BT062, an Antibody-Drug Conjugate Directed Against CD138, Given Weekly for 3 Weeks in Each 4 Week Cycle: Safety and Further Evidence of Clinical Activity

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Background

- Multiple myeloma (MM) is the second most common hematologic malignancy and, despite the availability of new therapies, it is invariably fatal.
- CD138 (Syndecan-1) is highly expressed on MM cells and represents one of the most specific antigens for the identification of MM cells.
- BT062 is an antibody-drug conjugate, comprised of the chimerized anti-CD138 antibody nBT062 and a tubulin-binding cytotoxic agent maytansinoid (DM4). BT062 is stable and inactive in blood plasma. Once BT062 binds to CD138 on a target cell, it is internalized and releases DM4, leading to target cell death.
- A first in human study of BT062, administered intravenously (IV) once every 3 weeks to patients with relapsed or relapsed/refractory MM (Study 969), demonstrated an acceptable toxicity profile and evidence of clinical activity, with the maximum tolerated dose (MTD) defined as 160 mg/m² (1).
- To further characterize the safety and efficacy of BT062 given on a more frequent dosing schedule, this Phase I/IIa study (Study 975) was initiated.

Objectives

- To determine the MTD and the dose-limiting toxicities (DLTs) of BT062 given on a repeated, multiple dose schedule (Phase I).
- To characterize multi-dose pharmacokinetic (PK) properties of BT062.
- To describe the anti-MM activity of BT062 given on days 1, 8, and 15 of a 4-week cycle.

Methods

- Study 975 is a prospective, open label, multicenter, Phase I/IIa study.
- After the Phase I dose-escalation, the Phase IIa part of the study comprises a cohort expansion at the MTD or Recommended Phase II Dose.
- Patients aged ≥18 years, with relapsed or relapsed/refractory MM who had failed previous treatment, including an immunomodulatory agent and proteasome inhibitor, were eligible to participate.
- BT062 was administered IV on days 1, 8, and 15 of a 4 week cycle.
- Patients were enrolled in cohorts of at least 3 patients for each of the 8 dose levels ranging from 40 mg/m² to 160 mg/m². DLT in the first cycle triggered cohort expansion.
- Patients who achieved clinical benefit, defined as stable disease or better without unacceptable toxicity, were eligible to receive repeated 4-week cycles with administration of BT062 on days 1, 8, and 15.
- Toxicities were assessed by CTCAE v4 and clinical response was assessed according to the International Myeloma Working Group criteria (2,3).

Results

Baseline demographics

- A total of 31 patients were enrolled. Patients were heavily pretreated (median 5 prior therapies) with the majority having relapsed/refractory disease (Table 1).

Table 1: Baseline patient characteristics

Patients	n	31
	Males, n	14 (45%)
	Females, n	17 (55%)
Age	Median years	65
	Range in years	47-80
	≥ 65 years, %	52
Time since initial diagnosis	Median years	5
	Range in years	1-14
Disease status	Relapsed, n	9 (29%)
	Relapsed/Refractory, n	22 (71%)
Prior therapies	Median, n (range)	5 (2-13)

Pharmacokinetics

- Preliminary PK data, comparing the theoretical C_{max} with the C_{max} measured at the end of infusion, indicate rapid clearance of BT062 from plasma. Approximately 19 to 36 µg/mL were cleared during infusion (Table 2), which takes between 0.5 and 2.5 hours, depending on the total dose administered.

Table 2: Pharmacokinetics: C_{max} after the first infusion

Dosage (mg/m²)	Patients (n)	BT062 plasma level (µg/mL)			Cleared during infusion (µg/mL)
		Theoretical C_{max}	Measured C_{max}		
			Median	Range	
40	4	27	7.8	5.6 – 9.9	19.2
50	3	34	7.8	7.5 – 9.2	26.2
65	4	44	22.4	6.8 – 25.2	21.6
80	3	54	21.8	20.2 – 26.4	32.2
100	4	68	32.1	25.8 – 75.6	35.9
120	2	81	56.0	52.0 – 60.0	25.0

- No relevant plasma levels were detectable at the end of the 28-day treatment cycle, with no relevant accumulation identified, even after the 2nd (Day 8) and 3rd (Day 15) infusion within a cycle (Figure 1).
- Complete occupancy of CD138 receptors in the bone marrow (mean=93%; n=4) was observed as early as 4 hours after end of infusion (Day 1) with BT062 at a dose of 140 mg/m² (Figure 2). This rapid binding to myeloma cells may contribute to the rapid clearance of BT062 from plasma (see Table 2). Receptor occupancy was markedly lower on Day 8 prior to BT062 administration (58%; n=1; Figure 2) suggesting that a significant percentage of the receptors on the myeloma cells were available for BT062 binding.

Figure 1: Pharmacokinetics: No accumulation with multiple doses

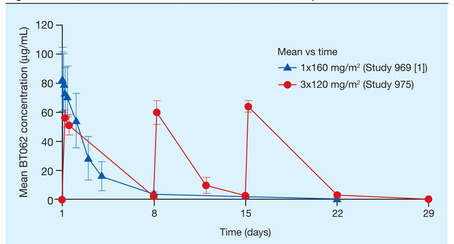
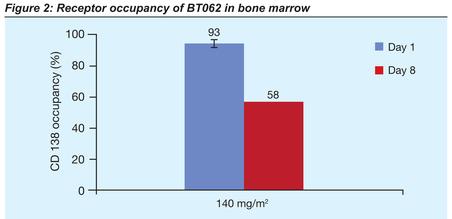


Figure 2: Receptor occupancy of BT062 in bone marrow



Safety (interim; data at November 7th, 2012)

- Dose limiting toxicity in Cycle 1 was experienced by 1 of 6 patients treated at 140 mg/m² and 2 of 4 treated with 160 mg/m² (Table 3 and Figure 3).
- The maximum administered dose (MAD) was therefore defined as 160 mg/m² and the MTD as 140 mg/m².
- There were 19 serious adverse events (SAEs) reported in 13 of 31 patients. Only 2 were reported as related to BT062. Both were also considered as DLTs. The other DLT was not classified as serious (Table 3).
- A total of 262 adverse events were reported; the majority (89%) were mild or moderate (CTC grade 1/2).
- The most frequent reported AEs were
  - anemia (13 events in 10 subjects)
  - diarrhea (11 events in 8 subjects)
  - fatigue (10 events in 7 subjects).

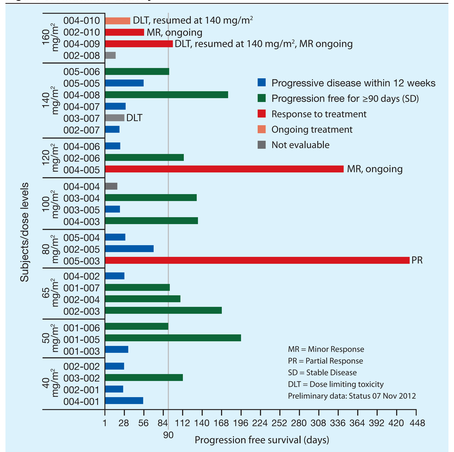
Table 3: Dose limiting toxicities and related serious adverse events

Cohort (mg/m²)	Patient Age Gender	Event	Severity (CTCAE)	Serious criteria	DLT in Cycle 1	Comments
140	003-007 70 years Female	Palmar-plantar erythro-dysaesthesia syndrome	3	Hospitaliz-ation	Yes	Grade 2 after 2nd dose, aggravation to grade 3 after 3rd dose
160	004-009 60 years Female	Increased Aspartate Aminotransferase	3	Non-serious	Yes	No other clinical symptoms, resumed at 140 mg/m², treatment ongoing
		Increased Alanine Aminotransferase	3			
160	004-010 76 years Female	Neutropenia	4	Medically significant	Yes	No other clinical symptoms, resumed at 140 mg/m², treatment ongoing

Efficacy

- 31 patients have been treated with 1 of the 8 dose levels ranging from 40 mg/m² to 160 mg/m² and 27 were evaluable for response (Figure 3).
  - 3 of these patients discontinued study prior to first response assessment on Day 1 of Cycle 2 (grey bars).
  - 1 patient (004-010) is ongoing and not yet evaluable for response.
- For 12 of the evaluable 27 patients, disease progression was observed within 12 weeks after first treatment (blue bars).
- 11 patients were progression free for at least 90 days and considered as stable disease (green bars).
- For 4 further patients response to treatment was reported (red bars). 1 patient with partial response (PR) for about 8 months completed the study due to disease progression in Cycle 16 (435 days). 3 patients with minor response (MR) are receiving ongoing treatment with BT062.
- Stable disease or better was achieved by 56% (15/27) of the evaluable patients, with a median progression free survival of 121 days (range 90–435).

Figure 3: Antitumor activity



Conclusions

- Preliminary data from this ongoing study indicate that BT062 is well tolerated even at this multiple dose schedule; administration of BT062 on days 1, 8, and 15 every 4 weeks.
- In the Phase I dose escalation part of the study stable disease or better was achieved by 56% of evaluable patients, providing further evidence of the clinical activity of BT062 in heavily pretreated patients with relapsed or relapsed/refractory MM.
- The MTD was defined as 140 mg/m² and selected as Recommended Phase II Dose for cohort expansion in the Phase IIa part of the study. Recruitment into this expansion cohort is currently ongoing to further evaluate the safety and efficacy of BT062.
- Based on the favorable safety profile, a Phase I/IIa study (Study 983) has been initiated to evaluate the safety and efficacy of BT062 in combination with lenalidomide and dexamethasone.
- If confirmed in larger clinical studies, the antibody-drug conjugate BT062 could offer a novel, active therapeutic option in MM.

Disclosures: Heffner: *Millennium:* Research Funding. **Jagannath:** *Millennium:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Onyx:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Merck:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Celgene:* Honoraria, Membership on an entity's Board of Directors or advisory committee. **Zimmerman:** *Novartis:* Consultancy; *Millennium:* Honoraria; *Celgene:* Honoraria. **Lonial:** *Onyx:* Consultancy; *Bristol-Myers Squibb:* Consultancy; *Novartis:* Consultancy; *Celgene:* Consultancy; *Millennium:* Consultancy; *Merck and Co:* Consultancy. **Lutz:** *ImmunoGen, Inc.:* Employment. **Czeloth:** *Biotest AG:* Employment. **Osterroth:** *Biotest AG:* Employment. **Ruehle:** *Biotest AG:* Employment. **Beelitz:** *Biotest Pharmaceuticals Corporation:* Employment. **Wartenberg-Demand:** *Biotest AG:* Employment. **Haeder:** *Biotest AG:* Employment. **Anderson:** *Celgene:* Consultancy; *Onyx:* Consultancy; *Merck:* Consultancy; *Bristol-Myers Squibb:* Consultancy; *Acetylon:* Membership on an entity's Board of Directors or advisory committees; *Oncopep:* Membership on an entity's Board of Directors or advisory committees; *Millennium Pharmaceuticals:* Consultancy. **Munshi:** *Oncopep:* Patents & Royalties; *Merck:* Consultancy; *Onyx:* Membership on an entity's Board of Directors or advisory committees; *Millennium:* Membership on an entity's Board of Directors or advisory committees; *Celgene:* Membership on an entity's Board of Directors or advisory committees.

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