Clinical Study Synopsis for Public Disclosure

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**Name of company:**
Boehringer Ingelheim

**Name of finished product:**

**Name of active ingredient:**
BIWI1, bivatuzumab mertansine

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**Report date:**
21 October 2005

**Number:**
U05-2219

**Title of study:**
An open phase I single dose escalation study of bivatuzumab mertansine administered intravenously in female patients with CD44v6 positive metastatic breast cancer with repeated administration in patients with clinical benefit

**Investigator:**

**Study centers:**

**Publication (reference):**
Data of this trial has not been published

**Clinical phase:**
I

**Objectives:**
Maximum tolerated dose (MTD), safety, pharmacokinetics, efficacy of bivatuzumab mertansine

**Methodology:**
Uncontrolled, open, accelerated dose titration

**No. of subjects:**

- **planned:**
  - Entered: up to 30
  - Enrolled: 26, entered: 24, treated: 24

- **actual:**
  - 25 mg/m²:
    - entered: 1 treated: 1 analysed (for primary endpoint): 1
  - 50 mg/m²:
    - entered: 1 treated: 1 analysed (for primary endpoint): 1
  - 75 mg/m²:
    - entered: 1 treated: 1 analysed (for primary endpoint): 1
  - 100 mg/m²:
    - entered: 1 treated: 1 analysed (for primary endpoint): 1
  - 125 mg/m²:
    - entered: 3 treated: 3 analysed (for primary endpoint): 3
  - 150 mg/m²:
    - entered: 6 treated: 6 analysed (for primary endpoint): 6
  - 175 mg/m²:
    - entered: 3 treated: 3 analysed (for primary endpoint): 3
  - 200 mg/m²:
    - entered: 3 treated: 3 analysed (for primary endpoint): 3

**Diagnosis and main criteria for inclusion:**
Patients with CD44v6 positive metastatic breast cancer
**Name of company:**
Boehringer Ingelheim

**Name of finished product:**
SUPPLEMENTARY SHEET

**Name of active ingredient:**
BIWI1, bivatuzumab mertansine

**Ref. to Documentation:**
Volume:
Page:
Addendum No.:  

**Report date:**
21 October 2005

**Test product:**

- **dose:** Starting dose of 25 mg/m² bivatuzumab mertansine with dose escalations of 25 mg/m², maximum dose 200 mg/m²
- **mode of admin.:** Intravenous
- **batch no.:**
  - E2612LO01 (2612LO01),
  - E3612LO02 (B030609, B030721, B030802, B030914),
  - E3612LO03 (B031101, B031204, B040102),
  - E3612LO05 (B040206, B040307),
  - E3612LO06 (B040402, B040407)
  - E3612LO07 (B040507, B040711)

**Duration of treatment:**
Single dose (first course), additional courses in case of clinical benefit

**Reference therapy:**

- **dose:** Not applicable
- **mode of admin.:** Not applicable
- **batch no.:** Not applicable

**Criteria for evaluation:**

- **Efficacy:**
  - Objective tumour response assessed by magnetic resonance imaging (MRI), computed tomography (CT) scan, ultrasound (US), pharmacokinetics
- **Safety:**
  - Adverse events, common toxicity criteria (CTC), laboratory evaluation, vital signs, human anti human antibodies (HAHA)

**Statistical methods:**
Descriptive statistics of safety, pharmacokinetic parameters and efficacy

**SUMMARY – CONCLUSIONS:**

**Efficacy results:**
No clinical objective response to treatment with bivatuzumab mertansine could be shown in this study. Fifty percent of the patients treated had stable disease after the first treatment course. Seven patients received more than one treatment course. Data suggest that at higher doses there are more patients with repeated treatment courses.

A conclusive evaluation of the efficacy of the trial drug in metastatic breast cancer is not possible due to the premature termination of the trial. The maximum tolerated dose could not be determined.
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<td>Twenty-four patients were treated with bivatuzumab mertansine single dose in this dose escalation trial. The starting dose was 25 mg/m² and the highest dose administered was 200mg/m². Seven of the 24 patients treated received more than one treatment course. Dose limiting toxicities were observed in two patients at doses of 125 mg/m² (increase in liver enzymes) and 175 mg/m² (acute renal failure, vomiting), respectively. All patients experienced at least one adverse event during the trial. Trial drug related adverse events were reported in 18 (75%) patients. Most frequently reported trial drug related adverse events were skin and subcutaneous tissue disorders observed in 18 patients (75%) at doses above 75 mg/m². The skin reactions did not exceed CTC grade 2 and almost all of the events were reversible. Most frequently reported skin reactions were erythema and exanthem in nine (38%) and in six (25%) patients, respectively. Two patients experienced an adverse event (CTC grade 2 or less) which might be considered an allergic or anaphylactoid reaction due to infusion of bivatuzumab mertansine. Twenty patients experienced a serious adverse event during or after the trial. All had progression of their tumour disease. Six patients experienced other serious adverse events in addition. Four patients died during or after the trial (three due to progressive disease, one due to renal failure). The maximum tolerated dose could not be reached due to the premature discontinuation of the trial. A final assessment concerning the safety and tolerability of bivatuzumab mertansine in the treatment of CD44v6 positive metastatic breast cancer cannot be made due to the premature discontinuation of the clinical trials programme with bivatuzumab mertansine</td>
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Conclusions:
The results of the present study and other trials with bivatuzumab mertansine which were running in parallel to this study, have shown that the main toxicity of bivatuzumab mertansine is directed against the skin which may be explained by the strong expression of CD44v6 on skin keratinocytes.

While the majority of the skin reactions was fully reversible, one serious toxic epidermal necrolysis with subsequent death occurred in a trial running in parallel to this trial. After consideration of all information concerning the fatal event in one patient and the activity of bivatuzumab mertansine to cause apoptosis of skin keratinocytes with the potential to induce a toxic epidermal necrolysis, the risk-benefit assessment turned negative. As a consequence the clinical development with bivatuzumab mertansine was discontinued.