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

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Bortezomib (BT062) is a monoclonal antibody (mAb) conjugate containing a humanized anti-CD38 antibody (CD38 mAb) and the maytansine DM4 as a cytotoxic agent. BT062 was designed to remain intact in the bloodstream and bind specifically to CD38-positive cancer cells. When internalized, DM4 is released to kill the cancer cell. BT062 was studied as a single agent and found to have an acceptable safety profile and evidence of activity in patients with heavily pretreated relapsed and refractory MM. Preclinical studies showed enhanced anti-MM activity when BT062 and/or refractory multiple myeloma. Clinical Activity in Patients Already Exposed to Lenalidomide and Bortezomib.

Methods

- Study design: open-label, multicenter, Phase IIa study.
- After the Phase I dose-escalation study, the Phase IIa part of the study comprises a cohort expansion at the MTD or RPTD.
- Patients aged 18 years and older with relapsed and/or refractory MM who have failed at least one prior therapy will be eligible to participate.
- 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. DLTs in the first cycle triggered cohort expansion.
- Toxicity was assessed by CTCAE v4. Clinical response was assessed according to International Myeloma Working Group criteria.

Results

- All 47 patients were treated and enrolled into the study. Patients were heavily pretreated with at least 11 therapies (median = 5+) of which 94% had already been exposed to both lenalidomide and bortezomib.
- 72% (34/47) had prior lenalidomide and 30% (14/47) were reported as unacceptable tolerability profile and evidence of activity in patients with heavily pretreated relapsed and refractory MM.
- Independent Review Panel (IRP) included the study investigators.
- In the expanded RPTD cohort of 23 patients experienced a CR in Cycle 1 (Table 1) and 2 patients received treatment as a reduced dose of 90 mg/m² without reappearance of the unacceptable toxicity.

Figure 1: Treatment schedule

- Repeated treatment cycles until disease progression or unacceptable toxicity

Baseline demographics

- A total of 47 patients were treated and enrolled into the study. Patients were heavily pretreated with at least 11 therapies (median = 5+) of which 94% had already been exposed to both lenalidomide and bortezomib.
- 72% (34/47) had prior lenalidomide and 30% (14/47) were reported as unacceptable tolerability profile and evidence of activity in patients with heavily pretreated relapsed and refractory MM.

Table 1: Baseline patient characteristics

- No related events, with fatal outcome were reported from this study.

Figure 2: Antimyeloma activity

- The most commonly 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).
- The overall response rate (ORR) at all dose levels (n=41 patients) was 78%, with 42% achieving VGPR or better.

Table 2: Dose-limiting toxicities by dose level

- The median treatment duration was 233 days (range 1-717). At this dose level objective response, including CRs, was achieved by 83% of evaluable patients.
- The disease progression rate at cycle 2 was 20%.
- 27 patients have completed/discontinued the study (Figure 2). In the final report for study discontinuation was disease progression.

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

- 54 patients were evaluated 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 78% of the evaluable patients.
- Among the 22 patients with prior exposure to Len and bortezomib ORR was 66%, 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 75% was achieved in patients already exposed to lenalidomide and bortezomib, and also in relapsed/refractory-relapsed 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 two or less prior treatments including lenalidomide and bortezomib.

Efficacy

- 47 patients have been treated with BT062 at dose levels ranging from 80 mg/m² to 120 mg/m² (Table 4, Figure 2).
- The median treatment duration was 233 days (range 1-717).
- 20 patients are receiving ongoing treatment (2 patients in Phase 2 dose).
- 22 patients have completed/discontinued the study (Figure 2).
- The overall response rate for study discontinuation was disease progression.
- 4 patients were not evaluable for response as of November 11, 2014 (Table 4).
- 5 discontinued early and had less than 2 post baseline assessments reported.
- 1 received prohibited concomitant medication in Cycle 3.

Table 5: Response rates

References