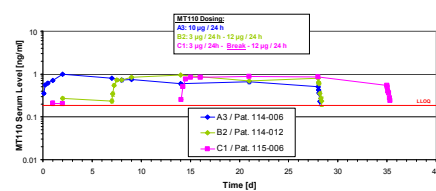
CLINICAL ADVERSE EVENTS	A1 (n=6)		A2 (n=3)		A3 (n=2)		B1 (n=4)		B2 (n=4)	
	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4
Pyrexia	2	0	1	0	0	0	1	0	0	0
Fatigue	2	0	0	0	0	0	0	0	0	0
LABORATORY CHANGES*										
Lymphopenia/lymphocyte count decreased	1	4	0	3	0	2	0	4	1	0
Gamma-glutamyltransferase increased	2	3	0	2	0	2	1	2	0	3
Aminotransferases increased	2	2	0	2	0	2	0	3	0	1
Blood amylase increased	0	0	1	0	1	0	0	1	0	1
Lipase increased	1	0	0	1	0	1	0	1	0	1
Blood alkaline phosphatase increased	1	1	0	0	0	0	0	0	1	0
Blood bilirubin increased	2	0	0	0	0	0	0	0	1	0
Blood lactate dehydrogenase increased	1	0	0	1	0	0	1	0	0	0
Hypocalcaemia	0	0	0	0	0	0	0	0	2	0

Table 4. Reported dose-limiting toxicities

Patient	MT110 dose	Tumor	Event	Action	Outcome
114-002 (A1)	1 µg/d	Gastric	Grade 4 increase in AST + ALT	Corticosteroid administration	Resolved
114-007 (A3)	10 µg/d	NSCLC	Grade 3 ALT for >72 hrs	MT110 infusion discontinued	Resolved

PHARMACOKINETIC PROFILE

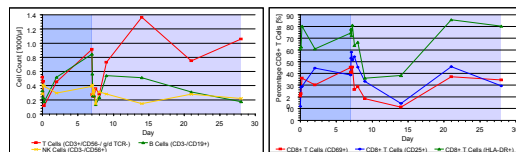
Figure 2. MT110 plasma levels of three patients treated with maintenance doses of 10 or 12 µg/day



- The serum half-life for MT110 was determined to be between 3.5-6.8 hours
- After normalization for dose and body weight, a dose linearity can be assumed for dose levels tested to date
- MT110 plasma levels are comparable for schedules A, B and C

PHARMACODYNAMIC MARKERS

Figure 3. Representative example of lymphocyte redistribution (left) and T cell activation (right) after start of MT110 infusion and after dose escalation on day 7 in patient #114-012 (cohort B2: 3 → 12 µg/d)



- None of the patients showed a significant systemic cytokine release. Low IL-6 levels were measurable at different time points and single measurable peak levels of IFN-γ and IL-10 were seen in some patients
- In all patients, redistribution of lymphocytes was observed after start of MT110 infusion and upon dose escalation (Fig. 3, left). First signs of T cell activation were observed in patients with clinical benefit after first cycle (Fig. 3, right)
- Initial analysis of circulating tumor cells via CellSearch® method revealed up to 6 cells per 7.5 ml sample from CRC patients

PATIENT OUTCOME

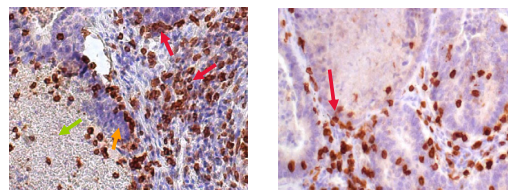
Tumor assessment according to RECIST criteria

- Disease stabilization was observed in 7 of 18 evaluable patients after first cycle with a median duration of 86 days (range of 29-150 days)

Case report

- Patient (female, 85 years) presented with metastatic CRC lesions in the lung at study entry
- Treatment with MT110 at 1 µg/d for 28 days
- Patient underwent surgical resection of a lung lesion 80 days after start of MT110, pathology revealed:
 - >70% of necrotic tissue in this lesion (Fig. 4 left)
 - High number of infiltrating T lymphocytes including CD8-positive cells in and around tumor tissue (Fig. 4 right)

Figure 4. Resected CRC lung lesion of patient #114-004



Left: CD3-positive lymphocytes (red arrows), necrotic tissue (green), tumor cells (orange). Right: Infiltration by CD8-positive lymphocytes (red arrow).

OVERALL SUMMARY

Up to date, 20 patients were treated in five dose cohorts and received a total of 25 cycles of MT110.

- I.v. infusion of MT110 over a treatment cycle of 28 days is clinically very well tolerated
 - Mild pyrexia and fatigue occurred in few patients
 - No signs of relevant systemic cytokine release were observed
 - Besides initial transient lymphopenia, a transient asymptomatic increase in liver enzymes up to Grade 3/4, was the most frequent laboratory abnormality
- First signs of biological activity
 - MT110 caused a rapid redistribution of lymphocytes shortly after start of infusion. Signs of T cell expansion and activation were seen in patients with clinical benefit after 4 weeks
 - Disease stabilization according to RECIST was confirmed in 7 of 18 patients, lasting 86 days in median
 - In one patient, a lung metastasis was resected 11 weeks after start of MT110 treatment. Immunohistochemistry revealed tumor cell necrosis and a massive T cell infiltration as possible evidence of MT110 activity
- None of the patients developed antibodies against MT110

CONCLUSIONS

- MT110 can be safely i.v. administered to patients with advanced, EpCAM-expressing solid tumors
- First signs of biological activity have been observed at clinically well tolerated doses
- Further evaluation of BiTE antibody MT110 at higher doses is ongoing

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