



## A phase I/II dose-escalation-trial of recombinant human histone H1.3 in subjects with relapsed or refractory AML

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### ABSTRACT

This is a single-center, open-label, Phase I dose escalation study to determine the maximum tolerated dose of recombinant human histone 1.3 (rhH1.3) when administered intravenously to patients with relapsed or refractory acute myeloid leukemia (AML) or with AML that does not qualify for any other treatment. So far, 18 subjects with eligible AML were screened after informed consent and 14 enrolled into the study on the first two dose levels. The drug was administered three times a week for three consecutive weeks and patients analyzed for response by one marrow biopsy on day 29. On both dose levels, one DLT had to be noticed which was mainly due to allergic reactions. All other patients only showed mild allergic reactions to the study drug. Three patients in the second cohort revealed a drop in blast count from 40% to 10% which was paralleled in one patient by an increase in platelet numbers from 22,000/ $\mu$ l up to 232,000/ $\mu$ l. This patient received two treatment cycles and seems to be now in a stable condition eight months after initiation of treatment. Since the primary objective of this study is to determine the maximal tolerated dose (MTD) and dose-limiting toxicities (DLT) of rhH1.3, recruitment will continue and, hopefully, more clinical responses been observed.

### BACKGROUND

A central issue in the therapy of leukemia subjects concerns the high relapse and failure rates after induction chemotherapy, the generation of chemo-resistant tumor cells, and the development of approaches to overcome these difficulties. Most of the efforts on more effective treatment strategies is directed towards the development of new chemotherapeutic and biologic agents, the refinement of dose and schedule as well as the use of immuno-modulators and the modulation of leukemic cell drug resistance. Histone H1 has been shown to eradicate leukemia-derived cell lines in vitro and to arrest the local growth of subcutaneous tumors in nude mice. There are no indications for drug resistance induced by histone H1. Histones are small molecules ubiquitous in eukaryotes with molecular masses ranging from 11 to 21 kDa. The functional role of histones goes beyond DNA stabilization and regulations of gene expression. Histones are believed to be an important component of the innate immune system. In addition to the anti-tumor effects, histone H1 also has a strong antibiotic activity surpassing that of penicillin by at least a factor of five. The evaluation of the toxicity and efficacy of histones in leukemia subjects seemed to be warranted.

## **METHODS AND CLINICAL PROTOCOL**

### **Study population**

Open-label, single center phase I dose escalation study in qualifying subjects with AML. Patients are qualified for the study if they are of either gender; age 18 or older; diagnosed AML; failed induction therapy or relapsed or are not eligible for chemotherapy or refused chemotherapy and have greater than 20% blasts in bone marrow. The final study protocol and the informed consent was reviewed and approved by the local ethics committee (Ethikkommission des Saarlandes, Saarbrücken, Germany). Screening, inclusion and exclusion criteria followed standard procedures.

### **Study design and study drug**

The study evaluates the tolerability of 9 infusions of rhH1.3 (3 infusions per week for 3 consecutive weeks) through Day 29 (28 days after the first rhH1.3 infusion). As screening may begin up to 14 days prior to the first infusion, each subject is expected to participate for up to 43 days. This study was designed to be a dose escalation trial. Therefore, the first cohort of patients entered at 37.5 mg/m<sup>2</sup> with a maximum dose of 2576 mg/m<sup>2</sup> at the tenth dose level.

The dose escalation scheme is depicted in figure 1.

Recombinant human H1.3 (rhH1.3) was produced under GMP guidelines at Eurogentec (Belgium) and provided as clinical grade batch to the study. The drug was stored at the study centre frozen at -18°C and thawed immediately prior to use.

The appropriate dose of rhH1.3 was administered in 0.9% saline solution (250 ml total volume) followed by intravenous hydration. Subjects are followed closely for toxicity with particular attention paid to hypersensitivity reaction, tumor lysis syndrome and the development of neutralizing anti-rhH1.3 antibodies. Evaluations of tolerance are based on Common Toxicity Criteria developed by the US National Cancer Institute (section 21.2). Additional clinical assessments include the measurement of detectable disease and progenitor cell dynamics and functionality.

### **Post-treatment Follow-up**

Subjects are evaluated on day 29 (28 days after the first rhH1.3 infusion) for signs of delayed toxicity. Long-term follow up will be done by standard clinical criteria through regular visits of patients. Due to the severity of the disease and due to the inclusion criteria, long-term follow up will be performed for a maximum of 6 months. Patients may qualify for additional treatment (9 infusions) in case of clinical response or benefit, which will extend the duration of study participation.

## **OBJECTIVES**

### **Primary Objective**

The objective of this study is to determine the maximal tolerated dose (MTD) and dose-limiting toxicities (DLT) of rhH1.3

## Secondary Objectives

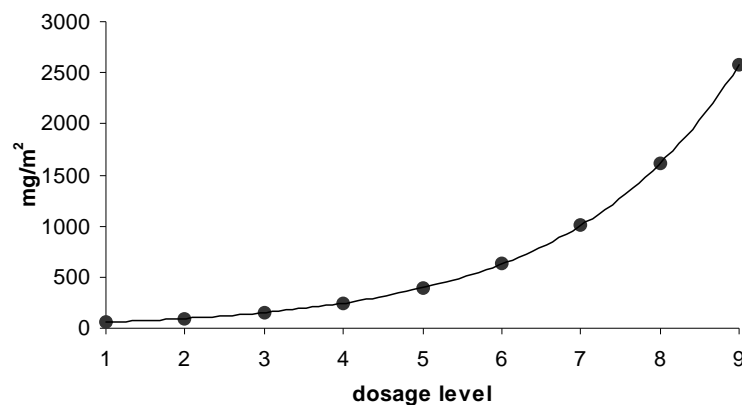
### Efficacy objectives

- Patient's best disease response measured by means of laboratory tests (profile and subset distribution of circulating cells in the peripheral blood and bone marrow biopsy)
- Duration of remission (established by standard clinical criteria during scheduled routine visits)
- Survival (confirmed by telephone contact or if it becomes otherwise publicly known)

### Safety objectives

- Adverse events, Toxicity (NCI-CTC), Vital signs

Dosage Level	rhH1.3 [mg/m <sup>2</sup> body surface area]
1	37.5
2	60
3	96
4	153
5	245
6	392
7	628
8	1005
9	1609
10	2576



**Fig. 1: Dose level design and justification.** If one of the first 3 subjects in any cohort experiences DLT within 4 weeks after the first infusion of rhH1, 3 more subjects will be added to that cohort. If no more than one of the now six subjects in that cohort experiences DLT, a new cohort will enter the study at the next dosage level. If two or more of those six subjects experience DLT, dose escalation is terminated. This dose is declared the maximally administered dose (MAD) and 3 more subjects are entered at the next lower dosage level, if only 3 subjects were treated at that level.

## RESULTS

Out of 18 patients screened, four could not enter the trial because of circulating anti Histone-antibodies. So far, 6 pts. have completed dose level one and 6 have finished dose level two with one drop out at each dose. With one DLT at each dose level the study end point has not been reached and recruitment continues. Almost all patients develop infusional reactions such as shivering, fever and hypo-/hypertension. These reactions typically occur one hour after the start of the infusion and last for a max. of 30 min. Some patients needed additional treatment (steroids and diphenhydramine). There was no significant change in hemoglobin level (Fig. 2), three pts. revealed a significant increase in CRP level at the end of the study (Fig. 3), one patient developed a rise in leucocyte numbers (Fig. 4) and one an increase in blast count (Fig. 5). Patient #13 did show a strong infusional reaction at the first administration (Jan 05) but could receive all 9 infusions. His platelets increased during the course of treatment from 22,000/ $\mu$ l to 51,000/ $\mu$ l which was paralleled by a drop of BM blasts from 40% down to 10%. He received a second course of treatment during which his platelets first dropped and then started to increase again. His platelet levels are now (Sept 05) stable at 232,000/ $\mu$ l and he has BM blast count of 20% (Fig. 6 and Fig 7).

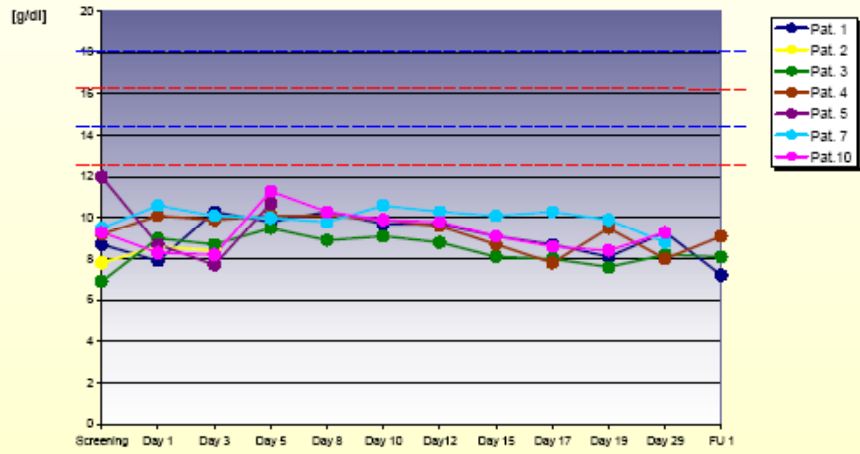
## CONCLUSIONS

1. Recombinant human Histone (rhH1.3) can be safely administered to patients with refractory AML
2. Major side effects are infusional reactions including fever, shivering and coldness
3. MTD has not been reached yet and accrual will continue at 96 mg/m<sup>2</sup>
4. Out of twelve evaluable patients, nine revealed persistent leukemia at day 29
5. Three patients showed a significant drop in AML blast count in their bone marrow which was paralleled in one patient by an increase in platelet numbers.

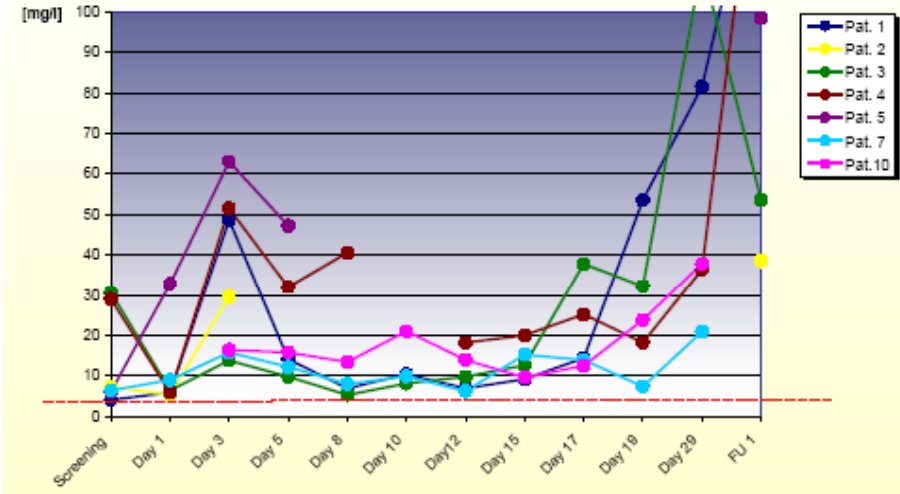
Poster contribution presented by C. Renner at the May 2005 meeting of the American Society for Clinical Oncology (ASCO).

Updated: 25. October 2005 by C. Renner

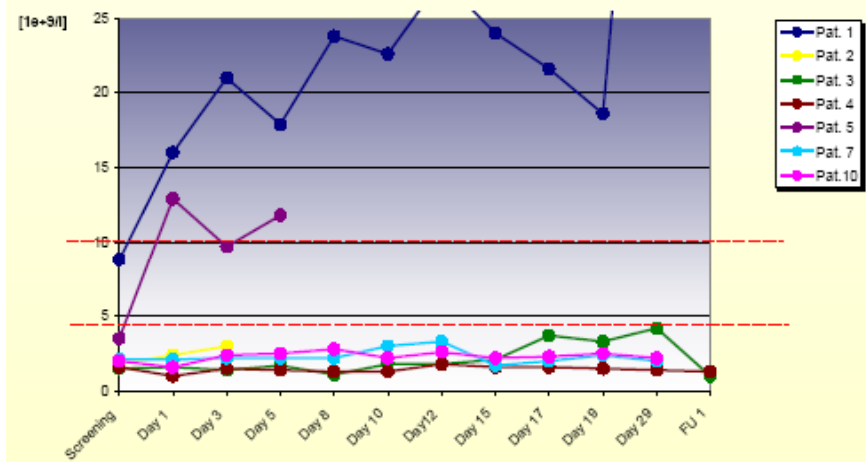
**Fig. 2: Hemoglobin level**



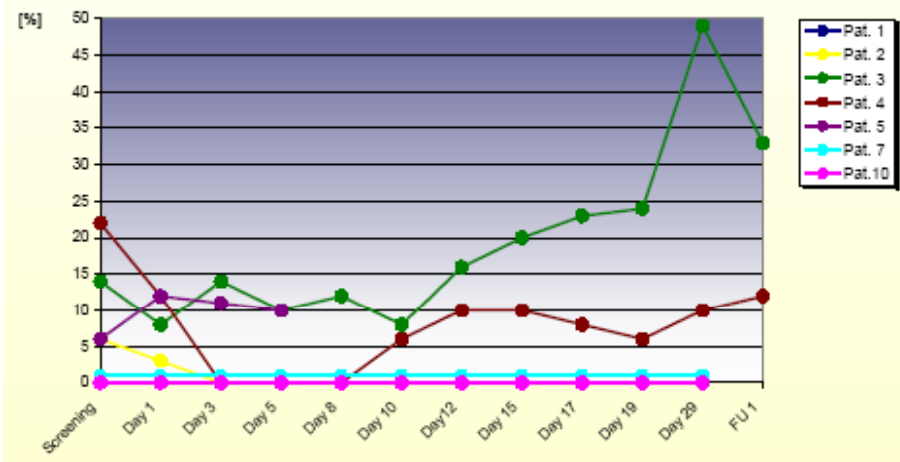
**Fig. 3: CRP level**



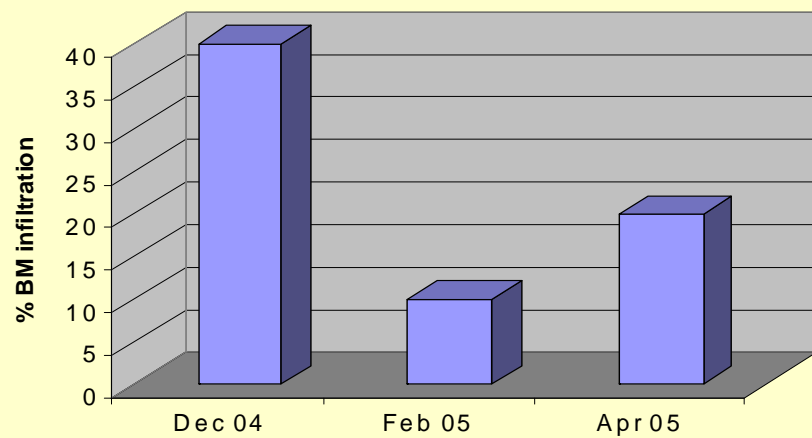
**Fig. 4: Leucocyte count**



**Fig. 5: Blast count**



**Fig. 6: BM blast count**



**Fig. 7: Platelet count**

