BT062, an Antibody-Drug Conjugate Directed against CD138, Shows Clinical Activity in a Phase I Study in Patients with Relapsed or Relapsed/Refractory Multiple Myeloma

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Background

- Multiple Myeloma (MM) is the second most common hematological malignancy and is invariably fatal.
- CD138 is highly expressed on MM cells and has been reported as a highly sensitive and specific diagnostic marker of MM cells (O'Connell et al., 2004).
- BT062 is a CD138-specific immunoconjugate comprised of the chimerized anti-CD138 MAb, nBT062, and the cytotoxic agent maytansinoid, DM4. Therefore, BT062 represents a promising new therapeutic approach for treating patients with MM.
- BT062 binds to CD138 on a target cell and once internalized releases DM4 to kill the target cell.
- Preclinical investigations demonstrated the significant in vitro and in vivo anti-MM activity and specificity of BT062, providing the rationale for conducting clinical trials (Ikeda et al., 2009).

Objectives

Primary Objectives
- To determine the maximum tolerated dose (MTD) and the dose-limiting toxicities (DLTs) of BT062.

Secondary Objectives
- To determine qualitative and quantitative toxicities and to demonstrate pharmacokinetics (PK) and anti-MM activity of BT062 according to the International Working Group Criteria (Durie et al., 2006, Kyle and Rajkumar 2009).

Methods

Study Design
- This is a prospective, open label, dose-escalation multicenter study.
- Patients aged ≥ 18 years with relapsed or relapsed/refractory MM who have failed previous treatments including an immunomodulating agent and a proteasome inhibitor were eligible to participate.
- Patients were enrolled in cohorts of 3 at each dose level, with assessment of DLT during the first treatment cycle triggering cohort expansion or dose escalation.

Treatment
- Patients first received a single dose of BT062.
- Only patients with clinical response (or no evidence of progressive disease) and without unacceptable toxicities were eligible for further treatment cycles once every 3 weeks.

Results

- A total of 32 patients have been treated with BT062, receiving one of 7 dose levels ranging from 10 mg/m² to 200 mg/m². The maximum administered dose (MAD) was defined at 200 mg/m². The MTD was defined at 160 mg/m² and a total of 13 patients have been treated in an expanded MTD-cohort to further evaluate safety and antitumor activity of BT062 at this dose level.

Table 1: Baseline Characteristics

Patients	n	30
	Males, n (%)	15 (50)
	Females, n (%)	15 (50)
Age	Median years	63
	Range in years	45-78
	≥ 65 years, %	40
Time since initial diagnosis	Median years	6
	Range in years	3-10
Disease status	Relapsed, n (%)	14 (47)
	Refractory, n (%)	7 (23)
	Relapsed/Refractory, n (%)	9 (30)
Prior therapies	Median, n	7
	Range, n	2-14
	≥ 10, %	33

Pharmacokinetics

- Different pharmacokinetic properties are noted for dose levels up through 120 mg/m² compared to the higher dose levels of 160 mg/m² and 200 mg/m².
- For dose levels up to 120 mg/m², preliminary PK results indicate an unusually rapid clearance from plasma in the early elimination phase, resulting in a low Cmax value directly after the end of infusion. This rapid clearance is followed by a generally normal terminal elimination phase.
- A plasma level approaching the calculated Cmax and a more typical clearance profile was observed for patients at dose levels of 160 mg/m² and 200 mg/m².

Figure 1: The pharmacokinetic behavior of BT062 changes at higher dose levels

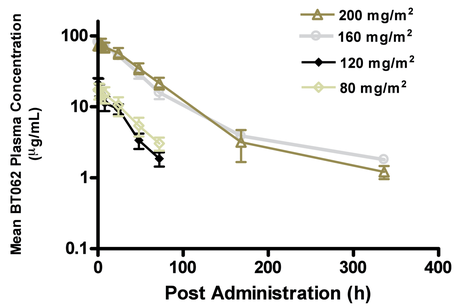


Table 2: Cmax values of BT062 at different dose levels

dosage (mg/m²)	plasma level (µg/mL)			
	theoretical cmax	effective cmax		
		mean	range	n
10	7	1.11	1.08-1.14	2
20	14	2.9	1.66-4.44	4
40	27	4.31	1.08-9.68	3
80	54	18.8	13.4-23.6	3
120	81	21.4	15.1-28.7	3
160	109	89.4	42.9-120.7	12
200	136	82.0	68.0-102.4	3

- As a consequence of the different clearance during early elimination phase, the half-life for the higher dose levels (160 and 200 mg/m²) is about 54 hours compared to about 35 hours for lower dose levels (80 and 120 mg/m²) and the area under the curve is much higher for the higher dose levels levels (about 5000 h*µg/mL vs. about 760 h*µg/mL).

Safety

DLTs and MAD[1]:
- 3 DLTs reported
  (2 DLT at 200 mg/m²: 1x mucositis and 1x mucositis and hand-foot syndrome; 1 DLT at 160 mg/m² expansion cohort, increased GGT)
- MAD defined at 200 mg/m²
- MTD defined at 160 mg/m²

Adverse events[1]:
AEs were assessed according to the NCI-CTCAE, v3
- Over 85% of the adverse events reported were of mild or moderate severity (patients displayed typical symptoms/complications of the underlying disease).
- No serious hypersensitivity reactions reported
- One fatal outcome after bacterial pneumonia reported (not related to BT062, onset about 2 months after last study drug application).

[1] interim data, clinical database 22-Oct-2010

Table 3: SAEs assessed to be related to BT062

Cohort	Patient #, Age/Gender	Verbatim	Severity (CTC/AE)	Comments
80 mg/m²	004-001 71/Male	Gastrointestinal bleed	3	Hospitalization. 3 episodes, 1st episode started 21 days after 2nd cycle. No clear etiology; alternative explanations included pre-existing low platelet count, presence of angiectasia in colon.
160 mg/m²	002-007 45/female	Acneiform Rash	2	Medically significant. BT062 treatment continued with patient concomitantly receiving prednisone.
		Dry eyes, blurred vision	2	Medically significant. Onset of event 4 days after 4th cycle of BT062.
	002-008 47/male	Epithelial damage in cornea and crystal inclusions	2	Medically significant. Onset of event 3 days after 3rd cycle.
	003-005 67/male	Stomatitis	2	Medically significant. Event onset 5 days after 1st cycle. Patient continued in study.
200 mg/m²	004-003 73/female	Mucositis, grade 3 hand-foot-syndrome	3	DLT. Hospitalization. Onset of event 4 days after 1st cycle.

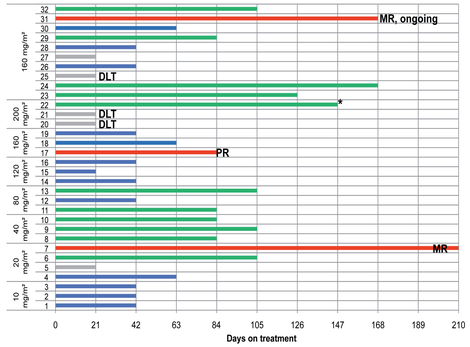
Serious Adverse Events (SAEs)[2]
- 19 SAEs have been reported in 15 of 32 patients.
- 6 SAEs related to BT062 have been reported in 5 patients.
- Skin, eye and GI represent main target tissues for toxicity at high dose levels.

[2] Status safety database 01 Nov 2010

Antitumor Activity

- Patients with clinical response (or no evidence of progressive disease) and without unacceptable toxicities were eligible for repeated treatment cycle.
- Of 32 patients treated to date, 27 received more than one treatment cycle and were evaluable for response. Most patients came off study due to disease progression. For one of the patients (No. 31), study treatment is ongoing.
- For 13 of the 27 evaluable patients, progressive disease was observed within 9 weeks after first treatment (blue bars). Duration of study treatment (defined by days from first treatment till end of last treatment cycle) was up to 63 days.
- For 7 further patients, clinical benefit has been observed (green bars) with early stabilization of M-protein levels (and light-chain burden) in serum and/or urine for more than 9 weeks. Duration of study treatment was up to 168 days.
- Objective response has been observed in 3 patients (red bars). One of these patients (No. 7, without detectable M-Protein in serum) showed a decrease in urine M-Protein by more than 50% (Minimal Response) after administration of 8 repeated low doses (20 mg/m²) and has been on study treatment for 210 days. At a high dose level (160 mg/m²) another patient (No.17) without detectable M-Protein levels, showed a decrease of serum FLC by more than 50% (Partial Response) after having received the second dose of BT062 (see also Figure 3). Duration of study treatment was 84 days. Another patient at the 160 mg/m² dose level (No. 31), shows reduction of M-Protein in serum by more than 25% (Minor Response) after having received the fifth treatment. To date, duration of response is confirmed for 9 weeks and the study treatment is ongoing, having reached 168 days on study.
- Patients with clinical benefit received a median of 5 cycles of therapy (range 3-10).

Figure 2: Duration of Treatment



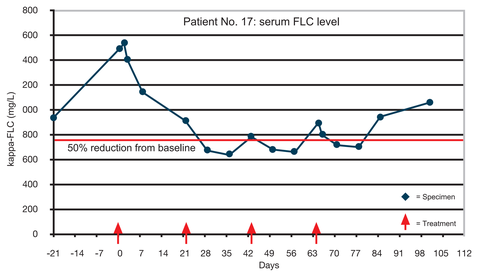
red = objective response, green = stable disease for more than 9 weeks, blue = progressive disease within 9 weeks, grey = not evaluable for response, * = 1x 200 mg/m², 6x 160 mg/m², MR = minor response, PR = partial response, DLT = dose limiting toxicity

- Objective response (MR and PR) was described for 11 % of the evaluable patients.
- Clinical benefit (SD, MR and PR) was described for at least 52% of the evaluated patients.

Table 4: Response and Clinical benefit

Number of patients:	Total (n)	%	Objective response (%)	Clinical benefit (%)
treated with BT062	32			
evaluable for response	27	100		
- disease progression within < 9 weeks	13	48		
- stable disease for ≥ 9 weeks	11	41		52
- minor response	2	7	11	
- partial response	1	4		

Figure 3: Response to Treatment



- Patient No. 17 with oligo-secretory Multiple Myeloma showed reduction of serum FLC levels by more than 50% (PR) after 2nd, 3rd and 4th treatment.
- However, serum FLC levels increased before each following treatment.
- Data suggest a more intense dosing may be required to achieve a sustained response in this heavily pretreated patient population.

Conclusions

Development of highly active therapies remains a medical need for the treatment of Multiple Myeloma. CD138 is highly expressed on MM cells and is involved in their development and/or proliferation, therefore representing an attractive therapeutic target. The CD138-specific immunoconjugate BT062 demonstrated significant in vitro and in vivo anti-MM activity, providing the rationale for conducting clinical trials. Preliminary data from this phase I study demonstrate an acceptable and manageable toxicity profile of BT062 in the clinic. Even in this early phase of the clinical development, evidence of clinical activity is observed. Based on the favourable safety profile, the pharmacokinetic properties and early signs of clinical activity, a Phase I/II study in Multiple Myeloma is initiated to further evaluate the safety and anti-MM efficacy of BT062 in a more frequent dosing regimen.

References

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