BKT140 Is a Novel CXCR4 Antagonist with Stem Cell Mobilization and Antimyeloma Effects: An Open-Label First Human Trial In Patients with Multiple Myeloma Undergoing Stem Cell Mobilization for Autologous Transplantation

Arnon Nagler, M.D.1, Avichai Shimoni1,3, Iris Avivi1,2, Jacob M. Rowe1, Katia Beider4, Izhar Hardan5,6, Michal Abraham1,6, Hanna Wald1,6, Eitan Galun7, Howard Laurence Shaw2,4, Orly Eizenberg5,7 and Amnon Peled5,7

1 Bone Marrow Transplantation, Chaim Sheba Medical Center, Tel-Hashomer, Israel, 2 Hematology, Rambam Medical Center, Haifa, Israel, 3 Rambam Medical Center, Technion, Haifa, Israel, 4 Hematology Division, Chaim Sheba Medical Center andTel Aviv University, Guy Weinshtock Multiple Myeloma Foundation, Tel-Hashomer, Israel, 5 Sheba Medical Center, Tel-Hashomer, Israel, 6 Biokine Therapeutics Ltd, New Zion, Israel, 7 Goldyne Savad Institute of Gene Therapy, Hebrew University Hospital, Jerusalem, Israel

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Background: BKT140 is a high affinity CXCR4 inhibitor with an extended K off-rate. Pre-clinical studies in animal models with BKT140 showed a robust mobilization of white blood cells (WBC) and hematopoietic stem cells (HSC). Furthermore, BKT140 also showed a direct anti-tumor effect against human-derived multiple myeloma (MM), lymphoma and primary leukemia cells and cell lines in vitro and in vivo, causing significant apoptosis.

Aims: To assess BKT140 toxicity (primary endpoints), the mobilization capacity of CD34+ hematopoietic progenitors and CD138 MM cells, and pharmacokinetic (PK) and pharmacodynamic (PD) (secondary endpoints).

Methods: 16 MM patients in first CR/PR were included in a phase I/II study, in which escalating doses of BKT140 (30, 100,300,900 µg/kg) were administered together with a high-dose cyclophosphamide (Cy) (2 g/m²) and G-CSF (5 µg/Kg) for stem cell mobilization. G-CSF was started on day 5 post Cy and BKT140 was injected subcutaneously (SC) once on day 10. Toxicity, PK, and mobilization capacity (assessed by serial measurements of number of WBC and CD34+ and CD138+ cells) were measured pre- and post BKT140 administration.

Results: BKT140 was well tolerated at all doses 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 0.69h. BKT140 administration resulted in a significant dose-dependent increase in the number of peripheral blood neutrophils, monocytes, lymphocytes, and CD34+ cells compared to the G-CSF/Cy individual patient baseline. The maximum increase in the number of WBC from baseline was observed within 8h following BKT140 injection, 2.5-, and 3.0-, 4.1- and 4.8-fold, for the 4 BKT140 doses, respectively. Furthermore, BKT140 administration resulted in a significant increase in the mean absolute PB CD34+ cells mobilized (6.6, 7.5, 11.2 and 20.6 x10⁶/kg) for the 4 BKT140 administered doses, respectively. Moreover, the number of aphaeresis was reduced from 2.25 procedures at the first two BKT140 doses to 1.25 and 1 aphaeresis at the highest BKT140 doses, respectively. An increase in the number of CD138+ cells was observed in 6 out of 6 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, whereas in 4 pts, an increase in the number of CD138+ cells was shown. Three pts who did not have CD138+ cells in their blood were not affected by BKT140. 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 rapidly
engrafted (n=15). The median day for neutrophil (>500/mm³) and platelet (>20,000/mm³, >50,000/mm³) was on day 11 (range, 0–13), day 11 (range, 0–14), and day 14 (range, 0–23), respectively.

**Conclusions:** The current data suggests that **BKT140** can safely be added to G-CSF-based harvesting regimens, can increase CD34+ cell mobilization and reduce the number of collection days. Furthermore, due to its ability to release MM cells from the bone marrow and stimulate their cell death, additional studies are warranted to further evaluate the effect of **BKT140** as an anti-MM agent.


**Footnotes**

* Asterisk with author names denotes non-ASH members.