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

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Background: BT062 (Biotest AG Dreieich, Germany) is an antibody-drug conjugate, comprising the anti-CD138 chimerized MAb (nBT062) and the maytansinoid DM4 as cytotoxic agent. Once bound to CD138 on a target cell, the conjugate is internalized and releases DM4, leading to target cell death. CD138 (Syndecan-1) is highly overexpressed on various solid tumors and in hematological malignancies, and represents one of the most specific target antigens for identification of multiple myeloma (MM) cells. Data from two studies investigating BT062 as single agent demonstrated an acceptable tolerability profile and evidence of clinical activity in patients with heavily pretreated relapsed and/or refractory MM (1, 2). 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 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), the recommended phase II dose (RPTD), pharmacokinetics (PK), and anti-MM activity of increasing doses of BT062 (days 1, 8, and 15, every 4 weeks) in combination with Len (25 mg, daily on days 1-21) and low dose Dex (40 mg on days 1, 8, 15, and 22) in patients with relapsed and/or refractory MM. **Methods:** This is a prospective, open label, dose-escalation, multicenter Phase I/IIa study. The Phase I part includes dose escalation, and the Phase IIa the expansion of the MTD or RPTD cohort. 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. Patients with clinical response (or no evidence of progressive disease) and without unacceptable toxicities were eligible for additional treatment cycles. Patients were enrolled in cohorts of at least 3 at each dose level; DLT in the first cycle triggered cohort expansion. Toxicities were assessed by CTCAE v4 and clinical response was assessed according to International Myeloma Working Group criteria. **Results:** As of July 2013, a total of 15 patients have received BT062 at dose levels of 80 mg/m² (N=3), 100 mg/m² (N=6) or 120 mg/m² (N=6). Two patients at the highest dose level discontinued study due to toxicity (DLT), another patient withdrew consent. The other 12 patients remain on treatment; median duration 144 days (range 8–385). The median number of prior therapies was 4 (range 1–11), 87% of patients had prior Len exposure, and 50% were Len/Dex refractory. The maximum administered dose (MAD) has been reached at 120 mg/m², with mucosal inflammation (CTC grade 3) as DLT in one, and anemia (CTC grade 3) in a second of the 6 patients treated at this dose level. About 85% of

reported Adverse Events (AE) were of CTC grade 1 or 2. The most common reported AEs were fatigue, hypokalemia, and diarrhea. Amongst the 9 patients currently evaluable for efficacy, responses were observed across all dose levels with a overall response rate (ORR) of 78%; including 1 patient with complete response (120 mg/m^2), 1 patient with very good partial response (80 mg/m^2), and 5 patients with partial response (80 and 100 mg/m^2). Two other patients achieved disease stabilization, resulting in a clinical benefit in 100% of the evaluated patients. Interestingly, partial response was observed in 3 patients refractory to prior treatment with Len/Dex. The MTD has been defined as 100 mg/m^2 and is currently expanded to further evaluate the safety and efficacy of BT062 at the RPTD. **Conclusion:** Preliminary data from this ongoing study indicate that BT062 is well tolerated in combination with Len/Dex at dose levels that induce responses in patients with relapsed and/or refractory multiple myeloma, including Len/Dex-refractory patients. Updated results on safety and efficacy will be presented.

References

1. Jagannath *et al*, BT062, an Antibody-Drug Conjugate Directed Against CD138, Shows Clinical Activity in Patients with Relapsed or Relapsed/Refractory Multiple Myeloma. *Blood*. 2011; 118: Abstract 305.
2. Heffner *et al*, 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. *Blood.* 2012; 120: Abstract 4042.