BACKGROUND

The bone marrow (BM) niche protects Acute Myeloid Leukemia (AML) cells from chemotherapy. BM homing of AML cells is dependent on CXCR4 and its ligand CXCL12, and high levels of CXCR4 expression correlate with poor survival in AML patients. It is postulated that blocking the CXCL12/CXCR4 axis will disrupt the interaction of the malignant blasts with the BM and augment the anti-leukemic effect of chemotherapy. BL-8040 (BKT140) is a 14-residue, cyclic, synthetic peptide capped with an aromatic ring that acts as a selective inhibitor of the CXCR4 chemokine receptor. BL-8040 has strong affinity for the CXCR4 receptor and long receptor occupancy, resulting in a prolonged pharmacodynamic effect. BL-8040 has robust mobilization capacity, inverse agonism activity and direct pro-apoptotic activity against leukemia cells. Preclinical studies have shown that in addition to its expression correlate with poor survival in AML patients. It is postulated that blocking the CXCL12/CXCR4 axis will disrupt the interaction of the malignant blasts with the BM and augment the anti-leukemic effect of chemotherapy. BL-8040 (BKT140) is a 14-residue, cyclic, synthetic peptide capped with an aromatic ring that acts as a selective inhibitor of the CXCR4 chemokine receptor. BL-8040 has strong affinity for the CXCR4 receptor and long receptor occupancy, resulting in a prolonged pharmacodynamic effect. BL-8040 has robust mobilization capacity, inverse agonism activity and direct pro-apoptotic activity against leukemia cells. Preclinical studies have shown that in addition to its activity as a mobilizer of hematopoietic cells, BL-8040 exhibits a CXCR4-dependent selective anti-tumor effect against malignant cells. A clinical trial for the treatment of adult relapsed/refractory AML patients using a combination of BL-8040 and cytarabine (Ara-C) is currently ongoing (NCT01838395).

DESIGN

The phase IIa clinical trial in relapsed/refractory AML patients includes a dose escalation phase (3+3 design) followed by an expansion phase using the highest safe and efficacious dose. Each patient receives a once daily SC dose of BL-8040 monotherapy on days 1-2 followed by the same dose of BL-8040 plus Ara-C (1.5 mg/m2 for patients ≥60; 3 mg/m2 for patients ≤60) on days 3-7. For each of the BL-8040 tested doses (0.5, 0.75, 1.25 and 1.5 mg/kg) the safety and tolerability, pharmacokinetic profile and clinical responses are being evaluated. Additionally, CXCR4 expression on leukemia cells, receptor occupancy, mobilization kinetic of leukemic blasts and stem/progenitor cells and induction of apoptosis are being followed using frequent peripheral blood sampling (PB) and BM aspirates at baseline and on day 3 prior to Ara-C administration.

RESULTS

Safety

- Administration of BL-8040, in combination with Ara-C, was safe and well tolerated at all doses tested to date (0.5-1.25 mg/kg).
- There have been no DLTs, SAEs, delays in blood count recovery or early discontinuations attributable to BL-8040.
- Administration of BL-8040, in combination with Ara-C, was safe and well tolerated at all doses tested to date (0.5-1.25 mg/kg).
- There have been no DLTs, SAEs, delays in blood count recovery or early discontinuations attributable to BL-8040.
- 8/12 patients evaluable for analysis mobilized Leukemic blasts.
- Importantly, this effect was specific to the AML blasts as the levels of normal/progenitor cells (CD45+Low/CD34+/CD117+/HLA-DR+) remained stable post BL-8040 monotherapy.
- This decrease of BM AML blasts was evident regardless of whether the patient mobilized AML blasts or not.

RESULTS SUMMARY

- Administration of BL-8040, in combination with Ara-C, was safe and well tolerated at all doses tested to date (0.5-1.25 mg/kg).
- BL-8040 triggered substantial mobilization of AML blasts from the BM to the PB.
- Two days of BL-8040 monotherapy dramatically decreased the amount AML blasts in the BM.
- The levels of normal/progenitor cells remained stable post BL-8040 monotherapy.
- Long receptor occupancy (up to 24 hours post dosing) was observed by FACS analysis measuring surface CXCR4 staining.
- Pharmacokinetics analysis confirmed increase in BL-8040 exposure over doses with a short plasma half-life.

CONCLUSIONS

- BL-8040 was found to be safe and well tolerated at all doses tested to date.
- BL-8040 induced mobilization of AML blasts from the BM and has sustained receptor occupancy.
- Direct effect on AML blast viability has been observed in samples obtained during BL-8040 monotherapy.
- Differential effect of BL-8040 monotherapy on the level of AML blasts vs. normal progenitors in the BM was noted.
- Completion of dose escalation phase - expected in Q1 2015 and topline results expected in H2 2015.