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
- High CXCR4 expression correlates with poor survival in AML
- Blocking the CXCL12/CXCR4 axis with a potent CXCR4 antagonist may disrupt the protection by marrow niche and augment the anti-leukemic effect of chemotherapy
- BL-8040 (BKT140) is:
  - short synthetic peptide CXCR4 antagonist
  - long receptor occupancy
  - short synthetic peptide CXCR4 antagonist
- Mobilization of leukemic blasts, induction of granulocytic terminal differentiation (2.5 fold increase) with induction of granulocytic terminal differentiation
- BM aspirate samples from rrAML patients treated for 2 days with BL-8040 (0.75-2.0 mg/kg) were predictive to clinical response
- In the majority of treated patients the reduction in the number of AML blasts in the BM was associated with induction of granulocytic terminal differentiation.
- PD analysis further confirmed BL-8040’s long receptor occupancy and its ability to induce apoptosis.

Results

- Response was correlated with efficient CXCR4 inhibition.
- Better clinical responses are seen in patients with more efficient CXCR4 inhibition
- Better clinical responses are seen in patients (n=34) with more efficient CXCR4 inhibition and lower peripheral circulating blasts (despite comparable marrow blasts) were predictive to clinical response
- BL-8040 + Ara-C was 38%.

Methods

Design: Dose escalation phase (3+3) followed by an expansion phase.

Response: Once daily SC dose of BL-8040 monotherapy on days 1-2 followed by BL-8040 plus Ara-C (1.5 mg/m2 for patients ≥60, 3 mg/m2 for patients <60) on days 3-7.

Six dose levels of BL-8040 (0.5, 0.75, 1.25, 1.5 and 2.0 mg/kg) have been tested with 1.5 mg/kg selected for the expansion phase.

Clinical Response

- CR+CRi
- 38%
- Overall response rate (CR+CRi+MR) was 38%.
- CR rate 31% in the majority of treated patients the reduction in the number of AML blasts in the BM was associated with induction of granulocytic terminal differentiation.

Conclusions

- In poor prognosis relapsed/refractory AML patients, BL-8040 combined with Ara-C improved the clinical response rates achieved historically with Ara-C.
- The ongoing follow-up of responding patients suggests long durability of the remissions achieved.
- Better clinical responses are seen in patients with more efficient CXCR4 inhibition and lower peripheral circulating blasts (despite comparable marrow blasts) at baseline.

Patients Characteristics (n=42)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
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<tbody>
<tr>
<td>Median age (yr)</td>
<td>61 (38-79)</td>
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<tr>
<td>Male (%)</td>
<td>60</td>
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<tr>
<td>Female (%)</td>
<td>40</td>
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| ECOG performance status (%): 0 | 22 (52.4)
| 1 | 13 (30.1) |
| 2 | 6 (14.3) |
| BM aspirate samples from rrAML patients treated for 2 days with BL-8040 (0.75-2.0 mg/kg) were predictive to clinical response |

Safety Profile

- Better clinical responses were seen in patients (n=34) with more efficient CXCR4 inhibition
- Better mobilization and lower baseline peripheral blood circulating blasts (despite comparable marrow blasts) were predictive to clinical response

Correlation Between Clinical Response and Efficient CXCR4 Inhibition

- The most common AEs were injection site reactions and transient systemic reactions, all resolved while on study.
- One subject discontinued early due to an AE of systemic reaction

- Overall, 80% was safe and well tolerated
- Better clinical responses are seen in patients (n=34) with more efficient CXCR4 inhibition
- Higher mobilization and lower baseline peripheral blood circulating blasts (despite comparable marrow blasts) were predictive to clinical response

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BL-8040 induced granulocytic differentiation and blast apoptosis

- BL-8040 monotherapy induced leukemic death (apoptosis)