1 SYNOPSIS

Name of Sponsor/Company Amgen Research (Munich) GmbH (formerly known as Micromet GmbH), Staffelseestr. 2, 81477 Munich, Germany	Individual Study Table Referring to Part xx of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product n. a.		
Name of Active Ingredient Adecatumumab (MT201)		

Title of Study

A randomized, open-label, controlled, multicenter phase II study to evaluate the efficacy and safety of adecatumumab alone or sequentially to FOLFOX relative to FOLFOX after R0 resection of colorectal liver metastases.

Investigators

Coordinating Investigator Germany (LKP according to § 40 AMG): Prof. [redacted], MD
Coordinating Investigator France: Prof. [redacted], MD

Study Centers

Multicenter, binational study in Germany and France with a total of 11 active study centers (10 centers in Germany, 1 in France)

Publication (Reference)

Results of the study have not been published yet

Studied Period (Date of First Enrollment/Date of Last Completed)	**Phase of Development**
March 12, 2009 until July 29, 2011	II

Objectives

Primary objective:

- To assess the effect of the monoclonal antibody adecatumumab alone or sequentially to FOLFOX based on 1-year disease-free survival (DFS) rates in colorectal cancer patients with complete (R0) resection of liver metastases

Secondary objectives:

The secondary objectives according to amendment 03, dated August 11, 2010 were as follows:

- To assess the 1-year DFS rate after treatment with FOLFOX
- To compare 1-year DFS rate of the treatment with the monoclonal antibody adecatumumab alone or sequentially to FOLFOX to treatment with FOLFOX
- To assess the safety profile in the 3 treatment arms
- To assess the quality of life for the 3 treatment arms

Methodology

This study was designed as a prospective, randomized, open-label, controlled multicenter phase II study to evaluate the efficacy of adecatumumab either alone or following adjuvant systemic chemotherapy using the FOLFOX 4 regimen compared to adjuvant FOLFOX 4 chemotherapy alone in patients with R0-resected liver metastases from colorectal cancer (CRC).

At screening a dynamic randomization procedure based on the Clinical Risk Score (CRS) as described by Fong et al. (Ann Surg 1999; 230: 309) was performed. Patients were to be stratified as 'low risk' (CRS 0-2) or 'high risk' (CRS 3-5) and randomized equally distributed to 3 parallel treatment arms at a 1:1:1 ratio.

Treatment was to be started 3 weeks after resection of CRC liver metastases (CRLM). If the investigator decided that the clinical condition of the patient did not allow treatment start at week 3, the patient was to be reassessed weekly; in this case treatment start could be postponed up to a maximum of 6 weeks post surgery:

- In arm A, adecatumumab monotherapy was to be started at doses of 6 mg/kg body weight (BW) for 2 cycles (D1, D15) followed by doses of 9 mg/kg BW starting at D29 for the following 22 cycles every 2 weeks for a total of 48 weeks or until relapse of the disease.
- In arm B, patients were first to be administered treatment with FOLFOX 4 according to de Gramont et al. (J Clin Oncol 2000; 18 (16): 2938) consisting of 2-hour IV infusions of oxaliplatin 85 mg/m^2 and folinic acid 200 mg/m^2 given at the same time as recommended in the Summary of Product Characteristics (SmPC) followed by an IV bolus of 5-FU 400 mg/m^2 and a 5-FU continuous infusion of 600 mg/m^2 over 22 h at D1 and a 2-hour IV infusion of folinic acid 200 mg/m^2 preceding an IV bolus of 5-FU 400 mg/m^2 and a 5-FU continuous infusion of 600 mg/m^2 over 22 h at D2 every 2 weeks for a maximum of 12 cycles (duration of

Name of Sponsor/Company	Individual Study Table	*(For National Authority Use only)*
Amgen Research (Munich) GmbH (formerly known as Micromet GmbH), Staffelseestr. 2, 81477 Munich, Germany	Referring to Part xx	
Name of Finished Product	of the Dossier	
n. a.		
Name of Active Ingredient	Volume:	
Adecatumumab (MT201)	Page:	

24 weeks).Then, adecatumumab was to be started as described for arm A at D+14 after the last administration of chemotherapy at doses of 6 mg/kg BW for 2 cycles followed by doses of 9 mg/kg BW lasting for 12 cycles in total (duration of 24 weeks).

- In arm C, patients were to get standard chemotherapy with FOLFOX 4 as described for arm B every 2 weeks for up to 12 cycles or until relapse of the disease (duration of 24 weeks).

An independent safety data monitoring committee (DMC) was assigned to evaluate potentially unacceptable toxicities and to advise for treatment discontinuation of individual patients or discontinuation of the study. If treatment was interrupted for 1 cycle due to dose adjustments for adverse events (AEs) the cycle was not replaced at the end of the treatment.

This study was approved shortly after the 2 largest phase III studies on adjuvant systemic chemotherapy in CRLM closed prematurely because of slow accrual (Mitry et al., J Clin Oncol 2008, 26; 30: 4906). After Nordlinger et al. had reported a potential benefit of perioperative chemotherapy for patients with potentially resectable CRLM when compared to patients receiving best supportive care only (Lancet 2008; 371: 1007) their 'neoadjuvant' approach had become 'standard of care'. Subsequently, the majority of patients with CRLM were treated with chemotherapy prior to surgical resection and were not eligible for this study.

With amendment 03, dated August 11, 2010 patient recruitment was stopped and sample size was altered from 110 to 35, who were already enrolled at time of the amendment.

The study was reported after the 1-year DFS data were available from all patients. Therefore, the End-of-Study (EoS) visit was 1 year after randomization.

Number of Patients Planned:	**Number of Patients Analyzed:**
The initial number of 110 patients to be recruited was altered to 35 based on amendment 03 of August 11, 2010	22

Diagnosis and Criteria for Inclusion and Exclusion

Patients were eligible for this study if they met all the following inclusion criteria:

1. Histopathologically confirmed complete resection (R0) of liver metastasis(es) from colorectal adenocarcinoma (additional confirmation by CT scan at treatment start)
2. Age ≥ 18 years
3. ECOG performance status ≤ 2
4. Patient was informed, had read and understood the Patient Information/Informed Consent Form and had given written informed consent.

Patients were not eligible for this study if any of the following criteria applied:

1. Extrahepatic distant metastases or locally recurrent disease at time of enrollment
2. Neoadjuvant chemotherapy for liver metastases prior to surgery
3. Any anticancer chemotherapy within 4 weeks prior to study entry
4. Start of oxaliplatin-based chemotherapy within 9 months prior to study entry
5. Any biological anticancer therapy or immunotherapy within 4 weeks prior to study entry
6. Any radiotherapy or radio frequency ablation (RFA) to the liver prior to surgery
7. Treatment with any investigational product within a time range of 4 to 5 half-lives (t½) prior to study entry
8. Acute or chronic pancreatitis or history of alcohol-induced pancreatitis
9. Liver cirrhosis, acute hepatitis or chronic hepatic disease
10. Any unresolved complications from prior surgery
11. Persistent neuropathy
12. History of other malignancy within 5 years prior to study start, with the exception of basal cell carcinoma of the skin, carcinoma *in situ* of the cervix (CIS) and ductal carcinoma *in situ* (DCIS)
13. History of inflammatory bowel disease
14. Active severe infection, any other concurrent disease or medical condition that was deemed to interfere with the conduct of the study as judged by the investigator
15. Use of immunosuppressive agents such as the regular use of systemic corticosteroids
16. HIV positivity

Name of Sponsor/Company	Individual Study Table	*(For National Authority Use only)*
Amgen Research (Munich) GmbH (formerly known as Micromet GmbH), Staffelseestr. 2, 81477 Munich, Germany	Referring to Part xx	
Name of Finished Product	of the Dossier	
n. a.		
Name of Active Ingredient	Volume:	
Adecatumumab (MT201)	Page:	

17. Known hypersensitivity or intolerability to immunoglobulin in general, other recombinant human or humanized antibodies, folinic acid, 5-fluorouracil, oxaliplatin or a component of the study drug formulations, known dihydropyrimidine dehydrogenase (DPD) deficiency
18. Pregnant or nursing women
19. Women of childbearing potential or male patients not willing to use an effective form of contraception during treatment phase of the study and at least 6 months thereafter
20. Not willing or incapable to comply with all study visits and assessments
21. Placed into an institution due to juridical or regulatory ruling
22. Vaccination with live vaccines (e.g. yellow fever)
23. Concomitant treatment with phenytoin

Eligibility criteria at treatment start/baseline:

The following eligibility criteria needed to be fulfilled before the patient was treated with study medication:

1. CT confirmation of complete resection (R0) of liver metastasis(es) (and histopathological confirmation of tumor-free margin)
2. Organ or bone marrow function at time of treatment start as defined below:
   - WBC > 3 x 10^9/L
   - Platelet count > 100 x 10^9/L
   - Creatinine clearance ≥ 50 mL/min (calculated e.g. according to MDRD ['Modification of diet in renal disease',method to calculate glomerular filtration rate])
   - Serum bilirubine < 2 x upper limit of normal (ULN)
   - AST(SGOT)/ALT(SGPT) ≤ 5 x ULN
   - Serum lipase ≤ 1.5 x ULN
   - Neutrophils > 2 x 10^9/L
3. Blood coagulation at time of treatment start as defined below:
   - INR < 1.5 x ULN (exception: patient received therapeutic anticoagulation)
   - PTT < 1.5 x ULN (sec)
4. Investigator's discretion that the clinical condition of the patient allowed start of treatment

Test Product, Dose and Mode of Administration, Batch Number

Adecatumumab, a fully human recombinant IgG_1 antibody specifically binding to the epithelial cell adhesion molecule (EpCAM) was formulated as a concentrate for solution for infusion, containing 10 mg/mL adecatumumab in [redacted] phosphate buffer.

Please refer to *CSR Appendices 16.1.6, Listing of Patients Receiving Investigational Products from Specific Batches* for respective batch numbers.

Duration of Treatment

Treatment was to be started 3 weeks after resection of CRLM. If the investigator decided that the clinical condition of the patient did not allow treatment start at week 3, the patient was to be reassessed weekly; in this case treatment start could be postponed up to a maximum of 6 weeks post surgery. If the disease did not relapse the treatment lasted

- 48 weeks in treatment arm A (adecatumumab monotherapy every 2 weeks for 24 cycles)
- 48 weeks in treatment arm B (FOLFOX 4 every 2 weeks for a maximum of 12 cycles [24 weeks] followed by adecatumumab every 2 weeks for 12 cycles [24 weeks])
- 24 weeks in treatment arm C (FOLFOX 4 every 2 weeks for up to 12 cycles)

Criteria for Permanent Discontinuation of Treatment

Treatment with the investigational product was discontinued in the event of any of the following:

- Toxicities/adverse events that could not be controlled with concomitant medication
- Causally related adverse events for which treatment discontinuation was recommended according to the protocol
- Progression of a medical condition which in the opinion of the investigator should preclude further treatment

Name of Sponsor/Company	Individual Study Table	*(For National Authority Use only)*
Amgen Research (Munich) GmbH (formerly known as Micromet GmbH), Staffelseestr. 2, 81477 Munich, Germany	Referring to Part xx	
Name of Finished Product	of the Dossier	
n. a.		
Name of Active Ingredient	Volume:	
Adecatumumab (MT201)	Page:	

of the patient

- Dose interruption for longer than 1 cycle (totaling 28 days of not receiving study drug)
- Occurrence of any adverse event which made discontinuation necessary in the investigator's and/or the patient's opinion
- The data monitoring committee advised to discontinue the treatment on the basis of available safety data

Criteria for Permanent Discontinuation of Study

Participation in the study was discontinued permanently in the event of any of the following:

- Permanent discontinuation of study drug before administration of 4 cycles of adecatumumab or 1 cycle of FOLFOX 4
- Disease relapse
- Withdrawal of patient's consent

If the patient withdrew consent during the study, the investigator was asked to perform all examinations scheduled for the End-of-Study visit. This data was recorded as it comprised an essential safety evaluation being performed prior to discharge of any patient from the study.

Reference Therapy, Dose and Mode of Administration, Batch Numbers

FOLFOX 4 chemotherapy consisted of 2-hour IV infusions of oxaliplatin 85 mg/m^2 and folinic acid 200 mg/m^2 given at the same time as recommended in the SmPC followed by an IV bolus of 5-FU 400 mg/m^2 and a 5-FU continuous infusion of 600 mg/m^2 over 22 h at D1 and a 2-hour IV infusion of folinic acid 200 mg/m^2 preceding an IV bolus of 5-FU 400 mg/m^2 and a 5-FU continuous infusion of 600 mg/m^2 over 22 h at D2 every 2 weeks for a maximum of 12 cycles (duration of 24 weeks).

Please refer to *CSR Appendices 16.1.6, Listing of Patients Receiving Investigational Products from Specific Batches* for respective batch numbers.

Criteria for Evaluation

Primary endpoint:

- One year DFS rate, defined by the ratio of disease-free patients 1 year after randomization to total patients per treatment arm.

Secondary endpoints:

The secondary endpoints according to amendment 03, dated August 11, 2010 were as described below:

- Safety endpoints: Adverse events, laboratory parameters
- Quality of life as assessed by EORTC-QLQ-C 30 and EORTC-QLQ-LMC 21

Statistical Methods

The Statistical Analysis Plan (SAP) of March 13, 2009 was amended on April 28, 2011 based on the adjustments of statistical methods and analyses defined in amendment 03 of the clinical study protocol (CSP), dated August 11, 2010. The number of patients to be recruited was altered from 110 to 35, who were already enrolled at time of the amendment. Due to the reduction of sample size the statistical hypotheses were not to be tested with a sufficient power. All parameters were analyzed using descriptive methods and no confirmatory testing was done.

Summary – Conclusions

Safety Results

In total, 32 of 35 patients (91.4%) were eligible for randomization; 22 (62.9%) were treated with study medication (n = 7 in treatment arm A, n = 7 in treatment arm B, n = 8 in treatment arm C). Tenpatients (45.5%) terminated the treatment prematurely either due to an AE (n = 3, 13.6%), progressive disease (n = 5, 22.7%), an EoS visit beyond the requested period (n = 1, 4.5%) or noncompliance (n = 1, 4.5%).

Overall, 491 AEs were reported, most for treatment arms B (n = 193, 39.3%) and C (n = 180, 36.7%), respectively and least for treatment arm A (n = 118, 24.0%). Most of them were mild to moderate in severity; 84.9% of AEs were related; 1.8% were serious.

The most common System Organ Class adverse events for patients exposed to adecatumumab were gastrointestinal disorders (diarrhea, nausea) and general disorders (chills, fatigue). These AEs corresponded to the safe-

Name of Sponsor/Company	Individual Study Table	*(For National Authority Use only)*
Amgen Research (Munich) GmbH (formerly known as Micromet GmbH), Staffelseestr. 2, 81477 Munich, Germany	Referring to Part xx	
Name of Finished Product	of the Dossier	
n. a.		
Name of Active Ingredient	Volume:	
Adecatumumab (MT201)	Page:	

ty profile known for adecatumumab.

The most frequent System Organ Class adverse events for patients exposed to FOLFOX 4 in arms B and C were gastrointestinal disorders (diarrhea, nausea, vomiting), general disorders (chills, pyrexia, fatigue), blood and lymphatic system disorders (mainly neutropenia) and nervous system disorders (dysgeusia, polyneuropathy, paresthesia). They were consistent with the expected toxicity profile of FOLFOX 4 agents as reported in the oxaliplatin, 5-fluorouracil, and folinic acid SmPCs.

The incidence, prevalence and severity of treatment-related AEs were lowest in treatment arm A and highest in treatment arm B during FOLFOX 4 administration. Adecatumumab monotherapy in treatment arm A was well tolerated. The sequential combination therapy of FOLFOX 4 and adecatumumab in treatment arm B was feasible and safe; specifically no cumulative effects for diarrhea were seen. There was no obvious signal of different types of adverse events in patients treated with adecatumumab in arm B compared with those patients who received adecatumumab in arm A without prior FOLFOX 4 administration.

No patient died due to an adverse event or for other reasons within this study. In total, 9 serious adverse events (SAEs) occurred throughout the study, 3 in 3 patients of treatment arm A (42.9%), 4 in 3 patients of treatment arm B (42.9%), and 2 in 2 patients of treatment arm C (25.0%). SAEs ≥ CTC grade 3 were seen once in every treatment arm. In treatment arm A, no SAE was assessed as being related to adecatumumab treatment. Two SAEs in treatment arm B (overdose of CTCAE grade 2, neutropenia of CTCAE grade 4) and 1 SAE in treatment arm C (vomiting CTCAE grade 2) were assessed as being related to FOLFOX 4 treatment.

In 3 patients treatment was discontinued prematurely due to 3 significant AEs; 2 of them were assessed as being related to study medication, both were probably based on concomitant diseases: In treatment arm A, 1 patient with a medical history of ongoing [redacted] experienced dementia (CTCAE grade 3) 9 days after the last dose of adecatumumab had been administered. [redacted] discontinued the study prematurely, but due to relapse of the disease. In treatment arm C, 1 patient with known [redacted] suffered increasing paresthesia in fingers and feet (CTCAE grade 4) 19 days following the last FOLFOX 4 cycle.

Treatment-emergent laboratory abnormalities were primarily blood and lymphatic system disorders, predominantly thrombopenia and neutropenia. Most other laboratory or vital sign abnormalities were rather based on medical history than related to study treatment. Serum lipase parameters were normal throughout the study indicating that adecatumumab did not target pancreatic epithelium. ECOG performance data demonstrated that the clinical condition of most patients either remained stable or even ameliorated during the study.

No patient who received adecatumumab developed anti-adecatumumab antibodies.

Efficacy Results

The 1-year DFS rate was 71.4% in treatment arm B (95% confidence interval [CI] from 29.0% to 96.3%), 28.6% in treatment arm A (95% CI from 3.7% to 71.0%) and 50.0% in treatment arm C (95% CI from 15.7% to 84.3%). Although the point estimates seem to differ markedly between the treatment groups the wide overlap of confidence intervals indicates that no difference between the treatment arms could be detected in this study.

Overall, 8 patients experienced relapse of the disease, 4 in treatment arm A (57.1%), 1 in treatment arm B (14.3%), and 3 in treatment arm C (37.5%). None of the patients in treatment arms A and B who relapsed had completed treatment, while 2 of 3 patients in treatment arm C did so. The ratio of patients who completed treatment and did not relapse versus all patients in the respective treatment arm was highest in treatment arm B. Some patients in treatment arm B who discontinued FOLFOX 4 treatment prematurely due to AEs switched to sequential adecatumumab therapy ahead of schedule and may have derived some benefit of anti-EpCAM directed therapy as manifested by being disease-free within the observation period.

EORTC QoL data observed in this study were probably not representative of all patients and needed to be interpreted with caution as the sample sizes were very small and the compliance rate of responding to questionnaires dropped from 73% at baseline to 55% at the end of the study across all treatment arms. Based on a conservative interpretation of QoL data overall global health and quality of life did not appear to worsen on any of the treatment arms.

Conclusion

The small sample size did not allow for any conclusion with regard to efficacy when comparing the different treatment arms. Anti-tumor activity demonstrated by 1-year DFS rate was observed in all 3 treatment arms. The limited sample size of this study may be sufficient for hypothesis generation but any conclusions are restricted and caution must be exercised until a more robust data set is available. The 1-year DFS rate was 71.4% in treatment arm B (95% CI from 29.0% to 96.3%), 28.6% in treatment arm A (95% CI from 3.7% to 71.0%) and

Name of Sponsor/Company Amgen Research (Munich) GmbH (formerly known as Micromet GmbH), Staffelseestr. 2, 81477 Munich, Germany	Individual Study Table Referring to Part xx	*(For National Authority Use only)*
Name of Finished Product n. a.	of the Dossier	
Name of Active Ingredient Adecatumumab (MT201)	Volume: Page:	

50.0% in treatment arm C (95% CI from 15.7% to 84.3%).

The incidence, prevalence and severity of treatment-related AEs were lowest in treatment arm A and highest in treatment arm B during FOLFOX 4 administration. Adecatumumab monotherapy in treatment arm A was well tolerated. The sequential combination therapy of FOLFOX 4 and adecatumumab in treatment arm B was feasible and safe. No changes from the prior safety profile of adecatumumab were observed.

[redacted].

Date of report April 20, 2012