Public Title	LBH589 Alone or in Combination With Erythropoietin Stimulating Agents (ESA) in Patients With Low or Int-1 Risk MDS
Scientific Title	A one year, open label, multicenter trial of LBH589 alone or in combination with ESA in red blood cell transfusion-dependent LOW and INT-1 MDS patients being either refractory to ESA or with a low probability of response – the GErman PAnobinostat low Risk MDS trial – GEPARD study
Short Title	GEPARD
Id KN/ELN	LN_DEUTSC_2009_328
Trialgoup	Deutsche MDS
Type of Trial	multicentric, open-label
Phase	Phase II
Disease	Myelodysplastic Syndrome(MDS) Low risk and intermedia I
Stage of Disease	.

Outcomes

- The primary objective of this study is to evaluate the hematological improvement of the erythropoietic system (HI-E) using modified IWG criteria (Cheson 2006; Table 10-1) in patients treated for 4 months with LBH589 single agent. (Primary Outcome)
- •To compare the hematological improvement of the erythropoietic system (HI-E) using modified IWG criteria (Cheson 2006; Table 10-2) in patients treated for 8 to 12 months with either LBH589 single agent or with LBH589 and ESA combination treatment.
- •To evaluate the objective response rate (CR + PR and HI-P and HI-N) at 4, 8 and 12 months of treatment according to modified IWG criteria (Cheson et al., 2006; Table 10-2).
- •To determine the IPSS status as well as the single scoring values of the IPSS for patients at baseline and EOS.
- •To determine time to response, event-free survival, progression-free survival (PFS), disease-free survival (DFS), time to cause-specific death, and overall survival (OS) in this patient population.
- •To evaluate the safety and tolerability profile of LBH589 and LBH589 + ESA in low and INT-1 risk MDS patients treated for up to 12 months.

Inclusion Criteria

- 1. Signed and dated written informed consent by the patient prior to performance of any study-specific procedures or assessments. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, number of RBC transfusions) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol
- 2. Patients of either gender and age >=18 years
- 3. De novo MDS LOW or INT-1 according to IPSS
- 4. Red blood cell transfusion dependency of at least 4 Units/8 weeks. Only RBC transfusions given for a Hgb < 9.0 g/dL and > 9.0g/dL, if clinically indicated (e.g. coronary heart disease, long distance travel), respectively, will count
- 5. Either refractory to ESA or displaying a low chance (score of 1 or less according to Hellström-Lindberg, see also Figure 2-1) of response
- 6. No disease-specific treatment (e.g. Revlimid, Vidaza) within 4 weeks prior to study entry (treatment for transfusional iron overload with EMEA approved drugs
- 7. Age-adjusted normal cardiac, kidney, liver function (creatinine < 1.5 mg/dl unless MDS-related, total bilirubin < 2.0 x upper normal limits)
- 8. Patients must have the following laboratory values or corrected to within normal limits with supplements prior to the first dose of study medication:
- • Potassium >= Lower Limit of Normal (LLN)

- • Magnesium >= LLN
- • Phosphorus >= LLN
- • Total calcium (corrected for serum albumin) >= LLN
- • Aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) <= 2.5 x Upper Limit of Normal (ULN) or <= 5.0 x ULN if hepatic involvement is present
- • Serum bilirubin <= 1.5 x ULN
- • Serum creatinine <= 1.5 x ULN or 24-hour creatinine clearance >= 50 ml/min
- • Clinically euthyroid (TSH and free T4) (hypothyroidism correctable with supplements is allowed)
- 9. Females of childbearing potential must use double-barrier contraception, oral contraceptive plus barrier contraceptive, or must have undergone clinically documented total hysterectomy and/or bilateral oophorectomy, bilateral tubal ligation or be postmenopausal defined by amenorrhea for at least 12 months. Only contraception with a pearl-Index below 1% should be considered

Exclusion Criteria

- 1. Known hypersensitivity to study drugs or their compounds
- 2. Concomitant use of ESA
- 3. Concomitant use of any other investigational drug
- 4. Other malignancy that is not in remission for least 1 year (previous chemotherapy for other malignancies is not an exclusion criterion)
- 5. HIV or other uncontrolled infection
- 6. Any peripheral neuropathy >= CTCAE grade 2
- 7. Unresolved diarrhea >= CTCAE grade 2
- 8. Platelet Count < 75 x 109/L
- 9. Impaired cardiac function or clinically significant cardiac diseases, including any one of the following:
- •LVEF < Lower Limit of institutional Normal (LLN) as assessed by echocardiography
- • Complete left bundle branch block
- • Obligate use of a cardiac pacemaker
- • Congenital long QT syndrome
- • History or presence of ventricular tachyarrhythmia
- • Presence of unstable atrial fibrillation (ventricular response >100 bpm). Patients with stable atrial fibrillation are allowed in the study provided they do not meet other exclusion criteria
- • Clinically significant resting bradycardia (< 50 bpm)
- • QTc > 470 msecs on pre-study ECG
- • Right bundle branch block + left anterior hemiblock (bifasicular block)
- • Angina pectoris <= 3 months prior to starting study drug
- • Acute MI <= 3 months prior to starting study drug
- • Other clinically significant heart disease (e.g., CHF, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
- • History (within previous 6 months prior to starting study drug) of deep venous thrombosis (DVT) or cerebrovascular accident (CVA)
- 10. Impairment of GI function or GI disease that may significantly alter the absorption of LBH589 (e.g. acute or chronic ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)

- 11. Other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes, active or uncontrolled infection, chronic obstructive or chronic restrictive pulmonary disease) that could cause unacceptable safety risks or compromise compliance with the protocol
- 12. History of non-compliance to medical regimens and patients who are considered potentially unreliable and/or not cooperative
- 13. History of drug or alcohol abuse within the 12 months prior to starting study drug
- 14. Pregnancy or breast feeding

Age >= 18 years

Status Closed

start of Recruitment 16.12.2009

Recruiting countries Germany

Target Sample Size 55

Leader
Platzbecker, Prof. Dr. med., Uwe
Universitätsklinikum Dresden
Medizinische Klinik und Poliklinik
Fetscherstr. 74
01307 Dresden
Tel: +49 (0)351 4582583
Fax: +49 (0)351 458-5362
Email: Uwe.Platzbecker@uniklinikum-dresden.de

Scientific Contact (WHO)
Platzbecker, Prof. Dr. med., Uwe (Studienleiter)
Universitätsklinikum Dresden
Medizinische Klinik und Poliklinik
Fetscherstr. 74
01307 Dresden
Tel: +49 (0)351 4582583
Fax: +49 (0)351 458-5362
Email: Uwe.Platzbecker@uniklinikum-dresden.de

Contact Person
principal investigator
Platzbecker, Prof. Dr. med., Uwe
Tel: +49 (0)351 4582583
Fax: +49 (0)351 458-5362
Email: Uwe.Platzbecker@uniklinikum-dresden.de

Centre of Trial Universitätsklinikum Carl Gustav Carus, Dresden

Diagnostics
Zytomorphology
Hämatologisches Labor der Med. Klinik II, St. Johannes Hospital Duisburg

Cytogenetics
Labor für hämatologische Zytogenetik Göttingen

Interventions
- LBH589 (Panobinostat) p.o. in all patients. LBH589 + ESA (epoetin alfa (Hexal)) in group B only. : Oral LBH589 will be supplied as 5-mg or 20-mg hard gelatin capsules in bottles. Epoetin alfa (group B only) will be supplied as 10.000 international units [I.U.]/1ml in a ready to use syringe.