Indatuximab Ravtansine (BT062) in Combination with Lenalidomide and Low-Dose Dexamethasone in Patients with Relapsed and/or Refractory Multiple Myeloma: Clinical Activity in Patients Already Exposed to Lenalidomide and Bortezomib

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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 various solid tumors and in hematological malignancies, and represents one of the most specific antigens for identification of MM cells.
- BT062 is an antibody-drug conjugate (ADC), comprising an anti-CD138 chimerized monoclonal antibody (MAb) and the maytansinoid DM4 as a cytotoxic agent.
- BT062 is designed to remain intact in the bloodstream and bind specifically to CD138-positive cancer cells. After internalization, DM4 is released to kill the cancer cell.
- BT062 was investigated as a single agent and found to have an acceptable tolerability profile and evidence of activity in patients with heavily pretreated relapsed and/or refractory MM.[1]
- Preclinical studies showed enhanced anti-MM activity when BT062 was combined with lenalidomide and dexamethasone (Len/Dex).
- Based on these data, a Phase I/IIa study (Study 983) in MM was initiated to evaluate the safety and efficacy of BT062 in combination with Len/Dex.

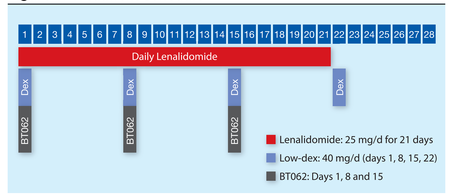
Objectives

- To determine the dose-limiting toxicities (DLTs), the maximum tolerated dose (MTD), and the recommended Phase II dose (RPTD) of BT062 in combination with Len/Dex.
- To characterize the pharmacokinetic (PK) properties of BT062 in combination with Len/Dex.
- To describe the anti-MM activity of BT062, given on days 1, 8, and 15, every 4 weeks, in combination with Len/Dex.

Methods

- Study 983 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 RPTD.
- Patients aged ≥18 years with relapsed and/or refractory MM who have failed at least one prior therapy were eligible to participate. Prior treatment with Len and/or Dex was allowed.
- BT062 was administered IV on days 1, 8, and 15 of a 4 week cycle in combination with Len (25 mg, daily on days 1-21) and low dose Dex (40 mg on days 1, 8, 15, and 22) (***Figure 1***).
- Patients were enrolled in cohorts of at least 3 patients for each of the 3 dose levels, which ranged from 80 mg/m² to 120 mg/m². DLT in the first cycle triggered cohort expansion.
- Patients with clinical response (or no evidence of progressive disease) and without unacceptable toxicities were eligible for additional treatment cycles.
- Toxicities were assessed by CTCAE v4. Clinical response was assessed according to International Myeloma Working Group criteria.[2-4]

Figure 1: Treatment schedule



- Repeated treatment cycles until disease progression or unacceptable toxicity

Results

Baseline demographics

- A total of 47 patients were treated and enrollment into the study is complete.
- Patients were heavily pretreated with up to 11 therapies (median = 3) with the majority having already been exposed to both lenalidomide and bortezomib (***Table 1***).
- 72% (34/47) had prior lenalidomide and 30% (14/47) were reported as refractory to prior lenalidomide-containing therapy.

Table 1: Baseline patient characteristics

Patients	n	47
	Males, n	29 (62%)
	Females, n	18 (38%)
Age	Median years	63
	Range in years	40-82
	≥65 years, %	36
Time since initial diagnosis	Median years	6
	Range in years	1-19
Prior therapies	Median, n (range)	3 (1-11)
	Lenalidomide (%)	72
	Bortezomib (%)	91
	Lenalidomide and Bortezomib (%)	64
	ASCT (%)	72
Response to prior lenalidomide	Relapsed, n	6 (13%)
	Refractory, n	14 (30%)
	Unknown (naive or prior to ASCT)	27 (57%)

Safety

- Dose-limiting toxicities in the first treatment cycle were considered for dose escalation and definition of the maximum administered dose (MAD).
  - At 120 mg/m² DLT in Cycle 1 was experienced by 2 of 6 treated patients (***Table 2*** and ***Figure 2***). The MAD was therefore defined as 120 mg/m².
  - At 100 mg/m² none of the first 6 patients experienced a DLT and this dose was therefore defined as MTD. The dose of 100 mg/m² was also selected as RPTD to further evaluate safety and efficacy in a total of 38 patients.
  - In the expanded RPTD cohort 2 of 38 patients experienced a DLT in Cycle 1 (***Table 2*** and ***Figure 2***). Both patients resumed treatment at a reduced dose of 80 mg/m² without reappearance of the unacceptable toxicity.

Table 2: Dose limiting toxicities by dose level

Dose level (mg/m²)	Patients n=47	Cycle 1 DLT (n)	DLT details	CTC grade
80	3	0	None	
100 (MTD)	38	2	Elevated Aspartate Aminotransferase	3
			Elevated Alanine Aminotransferase	3
120 (MAD)	6	2	Mucosal inflammation	3
			Anemia	3

Unvalidated preliminary data; cut off date 28 October 2014.

- The most common reported treatment-emergent adverse events (TEAEs) were diarrhea, fatigue, nausea, and hypokalemia (***Table 3***).
- Approximately 88% of TEAEs were CTCAE grade 1 or 2 (mild to moderate)
- No related events, with fatal outcome were reported from this study.

Figure 2: Antitumor activity

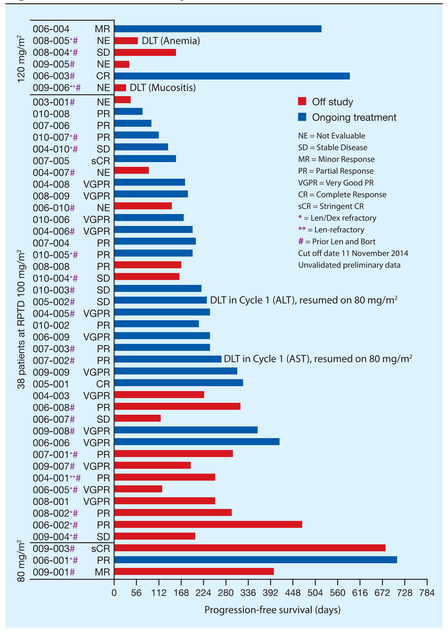


Table 3: TEAEs reported in ≥30% of patients regardless of relationship to study medications

MedDRA Preferred Term	Number of patients n=47 (%)
Diarrhea	29 (61.7%)
Fatigue	24 (51.1%)
Nausea	21 (44.7%)
Hypokalemia	17 (36.2%)

Unvalidated preliminary data; cut off date 28 October 2014.

- The majority of patients remain on study treatment (***Table 4***).
- For the 22 patients who discontinued the study, main reason was disease progression.
- Study discontinuation due to adverse events were mainly at the MAD of 120 mg/m² (4 of 6 patients; 67%).
- At the MTD of 100 mg/m², most patients are receiving ongoing treatment, only 3 of 38 discontinued due to adverse events (8%).

Table 4: Reasons for study discontinuation

	80 mg/m²	100 mg/m²	120 mg/m²	Total
Total	**3**	**38**	**6**	**47**
Ongoing	1	22	2	25
Discontinued	2	16	4	22
Disease progression	1	7	0	8
Adverse event	0	3	4	7
ICF withdrawal	1	3	0	4
Death	0	2	0	2
Non compliance	0	1	0	1

Unvalidated preliminary data; cut off date 28 October 2014.

Efficacy

- 47 patients have been treated with BT062 at dose levels ranging from 80 mg/m² to 120 mg/m² (***Figure 2, Table 4***).
  - The median treatment duration was 203 days (range 1–707).
  - 25 patients are receiving ongoing treatment (***Figure 2***; blue bars).
  - 22 patients have completed/discontinued the study (***Figure 2***; red bars), the main reason for study discontinuation was disease progression (***Table 4***).
- 6 patients were not evaluable for response as of November 11, 2014 (***Figure 2***; NE).
  - 5 discontinued early and had less than 2 post baseline assessments reported.
  - 1 received prohibited concomitant medication in Cycle 3.

Table 5: Response rates

	Evaluable patients[1]		RPTD cohort 100 mg/m²		Prior Len and Bortezomib		Len refractory[3]	
	n	%	n	%	n	%	n	%
Total N	41	100	35	100	25	100	12	100
ORR (≥PR)	32	78	29	83	17	68	8*	67
sCR	2	5	1	3	1	4	0	0
CR	2	5	1	3	1	4	0	0
VGPR	13	32	13	37	5	20	1	8
PR	15	36	14	40	10	40	7	58
MR	2	5	0	0	1	4	0	0
SD	7	17	6	17	7	28	4	33
PD	0	0	0	0	0	0	0	0

1=at least 2 post dose efficacy assessments, 3=non-responsive on Len containing therapy, or if at least MR progress on therapy or within 60 days of last dose; non-responsive defined as progressed or only achieved SD. Unvalidated preliminary data, *=7 Len/Dex refractory and 1 on last Len-containing therapy.

- 41 patients were evaluable for efficacy (***Table 5***).
  - The overall response rate (ORR) at all dose levels (n=41 patients) was 78%, with 42% achieving VGPR or better.
  - In addition, two patients achieved a minor response and 7 patients disease stabilization, resulting in a clinical benefit in 100% of the evaluable patients.
  - Among the 35 evaluable patients receiving the RPTD (100 mg/m²) ORR was 83%.
  - Among the 25 patients with prior exposure to Len and bortezomib ORR was 68%, and was 67% among the 12 patients refractory to Len.

Conclusions

- Preliminary data from this ongoing study indicate that BT062 is well tolerated in combination with lenalidomide and dexamethasone at dose levels that induce responses in patients with relapsed and/or refractory multiple myeloma.
- The MTD was defined as 100 mg/m² and selected as Recommended Phase 2 Dose. At this dose level objective response, including CRs, was achieved by 83% of evaluable patients.
- An objective response rate of approximately 70% was achieved in patients already exposed to lenalidomide and bortezomib, and also in lenalidomide-refractory patients.
- In addition to further development of BT062 in combination with lenalidomide and dexamethasone, it is planned to evaluate the safety and efficacy of BT062 in combination with pomalidomide and dexamethasone in patients who have failed at least two prior therapies including lenalidomide and bortezomib.

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Disclosures

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