Phase I/IIa clinical study demonstrated BKT140, a novel CXCR4 antagonist, as a powerful human stem cell mobilizer with the capacity to induce MM apoptotic cell death in patients with myeloma. (EMBT Updated abstract 9 2011)

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**Background:** BKT140 is a highly selective CXCR4 antagonist, with high affinity (1-2nM) and an extended Koff-rate. Pre-clinical studies in animal models with BKT140 showed a robust mobilization of hematopoietic stem cells. Furthermore, BKT140 also showed a direct anti-tumor effect against human-derived multiple myeloma (MM), cells in vitro and in vivo. We here report for the first time the preliminary results of a first in-human clinical study with BKT140 in MM patients.

**Study design:** 18 MM patients in first CR/PR and after induction chemotherapy that required stem cell collection for aHSCT were included in this Phase I/IIa study. Escalating doses of BKT140 (6 (n=2) 30 (n=4), 100(n=4), 300(n=4) and 900(n=4) µg/kg) were administered in a chemo-based mobilization of a single dose cyclophosphamide (Cy) (3-4 g/m²) and granulocyte colony-stimulating factor (G-CSF) 5 µg/Kg for stem cell mobilization. G-CSF was self administered daily in the evenings as of Day 5 post Cy until end of stem cells collection and BKT140 was injected subcutaneously (SC) once on Day 10.

**Results:** BKT140 was well tolerated at all the tested doses (30-900 µg/kg), and none of the patients developed grade II-IV toxicity. BKT140 was rapidly absorbed with no observed lag time, with peak plasma concentrations occurring 0.5h after administration. Clearance was rapid, with a median terminal half-life of 0.3-0.7h at 300 and 900 µg/kg respectively.

BKT140 administration resulted in a significant dose-dependent increase in the number of peripheral blood WBC, neutrophils, monocytes, lymphocytes, and CD34+ cells compared to the G-CSF/Cy individual patient baseline.

BKT140 administration resulted in a significant increase in the mean absolute PB CD34+ cells collected at the first aphaeresis following administration of BKT140. At the highest dose, the average number of CD34+ cells collected following one injection of BKT140 was 20 million per
kg, which is double the average number of CD34+ cells obtained with the use of G-CSF plus plerixafor for PBSCT practice.

Moreover, the number of aphaeresis was reduced from 2.0 (n=4) and 2.25(n=4) procedures at the first two BKT140 doses to 1.25 (n=4) and 1 (n=4) aphaeresis at the highest BKT140 doses, respectively.

Increase in the number of CD138+ cells was observed in pts that had CD138+ cells in their blood and were treated with lower doses of BKT140 (30 and 100 µg/Kg). Interestingly, in pts that were treated with the highest doses of BKT140 (300 and 900 µg/kg) a reduced number of CD138+ cells was observed in 3 out of 7 pts that had CD138+ cells in their blood.

The BKT140 mobilized grafts were used for AutoSCT following 200 mg/m² melphalan conditioning. Pts received an average of 5.3x10⁶ CD34+ cells/kg. All transplanted pts were rapidly engrafted (n=17).

The median day for neutrophil recovery (>500/mm3) was 12 days, with a range for all doses of 11-14 days. A dose dependent reduction time to platelet recovery was observed both when 20,000 platelets or 50,000 platelets were counted. The median day for platelets (>20,000/mm3) was 14.5, 12.5, 13, 12, 11 days with a range of 10-19, 12-14, 12-13, 12, 0-13 respectively. The median day for platelets (>50,000/mm3) was 20, 17, 14, 14, 14 days with a range of 14-26, 14-20, 11-15, 12-19, 12-16 respectively.

**Conclusion:** BKT140 was safely added to G-CSF/Cy -based SC mobilization regimen, it rapidly and consistently increased CD34+ cell mobilization and significantly and dose dependently reduced the number of aphaeresis collection days. Additional studies are warranted to further evaluate the effect of BKT140 as a mobilizing agent and an anti-cancer agent.