# HDAC-GaCa-2008

## An open-label, uncontrolled phase II trial of HDAC-Inhibitor LBH589 in patients with chemo-refractory metastatic gastric cancer overexpressing histone deacetylases (HDACs) (CLBH589BDE03T)

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First patient recruited : 21.08.2009 Last patient completed: 11.10.2012

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## List of abbreviations and definition of terms

| | |
|---|---|
| AE | Adverse Event |
| AMG | German Drug Law (Arzneimittelgesetz) |
| CR | Complete Response |
| CRF | Case Report Form |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events version 3.0 |
| CV | Curriculum Vitae |
| DSUR | Development Safety Update Report |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| FPI | First Patient In |
| GCP | Good Clinical Practice |
| GIST | GastroIntestinal Stroma Tumors |
| HDAC | Histone Deacetylases |
| HDI | HDAC inhibitors |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| INN | International Nonproprietary Name |
| ITT | Intent to Treat Population |
| KPS | Karnofsky Performance Status |
| LKP | Coordinating Investigator according to AMG (Leiter der Klinischen Prüfung) |
| LLN | Lower Limit of the Normal |
| LPI | Last Patient In |

| | |
|---|---|
| LPO | Last Patient Out |
| Med DRA | Medical Dictionary for Regulatory Activities |
| MWF | Monday Wednesday Friday |
| MRI | Klinikum rechts der Isar |
| MSZ | Münchner Studienzentrum |
| NCI CTC AE | National Cancer Institute Common Toxicity Criteria for Adverse Events |
| ORR | Objective Response Rate |
| OS | Overall Survival |
| PD | Progressive Disease |
| PFS | Progression-Free-Survival |
| PO | Per Os, orally |
| PR | Partial Response |
| RECIST | Response Evaluation Citeria in Solid Tumors |
| RR | Response Rate |
| SAE | Serious Adverse Event |
| SAP | Safety Analysable Population |
| SD | Stable Disease |
| SDV | Source Data Verification |
| SOP | Standard Operating Procedure |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TMF | Trial Master File |
| TTP | Time to Progress |
| TUM | Technische Universität München |
| ULN | Upper Limit of Normal |
| WHO | World Health Organization |

## Study Report Synopsis

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|---|---|
| **Name of Sponsor:** Technische Universität München (TUM), Fakultät für Medizin<br>Prof. Dr. med. Peter Henningsen, Dekan | |
| **Name of Finished Product:** Panobinostat | |
| **Name of Active Ingredient:** LBH 589 | |
| **Title of Study:** An open-label, uncontrolled phase II trial of HDAC inhibitor LBH 589 in patients with chemo-refractory metastatic gastric cancer overexpressing histone deacetylases ( HDAC-GaCa-2008) | |
| **Protocol Code**: CLBH589BDE03T | |
| **EudraCT**: 2008-002721-37 | |
| **Coordinating Investigator:**<br>LKP (AMG): Prof. Dr. med. Matthias Ebert | |
| **Participating Study Centres:**<br><br>**1.** Klinikum rechts der Isar (MRI) der TUM<br>II. Medizinische Klinik und Poliklinik<br>**Dr. med. Martina Mayr**<br>Ismaninger Str. 22<br>81675 München<br><br>**2.** Universitätsklinikum Mannheim<br>Coordinating Investigator (Leiter Klinische Prüfung, LKP)/Principal Investigator:<br>**Prof. Dr. med. Matthias Ebert**<br>Klinikum Mannheim GmbH<br>Universitätsklinikum Medizinische Fakultät Mannheim der Universität Heidelberg<br>II. Medizinische Klinik<br>Theodor-Kutzer-Ufer 1 – 3<br>68167 Mannheim | |
| **Publication (reference):** not published yet | |
| **Studied period (years)**<br>**first patient in:** 21.08.2009<br>**last patient out:** 11.10.2012<br>The clinical study was determined prematurely in 2013 due to slower than anticipated recruitment and lack of efficacy. | **Phase:** II |
| **Objectives**:<br>**Primary objective**: To evaluate the antitumor activity of HDAC Inhibitor LBH589 administered as a single agent in patients with metastatic gastric cancer overexpressing HDACs refractory to cisplatin- and/or irinotecan-based chemotherapy<br>**Secondary objectives**:<br>1. Effects of HDAC-Inhibitor LBH589 on the time to tumor progression (PFS)<br>2. Effects of HDAC-Inhibitor LBH589 on survival (one-year survival and overall survival) | |

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| **Name of Finished Product:** Panobinostat |
| **Name of Active Ingredient:** LBH 589 |
| 3. Safety and tolerability of HDAC-Inhibitor LBH589 |
| **Methodology:** open label, uncontrolled phase II trial in an optimal Simon two- stage design |
| **Number of patients (planned and analyzed):**<br>- planned sample size: 28 (first stage 11 patients; second stage (if at least one objective response was observed within first stage): 17 patients)<br>- analyzed sample size: 11 patients (all patients who were included into the trial) |
| **Diagnosis and main criteria for inclusion:**<br>**Indication**: Chemo-refractory metastatic adenocarcinoma of stomach or esophagogastric junction with overexpression of histone deacetylase<br>**Main inclusion criteria:**<br>Male or female patients age 18 - 90, with histologically proven irinotecan or cisplatin-refractory metastatic adeno-carcinoma of stomach or esophagogastric junction. Immunohistochemical analysis of cancer tissues before study inclusion confirmed overexpression of HDACs. Patients must have recovered from side effects of previous chemotherapy. Life expectancy must be more than 12 weeks, organ functions must be adequate and the patients must not suffer from any other severe chronic or acute medical or psychiatric disorder. They must be at least 4 weeks from last chemotherapy and must not receive any other conventional medicinal anti-cancer therapy during the treatment phase. |
| **Test product, dose and mode of administration:**<br>HDAC inhibitor Panobinostat LBH589 capsules of 20 and 5 mg active substance for oral administration; starting day 1: 30 mg three times a week (dose escalation to 40 mg three times a week permitted after 3 weeks of treatment);<br>(distributed by pharmacy of Klinikum rechts der Isar respectively Mannheim) |
| **Duration of treatment / treatment schedule:**<br>40 mg Monday, Wednesday, Friday. Start therapy with 30 mg, increase to 40 mg after first cycle (21 days). In case of toxicity, the dose can be reduced to 30 mg or 20 mg resp. and re-escalated when toxicities resolve.<br>Treatment duration was intended until progression of disease or until untolerable adverse events occur.<br>Dose reductions and brief pauses of medication were experienced in 10/11 patients for various reasons (e.g. due to adverse events, serious adverse events). |
| **Changes in Study Conduct:**<br>There was one protocol amendment (approval 26.10.2011). Main changes concerned the administration of a reduced dose of study drug (initial dose) from 30 mg LBH 589 to 20 mg first 21 days; 7 patients were included prior to the-amendment; 4 of 11 patients were included post-amendment.<br><br>According to the optimal Simon two-stage design an interim analysis was planned after a first stage of the trial including a total of 11 patients. No objective responses were observed during the first stage, the trial was stopped early and further investigation of |

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the drug not warranted.

**Reference therapy, dose and mode of administration, batch number:** n.a.

**1. Reference substance:** not applicable (n.a.)
**2. Reference substance:** n.a.

**Unblinding:**
n.a.

**Criteria for evaluation:**

**Primary endpoint**

The primary endpoint is the objective response rate (CR + PR) within the first six treatment cycles

**Secondary endpoints**

1. Progression free survival (PFS)
2. 1-year survival
3. Overall survival
4. Safety and tolerability of HDAC Inhibitor LBH589

**1. Progression free survival:**
Progression free survival was defined as the time from the first dose of trial medication to first documentation of objective tumor progression or to death due to any cause, whichever occurs first.

**2. 1-year survival:**
1-year survival was defined as the rate of patients surviving for at least one year after first dose of trial medication

**3. Overall survival:**
Overall survival was defined as the time from first dose of trial medication to date of death due to any cause

**4. Safety assessments**
Safety assessments consisted of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, regular measurement of vital signs, ECG and the performance of physical examinations.
These assessments should have been performed within ±2 days of the scheduled day of assessment except for adverse events that were evaluated continuously throughout the study. Safety and tolerability were assessed according to NIH/NCI CTCAEv3 and 4.

**Safety Review Team**
A Safety Review Team reviewed the safety data during study duration and assessed the safety profile.

**Statistical methods**
The number and proportion of patients achieving confirmed objective response (CR or PR) within the first six treatment cycles were summarized along with the corresponding exact one-sided 95% confidence interval. If 4 or more responses are observed by the end of the trial (n=28 patients) further investigation of the drug was indicated

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**Summary – Conclusions:**

**Patient Demographics and Patient Disposition**
In total 11 patients were included (first patient included: 21.08.2009; last patient included: 19.07.2012). The age range in this clinical trial was between 40 and 80 (median 59) years and the male/female ratio was 10/1. Main baseline patient characteristics were well-balanced.
None of the 11 patients who received study medication are still under treatment or concluded the one year follow-up (i.e. premature discontinuation of all patients).
Three of eleven patients discontinued study therapy due to disease progress (5 – 8 weeks after inclusion in the study), four patients discontinued prematurely for various reasons (abdominal pain suspect for ileus, reflux esophagitis, worsening of general condition) and four patients discontinued study therapy after withdrawn of consent.

**Safety and Efficacy Population**
Since all patients received at least one dose of LBH 589, all patients were included into the Safety Analysable Population (SAP) and Intent To Treat Population (ITT).
The evaluable patient population (EPP) is defined as the population of patients who have received at least one cycle of treatment and for which at least one tumor assessment has been documented after baseline for early responders.
All analyses will be carried out for the ITT/Safety poplation. For the PPP and the EPP only a subset of efficacy analyses will be performed.

**Efficacy Results:**

**Response to Treatment**

**Primary outcome:**

In our study, 7 of 11 patients were evaluable for the first tumor response (assessment cycle 3). Two of these 7 patients (2/7, 29%) achieved stable disease in the first tumor assessment. The other 5 patients (5/7, 71%) had progressive disease in the first tumor assessment. The time point of the second tumor assessment (cycle 6) was only reached by one patient (1/7, 14%), who achieved stable disease again. The different reasons for earlier discontinuation of the study conduct are listed and described in detail in the section on adverse events and serious adverse events.

**Secondary outcomes:**
**Progression free survival:**
Mean PFS in this study were 131 days (95% CI: 74,3; 188,3 days).

**1-year survival:**
In our study, all patients died in the course of the first year after start of study treatment,

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so the one-year survival rate was 0% (0/11 patients).

**Overall survival:**
Mean overall survival was 150 days (95% confidence interval 84,4;215,3) for the ITT population.

**Safety Results:**
Reported adverse events were consistent in quantity and quality with the known profile of side effects of LBH 589. SARs or SUSARs have not been reported during the course of the study.
During the conduct of the study safety information was also compiled in one Annual Safety Report (21.08.2009-31.03.2011) and two Development Safety Reports (DSUR, 01.04.2011-08.06.20012, and 09.06.12-08.06.13); a change in the risk-benefit evaluation of the study had not occurred from assessments of safety information or from changes in the IB, which were deemed non-substantial.

**Adverse Events (AE)**
A total of 74 adverse events (AEs) were reported in 11 patients. Severity grading revealed 34 (46%) events to be of mild severity, 28 (38%) events to be moderate and 12 (16%) to be severe. None of the AEs was graded as life-threatening or lethal. Relation to study drug was considered as certain only for three (4,1%) adverse events, a probable relationship was noted for 8 (11%) and a possible for 23 (31 %) adverse events. No relation to study drug was seen in 34 (46%) of the registered 74 adverse events. Only two (2,7%) of the 74 adverse events led to a hospitalization of the patients. In 31 (42%) cases patients recovered completely from the adverse events, 38 (52%) were ongoing – mainly due to underlying disease.

**Serious AE (SAE)**
A total of 7 SAEs were reported in 11 patients (see Table 8). In most cases, serious adverse events were due to underlying disease or related to progression of disease.

**Suspected Serious Adverse Reactions (SARs)**
The sponsor's assessment of expectedness was determined by referring to the IBs and no SARs have been reported.
**Suspected Unexpected Serious Adverse Reactions (SUSAR)**
The sponsor's assessment of expectedness was determined by referring to the IBs and no SUSARs have been reported in the study.

**Summary of Adverse Events**
All reported adverse events are consistent in quantity and quality with the known profile of side effects of both medications and their combination. Taken together, the current protocol was feasible according to the toxicity profile, considering the underlying disease and the stage of disease of the patients presented themselves upon inclusion into the study. It was deemed that the risk-benefit evaluation for the clinical trial was not affected.

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**Overall Conclusion:**

In summary, the treatment with HDAC inhibitor LBH 589 was well tolerated. Though, deterioration of patients` performance status according to advanced malignant disease limited the maximum applicable dose of the study drug to only 20 mg in most cases. The worsening of general condition and diverse symptoms caused by underlying disease complicated the conduct of the study trial corresponding to the study protocol. The withdrawals of informed consent were mainly based on these circumstances.

Even though one patient achieved stable disease for nearly six month no great activity of the study drug on tumor growth could be observed. Progression free survival and overall survival could also not be increased significantly. But considering the small number of patients assessable for response, no definite conclusion can be made**.**

So, this trial was feasible regarding the safety and tolerability of the study drug, but regarding the results for the primary and secondary objectives the data were disappointing. HDAC inhibitor does not seem to have the potential to substantially change outcome in the patient population of this study.

Date of the report: 29.03.2014

Date: 6.9.2014 Signature LKP:

## Ethics and Good Clinical Practice

This clinical study was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/83/EC), and with the ethical principles laid down in the Declaration of Helsinki.

# 1 Introduction

### 1.1.1 Gastric cancer epidemiology and treatment

Gastric cancer is the fourth most common cancer in Europe and the third leading cause of cancer mortality (1). Although gastric cancer has declined over the past 50 years, the incidence of tumors at the gastroesophageal junction has increased (2). The use of chemotherapy for the management of patients with advanced gastric cancer has become widely acceptable over the last 20 years (3-5). Interestingly enough, the survival advantage of chemotherapy was paralleled by an improvement in quality of life. So far, 5-fluorouracil (5-FU), usually in combination with leucovorin (LV, also referred to as folinic acid [FA]), formed the basis of most chemotherapy regimens used for the treatment of gastric cancer. A randomized phase III trial compared 5-FU combinations with other active drugs in advanced gastric cancer. The overall response rates ranged from 9% (etoposide, LV and 5-FU; ELF) to 20% (infusional 5-FU plus cisplatin; FUP). The observed differences were not statistically significant. Later on, epirubicin, cisplatin and continuous infusion 5-FU (ECF) has been proposed as standard first-line therapy for metastatic gastric cancer as a consequence of its significantly improved response rates (46%) and survival (8.7 months) when compared with the „old“ standard FAMTX (3-5).
In recent years, new anticancer drugs such as irinotecan, taxanes and oxaliplatin reported higher objective response rates of up to 70% and a possible improvement of overall median survival of up to 12 months in palliative firstline treatment. Consequently, two large phase III studies which compared irinotecan or docetaxel containing regimens with the cisplatin/5-FU standard, presented some better survival times for both irinotecan or docetaxel regimens, respectively, and in addition less hematologic, renal and neurologic toxicities for irinotecan.

### 1.1.2 HDACs and gastric cancer

In recent years evidence is accumulating that modifications of the acetylation status plays a central role in gastric carcinogenesis (6,7). Posttranslational modifications of the N-terminal tails of core histones by histone acetyltransferases (HAT) and histone deacetylases (HDAC) are known to profoundly change the nucleosomal conformation of tumor cells and normal cells alike. By this mechanism aberrant activation of histone deacetylases in tumor cells lead to transcriptional repression of a small set of genes mainly involved in the negative regulation of proliferation, migration, angiogenesis, dedifferentiation, invasion and metastasis (8,9). Equally important for tumor biology is the ability of HATs and HDACs to acetylate and deacetylate a large number of tumor relevant proteins directly, which alters their functional activity, subcellular localization and interaction partners (10). To date, 18 HDAC isoforms, grouped in three classes, have been described in humans (9). The best characterized and probably biologically most relevant HDACs are the NAD+ independent class I HDACs 1, 2 and 3.

In a recent study of our group we describe detailed class I HDAC expression patterns in two large patient cohorts with gastric adenocarcinomas and report that HDAC1, HDAC2 and HDAC3 are differentially expressed in this tumor entity. To the best of our knowledge this is the first detailed systematic report on class I HDAC expression in this tumor entity. Enhanced expression of single class I HDACs in small sets of gastric carcinomas, when compared to normal gastric mucosa as detected by immunohistochemistry (HDAC2), rtPCR (HDAC1) and SAGE (HDAC3) have been reported. In addition, a decrease in acetylation of Histone H4 in gastric cancer tissue has been observed (11). However, given the fact that stromal cells and inflammatory cells express considerable amounts of class I HDACs as well, expression analysis by RNA array, qPCR, western blot and SAGE should always be complemented by in situ tissue analysis to localize the cell compartment being responsible for putatively elevated HDAC expression levels.

Since HDI treatment of cancer cells including intestinal cancer cells leads to signs of cell differentiation (12,13), we validated this in vitro observation. In both cohorts investigated expression of HDAC2 but not of HDAC1 and HDAC3 correlated with dedifferentiation in gastric cancer. This leads to the conjecture that HDAC2 plays a prominent role in this regard, and should be the focus of future functional studies.

Survival data were available for 49 patients in the training group and 123 patients in the validation group. In the validation cohort, 3-year survival was 44% (95% CI 34–57) in the HDAC1- negative group, 50% (39–64) in the HDAC2-negative group, and 48% (34–67) in the gHDAC-negative group. 3-year survival decreased to 21% (11–37) when HDAC1 was positive, 16% (9–31) when HDAC2 was positive, and 5% (1–31) when gHDAC (all isoforms) were positive. Those patients highly expressing one or two isoforms (the gHDACintermediate group) had an estimated 3-year survival of 40% (29–56). In multivariate analyses, high gHDAC and HDAC2 expression were associated with shorter survival in the training cohort (gHDAC: hazard ratio [HR] 4·15 [1·23–13·99], p=0·0250; HDAC2: HR 3·58 [1·36–9·44], p=0·0100) and in the validation cohort (gHDAC: HR 2·18 [1·19–4·01], p=0·0433; HDAC2: HR 1·72 [1·08–2·73], p=0·0225), independent of standard clinical predictors (14).

This study indicates that HDACs are possible biomarkers for shortened patient survival and presence of nodal metastasis in this disease, which corresponds well with recently published data on prognostic implications of histone modifications in gastric cancer (15). As the evaluation of staining of all isoforms is very straightforward and easy to determine, evaluation of HDAC expression status might be determined on small biopsy samples and hence might result in a modification of lymphadenectomy performed in the context of gastrectomy or may be a new target for targeted therapy of this subgroup of patients with poor prognosis. The fact that small tissue samples can provide sufficient information about HDAC expression status was shown in our study by comparing tissue micro arrays (training cohort) with conventional tissue sections (validation cohort). It is therefore conceivable that HDAC expression status might predict the therapeutic response to HDI in the treatment of gastric cancer. Like in other targeted therapies, it seems feasible, that response to treatment might be especially prominent in those patients, overexpressing the target.

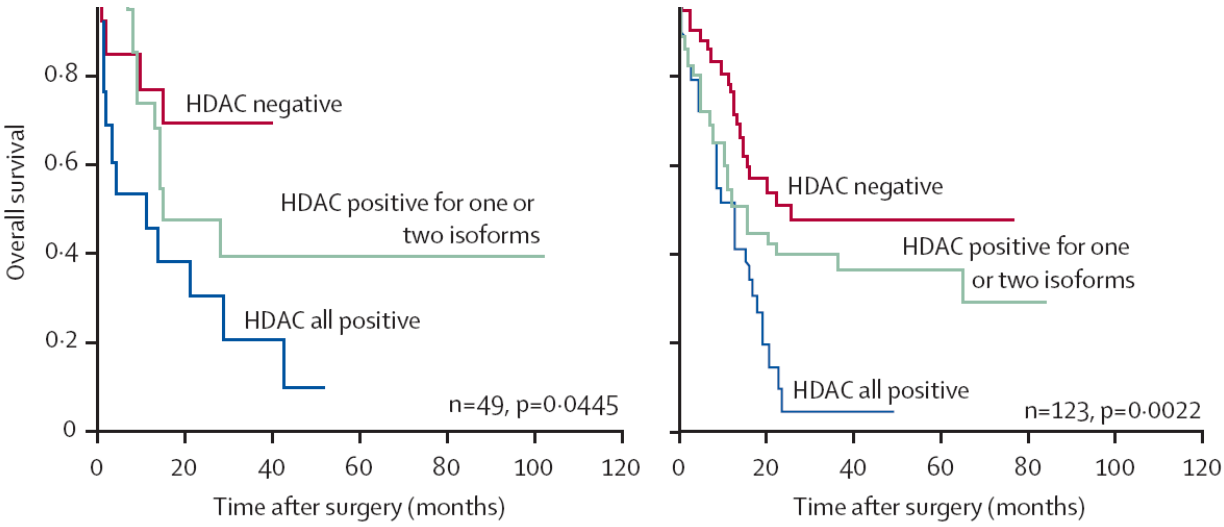



Figure 1: Survival in two cohorts of patients with gastric cancer overexpressing HDACs. Expression of at least one or more class I HDACs is associated with poor survival (Weichert et al., Lancet Oncology 2008).

This trial will be conducted to evaluate the efficacy, safety and tolerability of LBH589 as a second-line palliative therapy in patients overexpressing HDACs in metastatic gastric cancer.
Despite the efforts in front-line therapy, second-line protocols have not yet been established in randomized clinical trials for those patients. However, as many patients are still in good performance status and present with low tumor burden after failure of first-line chemotherapy, they may clearly benefit from second-line treatment. Even more, increasingly more metachronic metastatic patients urge for new platinum-free therapeutic options due to the fast-growing use of (neo-) adjuvant platin-based protocols.
So far, only sparse data on chemotherapy are available after failure of platin-based protocols. Irinotecan-containing combinations have been analyzed, and produced excellent response rates and survival times of up to 30% and 7.6 months, respectively (21,22 23). Furthermore, several trials have also confirmed that second-line regimens with irinotecan-based chemotherapy may be an option for patients with platin-refractory tumors.
Thus, there is an urgent need to establish new second-line treatment options for both, cisplatinum- or irinotecan-combination refractory patients with advanced or metastatic gastric cancer.
Our previous study indicates that HDAC expression is an independent prognostic factor for patients with gastric cancer. Targeting HDAC expressing cancers with HDI may therefore be a novel and valid approach to improve the overall poor survival of this patient group.

# 2 Study objectives

## 2.1 Primary Objective

The primary objective is to evaluate the antitumor activity of LBH589 administered as a single agent in patients with HDAC overexpressing metastatic gastric cancer refractory to Cisplatin- or Irinotecan-based chemotherapy.

The antitumor activity is determined by the confirmed objective response rate (CR and PR) according to RECIST-criteria measured by CT.

## 2.2 Secondary Objectives

The secondary objectives are:

- Effects of HDAC-Inhibitor LBH589 on the progression free survival (PFS)
- Effects of HDAC-Inhibitor LBH589 on survival (one-year survival and overall survival)
- Safety and tolerability of HDAC-Inhibitor LBH589

# 3 Investigational plan

## 3.1 Overall study design

This is an open-label, uncontrolled, phase II trial in an optimal Simon two-stage design evaluating the antitumor activity and safety of the oral HDAC-Inhibitor LBH589. The treatment started with 30 mg three times a week, on Monday, Wednesday and Friday in patients with chemo-refractory HDAC overexpressing metastatic adenocarcinoma of stomach, esophagogastric junction or lower esophagus (Barrett carcinoma). One cycle lasts 21 days. In case of good tolerability the dose is increased to 40 mg after the first cycle.
After the amendment performed on 26.10.2011 treatment started with 20 mg and was increased to 30 mg in case of good tolerability according to previous dose escalation scheme.
A total of 28 patients should be enrolled in this trial. In patients experiencing LBH589-related toxicity requiring treatment rest or dose reduction dose could be reduced to 30mg or 20 mg. Subsequent dose adjustment was permitted based on outcome. Treatment continued until disease progression or untolerable adverse events occurred. Subsequently, the patients were followed-up for one year.
According to the optimal Simon two-stage design an interim analysis was to be performed after a first stage of the trial including a total of 11 patients. If no objective responses were observed during the first stage then the trial should be stopped early and further investigation of the drug would not be warranted. Only if four or more objective responses are observed by the end of the trial (n=28 patients) further investigation of the drug was warranted.
Collection of data should be stopped one year after the recruitment of the last patient (except for SAE-data and drug accountability of the patients still on treatment).

## 3.2 Study population

The study sample consisted of 11 adult patients suffering from adeno-carcinoma of stomach or esophagogastric junction.

### 3.2.1 Inclusion and exclusion criteria

Inclusion Criteria:

1. Male and female patients aged 18 – 90 years
2. Signed and dated informed consent of the patient before the start of specific protocol procedures

3. Histologically proven adenocarcinoma of stomach, esophagogastric junction or lower esophagus (Barrett carcinoma)
4. Measurable metastatic disease according to the RECIST. If locally recurrent disease, it must be associated with at least one measurable lymph node (> 20 mm by CT scan or > 10 mm with spiral CT)
5. Overexpression of at least one class I HDAC in the cancer biopsy as assessed by immunohistochemistry.
6. Failure of prior palliative chemotherapy/chemotherapies (at least one Irinotecan- or Cisplatin-based). Failure is defined either by progression of disease or by significant toxicity that precludes further treatment.
7. At least 4 weeks from previous chemotherapy at first dose of trial drug
8. Resolution of all acute toxic side effects of prior therapy or surgical procedures to grade ≤ 1 NCI-CTC (except for the laboratory values)
9. Adequate organ function as defined by the following criteria:
    - Serum aspartate transaminase (AST; serum glutamic oxaloacetic transaminase [SGOT]) and serum alanine transaminase (ALT; serum glutamic pyruvic transaminase [SGPT]) ≤2.5 x upper limit of normal (ULN), or AST and ALT ≤5 x ULN if liver function abnormalities are due to underlying malignancy
    - Total serum bilirubin ≤1.5 x ULN
    - Absolute neutrophil count (ANC) ≥1500/μL
    - Platelets ≥100,000/μL
    - Hemoglobin ≥8.0 g/dL without support of growth factors (previous administration of erythrocyte concentrate is allowed)
    - Calculated CrCl ≥ 50 mL/min (MDRD Formula)
    - Serum calcium ≤12.0 mg/dL
    - Serum creatinine ≤2.0 x ULN
    - Lipase/Amylase ≤ 2,5 x ULN
    - All other laboratory values specified in chaper 7.5: resolution of all side effects of prior therapy or surgical procedure to grade < 3 NCI CTC
10. At least 4 weeks from any major surgery (at first dose of trial drug)
11. Karnofsky Performance Status (KPS) > 70
12. Life expectancy > 12 weeks
13. Patients must be able to swallow LBH589 capsules
14. Patients who understand the nature of the trial and are willing and able to comply with scheduled visits, treatment plans, laboratory tests and other trial procedures
15. Female patients who are capable of bearing children must have a negative pregnancy test result (serum or urine) at trial entry. All women included in the trial must be surgically sterile or postmenopausal or agree to employ adequate birth control measures for the duration of the trial and six months post-dosing. Male patients must be surgically sterile or must agree to use effective contraception during the trial and six months post-dosing

Exclusion Criteria:

1. Other tumor type than adenocarcinoma (e.g., leiomyosarcoma, lymphoma) or a second cancer except in patients with squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix which has been effectively treated. Patients curatively treated and disease free for at least 5 years will be discussed with the sponsor before inclusion
2. Patients with known brain or leptomeningeal metastases

3. Intake of non-permitted concomitant drugs (the coordinating investigator should be contacted to discuss the individual case), see chapter 5.4:

    - Concomitant treatment with antiarrhythmics and drugs with dysrhythmic potential (ie, terfenadine, quinidine, procainamide, disopyramide, sotalol, probucol, bepridil, haloperidol, risperidone, and indapamide)
    - Prior exposure to a HDAC inhibitor compound
    - Administration of potent CYP34A inhibitors during or within 7 days before start of LBH589-treatment (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin, diltiazem, verapamil, delavirdine, indinavir, saquinavir, ritonavir, atazanavir, nelfinavir, grapefruitjuice)
    - Administration of potent CYP3A4 inducers during or within 12 days before start of LBH589-treatment (e.g. dexamethason, rifampicin, rifabutin, carbamazepine, phenobarbital, phenytoin, St. John´s wort, efavirenz, tipranavir)
    - Ongoing treatment with therapeutic doses of anticoagulants such as Coumadin or heparins (however, low dose Coumadin up to 2 mg PO daily for deep vein thrombosis prophylaxis is allowed)
    - Any other medicinal anticancer therapy during treatment phase except treatment with non-conventional therapies (e.g. herbs or acupuncture) and vitamins/mineral supplements, provided that they do not interfere with the trial endpoint, in the opinion of the investigator
    - Concurrent systemic immune therapy, chemo- or hormone therapy
    - Concomitant or within a 4-week period administration (from first dose of trial drug) of any other experimental drug under investigation) and participation in another clinical trial

4. Any prior radiotherapy of target lesions
5. Bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection (> hemicolectomy or extensive small intestine resection with chronic diarrhea), Crohn's disease, ulcerative colitis
6. Current history of chronic diarrhea and/or diarrhea > CTCAE grade 3
7. Active disseminated intravascular coagulation, or patients prone to thromboembolism
8. Known human immunodeficiency virus (HIV) infection
9. Active uncontrolled infection
10. Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that would impart, in the judgment of the investigator, excess risk associated with trial participation or trial drug administration, or which, in the judgment of the investigator, would make the patient inappropriate for entry into the trial
11. Known allergic/hypersensitivity reaction to any of the components of the treatment; or known drug abuse/alcohol abuse
12. Impaired cardiac function or clinically significant cardiac diseases, including any one of the following:

    - Known history of QT interval prolongation, ongoing QT prolongation (>450 msec for males or > 470 msec for females), any cardiac ventricular dysrhythmias, atrial fibrillation of any grade
    - History or presence of sustained ventricular tachyarrhythmia. (Patients with a history of atrial arrhythmia are eligible but should be discussed with the Sponsor prior to enrollment)

- Any history of ventricular fibrillation or torsade de pointes
- Bradycardia defined as HR [heart rate, bpm beats per minute] < 50 bpm. Patients with pacemakers are eligible if HR ≥ 50 bpm.
- Screening ECG with a QTc > 450 msec
- Right bundle branch block + left anterior hemiblock (bifascicular block)
- Patients with myocardial infarction or unstable angina ≤ 6 months prior to starting study drug
- Other clinically significant heart disease (e.g., CHF NY Heart Association class III or IV , uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)

13. Patients who have received steroids (e.g. dexamethasone) ≤ 2 weeks prior to starting study treatment or who have not recovered from side effects of such therapy. Concomitant therapy medications that include corticosteroids are allowed if patients receive < 10 mg of prednisone or equivalent as indicated for other medical conditions, or up to 100 mg of hydrocortisone as pre-medication for administration of certain medications or blood products while enrolled in this study.

### 3.2.2 Interruption or discontinuation of treatment

Patients are free to discontinue the trial at any time without giving any reason.

The patient must be withdrawn from the trial in the event of any of the following:

- Withdrawal of patient consent
- Lack of compliance with trial procedures

The patient must be withdrawn from trial treatment, but will be followed-up for one year in the event of any of the following:

- Occurrence of an exclusion criterion which is clinically relevant and affects the patient's safety, if discontinuation is considered necessary by the investigator/sponsor
- Occurrence of progression of disease
- Occurrence of untolerable AEs, if discontinuation of LBH589 is desired by the patient or considered necessary by the investigator
- Any AE that results in a treatment interruption of more than 14 days within the active treatment cycle or more than 4 weeks between consecutive active treatment cycles
- Intolerance to trial treatment or necessity to reduce dose according to toxicity guidelines (see 5.2.), if current dose level is already at the lowest level used in the protocol (10 mg).
- Radiotherapy of target lesions or requirement for palliative radiotherapy for new lesions
- Pregnancy
- Intake of non-permitted concomitant drugs (the coordinating investigator should be contacted to discuss the individual case):

  - Concomitant treatment with antiarrhythmics and drugs with dysrhythmic potential (i.e, terfenadine, quinidine, procainamide, disopyramide, sotalol, probucol, bepridil, haloperidol, risperidone, and indapamide)

- Concomitant treatment with potent inhibitors of CYP3A4, e.g. ketoconazole, itraconazole, clarithromycin, erythromycin, diltiazem, verapamil, delavirdine, indinavir, saquinavir, ritonavir, atazanavir, nelfinavir, grapefruitjuice and potent inducers of CYP3A4, e.g. dexamethason, rifampicin, rifabutin, carbamazepine, phenobarbital, phenytoin, St. John´s wort, efavirenz, tipranavir

- Ongoing treatment with therapeutic doses of anticoagulants such as Coumadin or heparins (however, low dose Coumadin up to 2 mg PO daily for deep vein thrombosis prophylaxis is allowed)

- Any other medicinal anticancer therapy during treatment phase except treatment with non-conventional therapies (e.g. herbs or acupuncture) and vitamins/mineral supplements, provided that they do not interfere with the trial endpoint, in the opinion of the investigator

- Concurrent systemic immune therapy, chemo - or hormone therapy

- Any severe gastrointestinal perforation, thromboembolism, bleedings grade 3 or 4, new onset of nephrologic disease resulting in chronic kidney failure or severe hypertensive deterioration
- Insufficient patient compliance
- Lipase or Amylase ≥ 5 x ULN
- Major surgery
- Concurrent participation in another clinical trial

In case of withdrawal, the investigator should inquire about the reason of withdrawal, request by the patient to return all unused trial medication, request by the patient to come in for an end of treatment visit and follow up the patient regarding any unresolved adverse events.

## 3.3 Treatment

### 3.3.1 Investigational therapy and reference therapy

In the current study patients started treatment on day one (Monday, first week) with orally administered LBH 589, once daily (total daily dose 30 mg - after amendment 20 mg ) on Monday, Wednesday and Friday until day 21.
After a treatment duration with LBH 589 for 21 days (first treatment cycle), the dose was increased to 40 mg - after amendment to 30 mg.
Treatment duration for LBH 589 was intended until progression of disease or unacceptable toxicity.
Treatment after completion of the study was at the discretion of the investigator. If the drug was well tolerated and the patient was benefiting according to the investigator's assessment, the patient was eligible to continue on the treatment with LBH 589 until disease progression.
The study drug was supplied by Novartis to the pharmacy of Klinikum rechts der Isar respectively Mannheim and distributed to the study centers by the pharmacy.

### 3.3.2 Treatment assignment

Oral LBH589 was supplied as 5-mg or 20-mg pink/opaque-colored, hard gelatin capsules.

### 3.3.3 Blinding

Not applicable.

### 3.3.4 Concomitant therapy

Relevant additional treatments administered to the patient within two weeks before start of therapy or at any time during the trial are regarded as concomitant treatments and must be documented on the appropriate pages of the CRF.

All prior chemotherapy; biologic, immunologic, radiation therapy and surgery as cancer treatment or palliation, given > 4 weeks prior to the administration of study drug will be recorded in the prior antineoplastic therapy CRF. Prophylactic anti-emetics can be administered during the study at the discretion of the investigator. In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted with the following exceptions:

- Valproic acid (a known HDAC inhibitor) administration (even for the treatment of a non-malignant condition) is prohibited during the study.

### 3.3.5 Treatment compliance

Records of study medication used, dosages administered, and intervals between visits were kept during the study. Drug accountability was noted by the field monitor during site visits and at the completion of the trial. Patients were asked to return all unused medication at the end of the study.

## 3.4 Visit schedule and assessments

Table 1 lists all of the assessments and indicates with an “X” the visits when they were performed. Patients should have been seen for all visits on the designated day as close to it as possible. All data obtained from the assessments listed in Table 3.2 were to be supported in the patient’s source documentation.

### 3.4.1 Schedule of Assessments

Table 1 Schedule of Assessments

| | **Screening** | | **Treatment with LBH589** | | | **Post-Treatment** | | |
|---|---|---|---|---|---|---|---|---|
| **Protocol Activities and Forms to be Completed** | **Screening ≤ - 28 Days (+/-2d)** | **Screening ≤ - 7 Days (+/-2d)** | **Cycle 1** | | **Cycle 2 and subsequent** | **End of Treatment/ Withdrawal Visit <30 days after last dose (+/-2d)** | **28 Days Post-Treatment (+/- 2d) (5)** | **Survival Follow-Up Month 1,2,3,6, 9,12 ( +/- 2 weeks) (11)** |
| | | | **Day 1 (+/-2d)** | **Day 5 (+/-2d)** | **D1 of each following cycle 2,3,.. Each cycle 21 days** | | | |
| Signed Informed Consent | X | | | | | | | |
| In/Exclusion Criteria | X | X | | | | | | |
| Medical/Oncologiy History, Demographics | X | | | | | | | |
| Karnofsky Performance Status, Vital Signs, Weight | | X | X | X | X | X | | |
| Physical Examination (including Height) | | X | X | | X | | | |
| Concomitant Diseases/ Medication/Treatment | X | X | X | X | X | X | | X (2) |
| Toxicities from previous therapies | X | X | | | | | | |
| ECG | X | | X(12) | X | X | X | | |
| Hematology | | X | X (1) | | X | X | | |
| Clinical Chemistry | | X | X (1) | X | X | X | | |
| Urinalysis | | X | X (1) | X | X | X | | |
| Pregnancy Test (Urine or Serum) | | X | | | | | | |
| Tumor Assessment (CT/x-ray thorax, CT abdomen) | X(13) | | | | X (9) | (X) (4) | | (X) (6) |
| Registration of the Patient | | X | | | | | | |
| Adverse Events | | | X | X | X | X | X | X (3,5) |
| Compliance/Drug Accountability | | | X | X | X | X | | |
| Dose/Dose Adaptation | | | X (Mo,Mi 20 mg) | X (Fr 20 mg) | X (Mo,Mi,Fr 30 mg) | | | |
| | | | | | | | | |
| Post-Trial Survival/Progression Status | | | | | | | | X (7) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Scientific Programme** | | | | | | | | |
| Immunohistochemistry HDACs | (X) (8) | | | | | | | |
| Serum Biomarker discovery (freeze) | | X (10) | X (10) | | X (10) | | | |

(1) Cycle 1, day 1: Hematology, clinical chemistry and urinalysis not required if acceptable screening assessment is performed within 6 days prior to the start of treatment, if no relevant toxicity after cycle 1 Hematology, clinical chemistry and urinalysis only on day 1 necessary.
(2) Only further anticancer treatment
(3) Only follow-up of adverse events not resolved/stabilized at 28 days post-treatment visit
(4) If indicated. Preferably within 14 days after end of treatment; if not performed within the last 6 weeks
(5) Telephone contact sufficient. Only necessary if end of treatment visit was performed earlier than 26 days after end of treatment
(6) If data available
(7) Telephone contact sufficient, if possible visit preferred.
(8) Frozen tissue or paraffin-embedded tissue for immunohistochemistry from previous operations/biopsies
(9) Tumor assessment in cycles 3, 6, 9 and at the end of treatment visit (if indicated)
(10) Blood sampling: on day 1 of every cycle
(11) Telephone contact sufficient; 3,6,9 and 12 months after the end of treatment visit
(12) Cycle 1 ECG will be performed on day 1 and day 5: 3 predose ECGs over a period of -15 - 30 min before the patient receives their dose of LBH589 3 posttreatment ECGs at the following timepoints: 3h, 6h (only day 5), 24h (only if patients in hospital due to other treatment) From cycle 2 a predose ECG will be performed on day 1
(13) CT / X-Ray will be perfomed if previous scans older ca. > 3 weeks

### 3.4.2 Efficacy assessments

Efficacy of treatment was evaluated by clinical disease parameters, e.g. the response rate as determined by efficacy parameters from survival rates, rate and duration of response to treatment.

#### 3.4.2.1 Primary Endpoint

The primary endpoint was assessed by the objective response rate within 6 cycles ( 1 cycle = 3 weeks) defined as the percentage of patients with a confirmed reduction in tumor size compared to baseline fulfilling the criteria for complete or partial response as defined in chapter 7.
The response was measured by CT.

#### 3.4.2.2 Secondary Endpoints

**Efficacy assessments**

**Progression-free survival:**
Progression-free survival was defined as the time from first dose of trial medication to first documentation of objective tumor progression or to death due to any cause, whichever occurs first

**1-Year survival rate:**
1-Year survival rate was defined as the rate of patients surviving for at least one year after first dose of trial medication

**Overall survival:**
Overall survival was defined as a the time from first dose of trial medication to date of death due to any cause

**Safety assessments**

Safety assessments consisted of monitoring and recording all adverse events (AE) and serious adverse events (SAE), the regular monitoring of hematology, blood chemistry and urine values, vital signs, ECG and the performance of physical examinations. Safety and tolerability were assessed according to the NIH/NCI CTCAEv3 and 4.

**Safety Review Team**
A Safety Review Team reviewed the safety data during study duration and assessed the safety profile.

# 4 Protocol amendments, other changes in study conduct

## 4.1 Protocol amendments

There was one protocol amendment, approved 26.10.2011. Main changes concerned the administration of a reduced initial dose of study drug (initial dose) from 30 mg LBH 589 to 20 mg first 21 days. Seven patients were included prior to the amendment;.four of the patients were included post-amendment.

## 4.2 Other changes in study conduct

A new version of the Investigators Brochure (IB) has been released 23.05.2012 (approval EC 1.08.2012), but respectively a change of patients information was not necessary.

According to the optimal Simon two-stage design an interim analysis was planned after a first stage of the trial including a total of 11 patients. If no objective responses were observed during the first stage the trial should be stopped early and further investigation of the drug was not warranted.

Following the study protocol directives, in 2013 the clinical study has been closed prematurely due to the lacking efficacy of study drug.

# 5 Data management

## 5.1 Data collection

Designated investigator staff entered the information required by the protocol onto Case Report Forms (CRF) that were printed on paper. Field monitors reviewed the CRF for completeness and accuracy, and instructed site personnel to make any required corrections or additions. The CRF were forwarded to the MSZ by the investigational site, one copy being retained at the investigational site. Once the CRFs were received, their receipt was recorded, and they were forwarded to the responsible data management staff for processing.

## 5.2 Database management and quality control

Data items from the CRFs were entered centrally into the study database by MSZ staff using double data entry with verification upon second entry. Text items (e.g. comments) were entered once and checked manually against the CRFs. Adverse Events and SAEs were coded using the Medical dictionary for regulatory activities (MedDRA) terminology. When the database was declared to be complete and accurate, the database was locked. Any changes to the database after that time could only be made by joint written agreement between the Coordinating Investigator and the MSZ.

# 6 Statistical methods

## 6.1 Statistical methods

A detailed methodology for statistical analysis of the data collected in this trial has been documented in a Statistical Analysis Plan maintained by MSZ.

Descriptive statistical analyses were employed due to the observational nature of the study and the total sample size of N=11 patients.

**Primary endpoint:**

The number and proportion of patients achieving confirmed objective response (CR or PR) within the first six treatment cycles has been summarized along with the corresponding exact one-sided 95% confidence interval.

**Secondary endpoints:**

Progression-free survival (PFS), overall survival (OS) and 1-year survival rate have been estimated using Kaplan-Meier methods and displayed graphically where appropriate. The analysis of safety, response duration, symptomatic parameters and pathway activity outcomes is given as case reports due to small sample size.

**Other endpoints:**

Descriptive statistics were used to summarize all patient characteristics, treatment administration/compliance, and safety parameters.

### 6.1.1 Populations

The **Safety Analysable Population** includes all patients who received at least one dose of LBH 589.
The **ITT Population** includes all enrolled patients who received at least one dose of LBH 589. The ITT/Safety population is the primary analysis population.
The **per protocol population (PPP)** is defined as the population of patients without major protocol violation during trial. Examples for possible major protocol violations include a missing baseline assessment of disease or an incorrect histological cancer type based on prior histology.
The **evaluable patient population (EPP)** is defined as the population of patients who have received at least one cycle of treatment and for which at least one tumor assessment has been documented after baseline for early responders.
All analyses were carried out for the ITT/Safety population. For the PPP and the EPP only a subset of efficacy analyses was performed.

### 6.1.2 Background and demographic characteristics

The demographics (age, sex, and race), diagnoses and extent of cancer disease history and baseline characteristics (performance status) were summarized for all patients enrolled. All other data were listed for all patients enrolled.

### 6.1.3 Concomitant therapy

The use of concomitant therapy deemed necessary for the care of the patient was allowed with the exception of other investigational therapy, chronic treatment with immunosuppressive agents, other anticancer agents than study medication (leads to withdrawal of the patient from the study) during participation of the study. Certain concomitant therapy should be avoided (e.g. due to interference with study medication).

### 6.1.4 Efficacy evaluation

**Primary efficacy parameters**

**Complete Response (CR)** was defined as the disappearance of all target lesions.

**Partial response (PR)** was defined as a ≥ 30% decrease in the sum of the longest dimensions of the target lesions taking as a reference the baseline sum longest dimensions.

**Progressive disease (PD)** was defined as a ≥ 20% increase in the sum of the longest dimensions of the target lesions taking as a reference the smallest sum of the longest dimensions recorded since the treatment started, or the appearance of one or more new lesions.

**Stable disease (SD)** was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as a reference the smallest sum of the longest dimensions since the treatment started.

Target Lesions

**Complete response (CR)** was defined as the disappearance of all target lesions.

**Partial response (PR)** was defined as a ≥ 30% decrease in the sum of the longest dimensions of the target lesions taking as a reference the baseline sum longest dimensions.

Non-Target Lesions

**Complete response (CR)** was defined as the disappearance of all non-target lesions.
**Incomplete response (SD)** was defined as a persistence of ≥ 1 non-target lesions.

**Secondary efficacy parameters**

**PFS** was defined as the time between the first dose of study medication and first documentation of objective tumor progression or death, whichever occurs first. PFS data were censored on the day after the last tumor assessment during trial which documents absence of progressive disease for patients who do not have objective tumor progression

and who did not die while on trial or who are given antitumor treatment other than the trial treatment prior to observing objective tumor progression.

**1-year survival** was defined as the rate of patients surviving for at least one year after first dose of trial medication.

**Overall survival** was defined as the time from first dose of trial medication to date of death due to any cause.

### 6.1.5 Safety evaluation

Safety assessments included the recording of adverse events (AEs) and serious AEs (SAE), along with evaluation of their severity, duration and relationship to the study drug. In addition, regular monitoring of hematology and blood chemistry results, pregnancy tests, and assessment of vital signs and body weight were performed.

### 6.1.6 Interim analyses

An Interim Analysis was not conducted.

### 6.1.7 Other topics

Not applicable

## 6.2 Sample size and power considerations

Sample size was determined using the 'optimal Simon two-stage design', assuming that a objective response rate (ORR) of 20% would indicate potential usefulness of treatment, whereas a rate of 5% would be the lower limit of interest (historical objective response rate (ORR) of at most 0.05). A total of 28 subjects would have been required to establish this treatment effect with a power of 80% and a one-tailed 5% overall type I error level. According to the two stage design 11 patients have been accrued during stage 1 and 17 should have been during stage 2. If no responses were observed during the first stage then the trial should be stopped early. Only if 4 or more responses would have been observed by the end of the trial (n=28 patients) further investigation of the drug would have been warranted.
It has been assumed that a couple of enrolled patients would drop out before having received any dose of trial medication. These patients should have been replaced to achieve 28 patients in the ITT population.

# 7 Patients studied

## 7.1 Patient disposition

In total, 11 patients were included (first patient included: 21.08.2009; last patient included: 19.07.2012). None of the 11 patients who received study medication is still under treatment or concluded the one year follow-up (i.e. premature discontinuation of all patients).

Three of eleven patients discontinued study therapy due to disease progression (5 – 8 weeks after inclusion in the study), four patients discontinued prematurely for various reasons

(abdominal pain suspect for ileus, reflux esophagitis, worsening of general condition) and four patients discontinued study therapy after withdrawal of consent.

Table 2 Patient Disposition

| patient | first study drug adminstration | last study drug adminstration | progression of disease | study discontinuation | death |
|---|---|---|---|---|---|
| 0101 | 24.08.2009 | 28.09.2009 | | 28.08.2009 | 14.11.2009 |
| 0102 | 28.09.2009 | 02.10.2009 | | 08.10.2009 | 09.11.2009 |
| 0103 | 02.11.2009 | 01.01.2010 | 04.01.2010 | 04.01.2010 | 06.02.2010 |
| 0104 | 30.11.2009 | 23.04.2010 | 18.06.2010 | 23.04.2010 | 27.09.2010 |
| 0105 | 20.09.2010 | 08.10.2010 | 29.10.2010 | 08.10.2010 | 27.12.2010 |
| 0106 | 11.10.2010 | 19.11.2010 | 18.11.2010 | 19.11.2010 | 09.05.2011 |
| 0107 | 20.06.2011 | 05.08.2011 | 05.08.2011 | 08.08.2011 | 22.11.2011 |
| 0108 | 26.03.2012 | 08.06.2012 | | 08.06.2012 | |
| 0109 | 11.06.2012 | 20.07.2012 | | 27.07.2012 | |
| 0201 | 12.07.2012 | 30.07.2012 | 29.08.2012 | 09.08.2012 | 08.03.2013 |
| 0202 | 02.08.2012 | 01.10.2012 | | 11.10.2012 | 16.11.2012 |

## 7.2 Baseline demographic and background characteristics

A total of 11 patients were enrolled (first patient included: 21.08.2009; last patient included: 19.07.2012) at two different study centres:

Klinikum rechts der Isar (MRI) der TUM 9 patients
Universitätsklinikum Mannheim 2 patients

The median age in this clinical trial was 59 years (range, 40 - 80 years) and the male/female ratio was 10/1. Ethnicity of all patients was Caucasian.
Nine patients had a history of surgery, four patients underwent gastrectomy, three had an esophagectomy and one patient had an explorative laparotomy and one a laparoscopy. Three patients had a history of radiation therapy (RTX / RCTX). The prior administered chemotherapies are scheduled for each patient in table 4.

Table 3 Demographic and Background Characteristics

| Characteristics | N = 11 |
|---|---|
| | |
| Median age (range), years | 59 (40-80) |
| Male/female | 10 / 1 |
| **ECOG / PS** | |
| ECOG 0 | 7 |
| ECOG 1 | 4 |
| ECOG 2 | 0 |
| **Primary tumor site** | |

| | |
|---|---|
| Gastroesophageal junction | 8 |
| Stomach | 3 |
| **Histology** | |
| well / moderately differentiated | 3 |
| poorly differentiated / signet- ring cell type | 8 |
| **Disease status** | |
| Locally advanced | 7 |
| Metastatic | 8 |
| **Metastatic sites** | |
| Liver | 7 |
| Lymph nodes | 4 |
| Peritoneum | 2 |
| Lung | 4 |
| Bone | 0 |
| Other | 1 |

ECOG Eastern Cooperative Oncology Group
PS Performance status

Table 4 History of chemotherapy

| Patient Number | Drug/Combination | # cycles | Start Date | End Date | Best Response |
|---|---|---|---|---|---|
| Mannheim 1 | Flot | 4 | May-11 | Jul-11 | SD |
| | Flot | 4 | Sep-11 | Oct-11 | PD |
| | Folfin | 6 | Feb-12 | Apr-12 | PD |
| | Doxetacel Mono | 3 | Apr-12 | Jun-12 | PD |
| 2 | Flot | 6 | Nov-11 | Jan-12 | PD |
| | Folfiri | 5 | Jan-12 | Jun-12 | PD |
| München 1 | neoadjuvant ECX | | Jul-08 | Aug-08 | |
| | ILF | | Dec-08 | Jan-09 | PD |
| | Taxol mono | | Feb-09 | Mar-09 | PD |
| 2 | Glivec + Xeloda + Cisplatin | | Mar-09 | Apr-09 | PD |
| | FOLFIRI | | May-09 | Jul-09 | PD |
| 3 | Imatinib Xeloda Cispaltin | 2 | Feb-09 | Apr-09 | |
| | FOLFIRI | 5 | Jul-09 | Sep-09 | PD |
| 4 | Taxol/PLF | 3 | Mar-08 | Jun-08 | SD |
| | Capecitabin | 1 | Sep-08 | Oct-08 | CR |
| 5 | PLF neoadjuvant | 2 | Sep-09 | Dec-09 | SD |
| | FOLFIRI | | Mar-10 | Sep-10 | PD |
| 6 | Imatinib, Cisplatin, 5FU | 4 | Oct-09 | Feb-10 | PR |
| | FOLFIRI | 13 | Mar-10 | Sep-10 | PD |
| 7 | Imatinib, Cisplatin, 5 FU | 2 | Jun-09 | Jul-09 | PR |
| | FOLFOX | 2 | Aug-10 | Oct-10 | PD |
| | FOLFIRI | 2 | Mar-11 | May-11 | PD |
| 8 | FLOT | 12 | Mar-11 | Aug-11 | PR |
| | REMOVAB | 4 | Sep-11 | Sep-11 | SD |
| | FOLFIRI | | Nov-11 | Feb-11 | PD |
| 9 | Cisplatin / 5FU | 2 | Jul-10 | Aug-10 | |
| | Cisplatin / 5FU | 6 | Jun-11 | Nov-11 | PD |

| | | | | |
|---|---|---|---|---|
| Taxotere | 4 | Nov-11 | Feb-12 | PD |
| Irinotecan | 3 | Feb-12 | Apr-12 | PD |
| Mitomycin / Xeloda | 1 | Apr-12 | May-12 | PD |

## 7.3 Protocol deviations

Protocol deviations mainly concerned deviations in laboratory and ECG assessment (e.g. missing parameters, times), as well as delay in scheduled visits.

## 7.4 Groupings for analysis

Since all patients received at least one dose of LBH 589, by definition, all patients (n=11) were included into the Safety Analysable Population (SAP) and Intent to Treat Population (ITT). The ITT/Safety population was the primary analysis population.
For the Evaluable Patient Population (EPP), data of five patients were analysed. The other patients were excluded due to missing tumor assessment after baseline.

# 8 Medication

## 8.1 Study medication

Oral LBH 589 (Panobinostat) was supplied as 5-mg or 20-mg pink/opaque-colored, hard gelatin capsules.

Medication labels complied with the legal requirements of ICH-GCP and were printed in local language. They supplied no information about the patient. The storage conditions for study drug have been described on the medication label.

### 8.1.1 Dosage

In the current study, patients started treatment on day one (Monday, first week) with orally administered LBH 589. Study drug was taken once daily (dose 30 mg) on Monday (day 1), Wednesday (day 3) and Friday (day 5) until day 21. After a treatment duration with LBH 589 for 21 days (first treatment cycle), the dose was increased to 40 mg. According to the amendment approved on the 26.10.2011, starting dose was reduced to 20 mg and next dosage step was 30 mg.
Treatment duration for LBH 589 was intended until progression of disease or unacceptable toxicity.

Treatment after completion of the study was at the discretion of the investigator. If the drug was well tolerated and the patient was benefiting according to the investigator's assessment, the patient was eligible to continue on the treatment with LBH 589 until disease progression. The study drug was supplied by Novartis to the pharmacy of Klinikum rechts der Isar and distributed to the study centers by the pharmacy.

### 8.1.2 Patient exposure

For treatments administered please refer to Table 5:

Table 5 Treatments administered

| Patient Number | First | Last | Duration (days) | Completed Cycles | Start dose | Dose increase | continue dose |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| 0201 | 12.07.2012 | 30.07.2012 | 18 | 1 | 20 mg | - | 20 mg |
| 0202 | 02.08.2012 | 01.10.2012 | 60 | 2 | 20 mg | 30 mg | 20 mg |
| | | | | | | | |
| 0101 | 24.08.2009 | 28.09.2009 | 35 | 1 | 30 mg | 40 mg | 40 mg |
| 0102 | 28.09.2009 | 02.10.2009 | 4 | 0 | 20 mg | - | - |
| 0103 | 02.11.2009 | 01.01.2010 | 60 | 3 | 20 mg | - | 20 mg |
| 0104 | 30.11.2009 | 23.04.2010 | 144 | 7 | 20 mg | 30 mg | 20 mg |
| 0105 | 20.09.2010 | 08.10.2010 | 18 | 1 | 20 mg | - | 20 mg |
| 0106 | 11.10.2010 | 19.11.2010 | 39 | 2 | 20 mg | - | 20 mg |
| 0107 | 20.06.2011 | 05.08.2011 | 46 | 2 | 20 mg | - | 20 mg |
| 0108 | 26.03.2012 | 08.06.2012 | 74 | 3 | 20 mg | - | 20 mg |
| 0109 | 11.06.2012 | 20.07.2012 | 39 | 2 | 20 mg | 30 mg | 20 mg |

## 8.2 Concomitant medication

The use of concomitant therapy deemed necessary for the care of the patient was allowed with the exception of other investigational therapy, other anticancer agents than study medication (lead to withdrawal of the patient from the study) during participation of the study. Certain concomitant therapy should have been avoided (e.g. due to interference with study medication).

# 9 Efficacy results

## 9.1 Primary efficacy results

The primary objective was to evaluate the antitumor activity of LBH589 administered as a single agent in patients with HDAC overexpressing metastatic gastric cancer.
Primary evidence of antineoplastic activity was evaluated as a function of objective tumor response. An overall objective assessment of all measurable, evaluable, and non-evaluable disease was performed according to the Visit Schedules (see schedule attached). Tumor response has been defined by the RECIST criteria. Tumor assessments were performed by CT scans. Radiological studies had to account for all lesions that were present at baseline and had to use the same techniques as used at baseline. All known disease manifestations (measurable, evaluable, and nonevaluable) had to be accounted for when assessing objective tumor status. Current objective tumor status had to be captured on the Tumor Assessment/End of Cycle Information CRF.

In our study, 7 of 11 patients were evaluable for the first tumor response (assessment cycle 3). Two of these 7 patients (2/7, 29%) achieved stable disease in the first tumor assessment. The other 5 patients (5/7, 71%) had progressive disease in the first tumor assessment.

The time point of the second tumor assessment (cycle 6) was only reached by one patient (1/7, 14%), who achieved stable disease again.

The different reasons for earlier discontinuation of the study conduct are listed and described in detail in the section on adverse events and serious adverse events.

Table 6 Tumor response

| patient | study start | last study drug adminstration | first tumor assessment | second tumor assessment | progression of disease |
|---|---|---|---|---|---|
| 0101 | 24.08.2009 | 28.09.2009 | - | - | - |
| 0102 | 28.09.2009 | 02.10.2009 | - | - | - |
| 0103 | 02.11.2009 | 01.01.2010 | 04.01.10: PD | - | 04.01.2010 |
| 0104 | 30.11.2009 | 23.04.2010 | 25.01.10: SD | 20.04.10: SD | 22.06.2010 |
| 0105 | 20.09.2010 | 08.10.2010 | 29.10.10: PD | - | 29.10.2010 |
| 0106 | 11.10.2010 | 19.11.2010 | 18.11.10: PD | - | 18.11.2010 |
| 0107 | 20.06.2011 | 05.08.2011 | 05.08.11: PD | - | 05.08.2011 |
| 0108 | 26.03.2012 | 08.06.2012 | 22.05.12: PD | - | - |
| 0109 | 11.06.2012 | 20.07.2012 | - | - | - |
| 0201 | 12.07.2012 | 30.07.2012 | - | - | 29.08.2012 |
| 0202 | 02.08.2012 | 01.10.2012 | 12.09.12: SD | - | - |

## 9.2 Secondary efficacy results

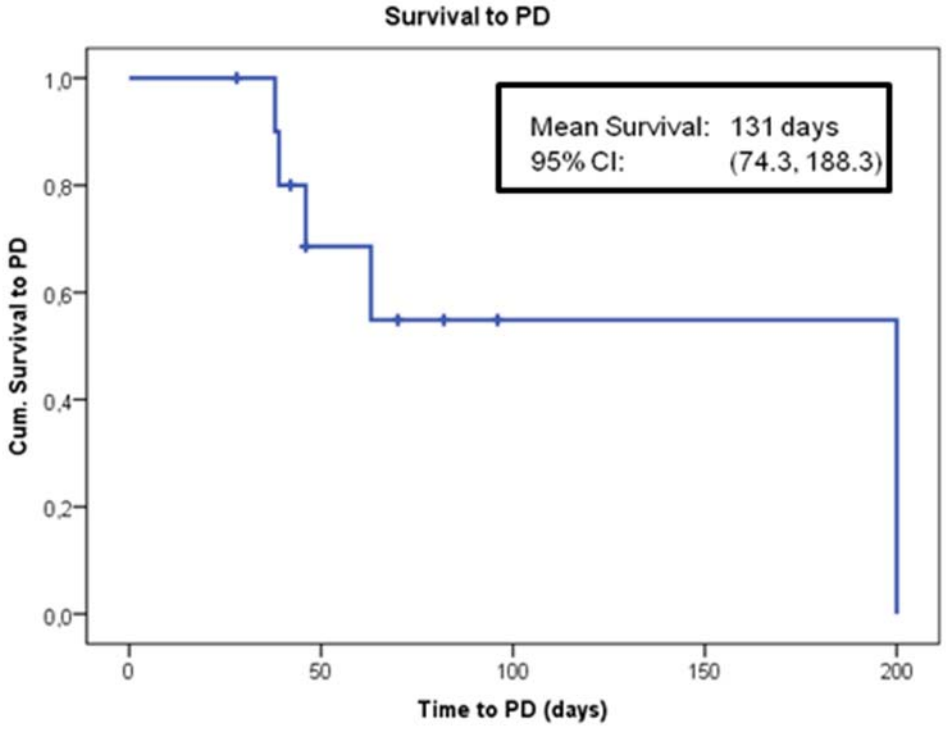
The secondary objectives of this study were the effects of HDAC-Inhibitor LBH 589 on the progression free survival (PFS), on the one-year survival and on the overall survival (OS) as well as the safety and tolerability of LBH 589.

**Progression free survival (PFS)** was defined as the time from first dose of trial medication to first documentation of objective tumor progression or death to any cause, whichever

occurs first. PFS data were censored on the day after the last tumor assessment during trial which documents absence of progressive disease for patients who do not have objective tumor progression and who did not die while on trial or who are given antitumor treatment other than the trial treatment prior to observing objective tumor progression.

Mean PFS in this study were 131 days (95% CI: 74,3; 188,3 days).

Figure 1: Kaplan-Meier estimate for PFS (time given in days) for the ITT:




| Total | Number of events | Censored | |
|---|---|---|---|
| | | N | Percent |
| 11 | 5 | 6 | 54,5% |

**One-year survival** was defined as the rate of patients surviving for at least one year after first trial medication. In our study, all patients died in the course of the first year after start of study treatment, so the one-year survival rate was 0% (0/11 patients).

**Overall Survival** was assessed by the time between the administration of the first dose of LBH 589 and death due to any cause.

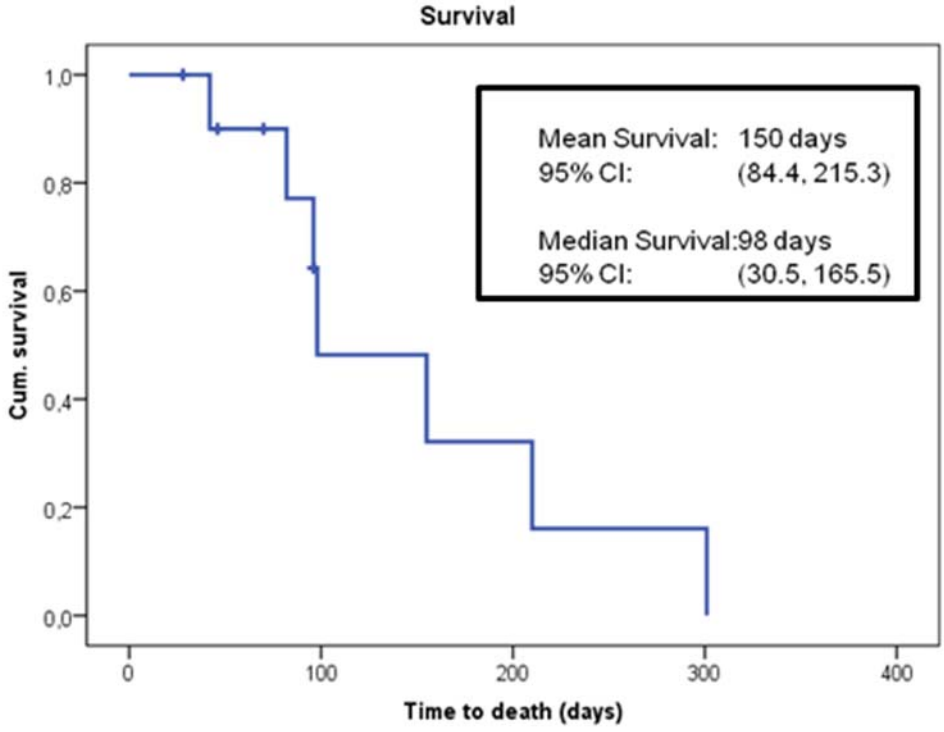
In table 7 the dates for start of therapy with LBH 589, premature discontinuation and death are listed:

Table 6 Start of therapy, premature discontinuation, death, withdrawal of consent

| patient | study start | Premature study discontinuation | death | Withdrawal of informed consent |
|---|---|---|---|---|
| 0101 | 24.08.2009 | 14.11.2009 | 14.11.2009 | |
| 0102 | 28.09.2009 | 08.10.2009 | 09.22.2009 | |
| 0103 | 02.11.2009 | 04.01.2010 | 06.02.2010 | |
| 0104 | 30.11.2009 | 12.04.2010 | 27.09.2010 | |
| 0105 | 20.09.2010 | 08.10.2010 | 27.12.2010 | |
| 0106 | 11.10.2010 | 19.11.2010 | 09.05.2011 | |
| 0107 | 20.06.2011 | 08.08.2011 | 22.11.2011 | |
| 0108 | 26.03.2012 | 30.06.2012 | | 30.06.2012 |
| 0109 | 11.06.2012 | 27.07.2012 | | 27.07.2012 |
| 0201 | 12.07.2012 | 09.08.2012 | | 09.08.2012 |
| 0202 | 02.08.2012 | 11.10.2012 | | 11.10.2012 |

Median overall survival was 98 days (95% confidence interval 30,5;165,5) for the ITT population.

Figure 2: Kaplan-Meier estimate for overall survival (time given in days) for the ITT:



# 10 Safety results

Safety information collected included in addition to adverse events (AE), serious adverse events (SAE) and serious adverse reactions (SAR) data on performance status, the regular monitoring of hematology, blood chemistry and urine values, regular measurements of vital signs, ECG and the performance of physical examinations.

Details on the data that had to be collected are provided in the clinical study protocol (Clinical study protocol: Safety assessments).
AEs were graded according to the NIH/NCI CTCAE v 4.

**Safety Review Team**
A Safety Review Team reviewed the safety data during study duration and assessed the safety profile.

During the conduct of the study safety information was also compiled in one Annual Safety Report (21.08.2009-31.03.2011) and two Development Safety Reports (DSUR, 01.04.2011-08.06.20012, and 09.06.12-08.06.13); a change in the risk-benefit evaluation of the study had not occurred from assessments of safety information or from changes in the IB, which were deemed non-substantial.

## 10.1 Overall experience of adverse events (AEs)

A total of 74 adverse events (AEs) were reported in 11 patients. Severity grading revealed 34 (46%) events to be of mild severity, 28 (38%) events to be moderate and 12 (16%) to be severe. None of the AEs was graded as life-threatening or lethal. Relation to study drug was considered as certain only for three (4,1%) adverse events, a probable relationship was noted for 8 (11%) and a possible for 23 (31 %) adverse events. No relation to study drug was seen in 34 (46%) of the registered 74 adverse events. Only two (2,7%) of the 74 adverse events led to a hospitalization of the patients. In 31 (42%) cases patients recovered completely from the adverse events, 38 (52%) were ongoing – mainly due to underlying disease.

Table 7 presents an overview of all adverse according to organ classes and severity grading (severity grading according to NIH/NCI CTCAE version 4 )

| Adverse event | n | Toxicity grade | | |
|---|---|---|---|---|
| | | 1/2 | 3 | 4 |
| ***Hematologic toxicity*** | | | | |
| Thrombocytopenia | 3 | 1 | 2 | |
| Increase of hemoglobin | 2 | 1 | 1 | |
| ***Gastrointestinal toxicity*** | | | | |
| Nausea | 6 | 2 | 4 | |
| Vomiting | 4 | 4 | | |
| Diarrhea | 3 | 3 | | |

| | | | | |
|---|---|---|---|---|
| Anorexia | 2 | 2 | | |
| Constipation | 4 | 4 | | |
| Abdominal pain | 5 | 3 | 2 | |
| Gastroesophageal reflux / gastritis | 3 | 1 | 2 | |
| Gastrointestinal bleeding | 1 | 1 | | |
| Dysphagia | 3 | 3 | | |
| Dyspepsia | 1 | 1 | | |
| Ascites | 1 | 1 | | |
| Sub-(ileus) | 2 | | 2 | |
| ***Infections*** | | | | |
| Urinary tract infection | 2 | 2 | | |
| Pneumonia | 1 | | 1 | |
| ***Others*** | | | | |
| Fatigue | 6 | 6 | | |
| Worsening of general condition | 3 | 2 | 1 | |
| Sleep disorder | 3 | 3 | | |
| Proctitis | 1 | 1 | | |
| Edema | 3 | 3 | | |
| Sensory neuropathy | 3 | 3 | | |
| Rash | 1 | 1 | | |
| Inguinal hernia | 1 | 1 | | |
| Hypertension | 1 | 1 | | |
| Angina pectoris | 1 | 1 | | |
| Dyspnoea | 1 | 1 | | |
| Alopecia | 1 | 1 | | |
| Arthralgia / back pain | 3 | 3 | | |
| Exsiccation | 1 | 1 | | |
| Cachexia | 1 | 1 | | |
| Cold | 1 | 1 | | |

## 10.2 Deaths, other serious and other significant adverse events

### 10.2.1 Deaths and other serious adverse events (SAEs)

A total of 7 SAEs were reported in 11 patients (see Table 8).
In most cases, serious adverse events were due to underlying disease and or related to progression of disease.

Table 8 Overview of SAEs

| PatNr | date | SAE | Relation to study drug | outcome |
|---|---|---|---|---|
| 0101 | 28.09.2009 | thrombocytopenia grade 3 | suspected | recovered |
| 0102 | 08.10.2009 | subileus | unrelated | recovered |
| 0103 | 07.01.2010 | worsening of general condition | unrelated | recovered |
| 0105 | 08.10.2010 | refluxesophagitis | unrelated | recovered |

| | | | | |
|---|---|---|---|---|
| 0105 | 05.09.2010 | nausea / esophageal reflux | unrelated | not recovered |
| 0108 | 13.04.2012 | gastric outlet stenosis | un related | not recovered |
| 0109 | 23.07.2012 | pneumonia | unrelated | recovered |

### 10.2.2 Other significant adverse events

**Suspected Serious Adverse Reactions (SARs)**

The sponsor's assessment of SARs was determined by referring to the IBs and SMPCs. There have no SARs been reported in the study.

**Suspected Unexpected Serious Adverse Reactions (SUSAR)**
The sponsor's assessment of SUSARs was determined by referring to the IBs and SMPCs. In this study no SUSARs have been reported.

### 10.2.3 Evaluation of deaths and other serious or significant adverse events

During the conduct of the study safety information was compiled in one Annual Safety Report (21.08.2009-31.03.2011) and two Development Safety Reports (DSUR, 01.04.2011-08.06.20012, and 09.06.12-08.06.13) and provided to the Health Authority and Ethics Committee. A change in the risk-benefit evaluation of the study had not occurred from assessments of safety information or from changes in the IB, which were deemed non-substantial.

## 10.3 Laboratory values, vital signs, ECG

Relevant changes in laboratory parameters, vital signs or ECG were assessed at predefined time points and captured as AEs throughout the conduct of the study (refer to table 7).

## 10.4 Special safety topics

There are no additional topics for discussion.

# 11 Discussion and overall conclusions

## 11.1 Discussion

Gastric cancer is still the third leading cause of cancer death, although mortality has declined over the past 50 years (1). Chemotherapeutic regimes to improve quality of life and survival have been established over the last 20 years. Despite the improvements in first-line therapy, chemotherapy second-line protocols have only insufficiently been applied to date. After failure of platin-based or irinotecan-containing regimens, many patients are still in good performance status and may benefit from further treatment – so there is a great need for new therapeutic approaches.

Due to our previous studies about the prognostic relevance of HDAC expression in gastric cancers it seems obvious that targeting HDAC expression might be promising in this patient group with poor overall survival.
This trial was conducted to evaluate efficacy, safety and tolerability of the HDAC inhibitor LBH 589 as a single agent in patients with HDAC overexpressing metastatic gastric cancer refractory to cisplatin- or irinotecan-based chemotherapy.
According to an optimal Simon two-stage design 28 patients were planned to be enrolled with performing an interims analysis after the first stage of the trial including 11 patients. Objective tumor response of at least one patient of these 11 was postulated for continuing this trial.
In summary, previous HDAC-analyses of tumor tissue were perfomed in 52 cases between 30.06.2009 and 20.06.2012 to detect 11 patients positive for HDAC-1 which could be finally included in the study ( first patient included 21.08.2009, last patient included 2.08.2012).
Patient baselines characteristics were well-balanced aside from gender distribution and histological tumor grading. Only three patients suffered from well or moderate differentiated tumors compared to 8 suffering from poorly differentiated tumors – potentially consistent with the poorer prognosis expected in HDAC-positive tumors.
The mean time of treatment duration was 49 days (range 4 to 144 days). In four patients (4/11; 36%) discontinuation of study treatment was based on objective tumor progression. Another four patients withdrew their informed consent mainly due to worsening of general condition unrelated to study drug. Three patients stopped study treatment due to serious adverse events or adverse events that disqualified them from further tumor treatment respecting their performance status and life quality.

Regarding the primary objective in our study, 7 of 11 patients were evaluable for the first tumor response (assessment cycle 3). Two of these 7 patients (2/7, 29%) achieved stable disease in the first tumor assessment. The other 5 patients (5/7, 71%) had progressive disease in the first tumor assessment. One patient (1/7, 14%) with stable disease in first tumor assessment achieved stable disease in the second tumor assessment (cycle 6) also. The second patient with stable disease at the first staging during trial withdrew informed consent before date of second tumor assessment due to personal decision. So, there was no case of objective tumor reduction in the 11 included patients but stable disease in over 20% of the patients at the first tumor assessment – aware of the reduced significance regarding the small sample size.

Regarding the secondary objectives of our study the small sample size and the great variety in the clinical course of the included and evaluable patients have to be considered. For determination of progression free survival (PFS) 5 patients have to be censored in the course of evaluation due to premature study discontinuation. In summary, the mean progression free survival (PFS) in our trial was 131 days (95% CI: 74,3; 188,3 days). Compared with available historical controls this result correlates with expectable time to progression and is notable regarding the assumed extraordinary poor prognosis of our study patients.
Another secondary objective was the overall survival (OS) of our study patients assessed by the time between the administration of the first dose of LBH 589 and death due to any cause.
The median overall survival was 98 days (95% confidence interval 30,5;165,5 days) and the mean overall survival was 150 days (95% confidence interval 84,4; 215,3 days) for the ITT population. These data are behind those of historical controls maybe confirming the poorer prognosis of our trial patients due to HDAC-expression. However the small sample size of our trial and the varying courses of disease during the trial have to be considered while interpreting these data.
The safety and tolerability evaluation of trial medication HDAC inhibitor LBH 589 revealed no really unexpected toxicity. Of the total 74 adverse events only 16% were judged as severe, 46% as mild and 38% as moderate. No adverse event was life-threatening or lethal. Relation

to study drug was considered as certain only for three (4,1%) adverse events, all other AEs might be due to symptoms of underlying disease. Also regarding the serious adverse events only one might be related to study drug because thrombocytopenia is a well-known side effects of study drug. According to most of the AEs and SAEs being probably rooted in underlying tumor disease, a great part (52%) of their symptoms were ongoing.
Regarding the maximum dose of administered study drug, we got to state that in most cases 20 mg of LBH 589 were the best tolerable dosage. In spite of lacking study drug specific side effects diverse other complains of the patients led to an early reduction of the LBH 589 dose to 20 mg (refer to table 5) Mainly gastrointestinal disorders like nausea, vomiting or constipation as well as diarrhea caused a reduced dosage. For this reason the protocol amendment approved 05.05.2011 was performed.

## 11.2 Conclusions

In summary, the treatment with HDAC inhibitor LBH 589 was well tolerated. Though, deterioration of patients` performance status according to advanced malignant disease limited the maximum applicable dose of the study drug to only 20 mg in most cases. The worsening of general condition also and diverse symptoms caused by underlying disease complicated the conduct of the study trial corresponding to the study protocol. Even the withdrawals of informed consent were mainly based on this.

Even though one patient achieved stable disease for nearly six month no great activity of the study drug on tumor growth could be observed. Progression free survival and overall survival could also not be increased significantly. But considering the small number of patients assessable for response, no definite conclusion can be made**.**

So, this trial was feasible regarding the safety and tolerability of the study drug, but regarding the results for the primary and secondary objectives the data were disappointing. HDAC inhibitor does not seem to have the potential to substantially change outcome in the patient population of this study.

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