Immune Effects of AXL Inhibition via Bemcentinib

Bemcentinib, selective, oral small molecule inhibitor of AXL.

The receptor tyrosine kinase AXL represents a novel therapeutic target in AML promoting proliferation and therapy resistance (Gjertsen B-T2, Heuser M3, Chromik J5, Ben-Batalla I1, Akyüz N1, Micklem D4, Holt R4, Brown A4, Lorens J4, Yule M4, Kebenko M1, Janning M1, Binder M1, Fiedler W1 and Cortes J6 1University Medical Center Hamburg-Eppendorf, Hamburg, Germany; 2University of the Sciences in Philadelphia, Philadelphia, USA; 3University Hospital Freiburg, Freiburg, Germany; 4University Medical Center Utrecht, Utrecht, The Netherlands; 5The University of Western Australia, Perth, Australia; 6Baylor College of Medicine, Houston, TX, USA). AXL expression is increased in myeloid leukemias and associated with poor clinical outcome and treatment resistance. Bemcentinib, a first-in-class selective, oral AXL inhibitor (BGB324), has shown preclinical efficacy in myeloid leukemia cell lines and xenograft models. The immunomodulatory activity of bemcentinib (BGB324) – a first-in-class selective, oral AXL inhibitor in patients with relapsed/refractory Acute Myeloid Leukemia or Myelodysplastic Syndrome. (Loges S1, The immunomodulatory activity of bemcentinib (BGB324) – a first-in-class selective, oral AXL inhibitor in patients with relapsed/refractory Acute Myeloid Leukemia or Myelodysplastic Syndrome. (Loges S1, The immunomodulatory activity of bemcentinib (BGB324) – a first-in-class selective, oral AXL inhibitor in patients with relapsed/refractory Acute Myeloid Leukemia or Myelodysplastic Syndrome. (Loges S1, The immunomodulatory activity of bemcentinib (BGB324) – a first-in-class selective, oral AXL inhibitor in patients with relapsed/refractory Acute Myeloid Leukemia or Myelodysplastic Syndrome. (Loges S1, The immunomodulatory activity of bemcentinib (BGB324) – a first-in-class selective, oral AXL inhibitor in patients with relapsed/refractory Acute Myeloid Leukemia or Myelodysplastic Syndrome. (Loges S1, The immunomodulatory activity of bemcentinib (BGB324) – a first-in-class selective, oral AXL inhibitor in patients with relapsed/refractory Acute Myeloid Leukemia or Myelodysplastic Syndrome. (Loges S1

Methods: The TCR repertoire was assessed by next generation sequencing of DNA isolated from peripheral blood mononuclear cells using Illumina MiSeq sequencing. TCR, gene co-expression and application of immune gene sets were analyzed by the Weighted Gene Co-expression Network Analysis (WGCNA) method.

Summary table of observed B-cell and T-cell receptor repertoire diversification in peripheral blood (PB) and bone marrow (BM)

<table>
<thead>
<tr>
<th>Patient</th>
<th>In Bone Marrow</th>
<th>Dose (mg/d)</th>
<th>Age</th>
<th>Gender</th>
<th>Duration of treatment (days)</th>
<th>Best Response</th>
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<tr>
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</table>

TCR repertoire in peripheral blood

Identification of Candidate Biomarkers Potentially Indicative of Response to Bemcentinib Monotherapy

Bemcentinib induces diversification of the T-cell receptor repertoire in AML patients. Bemcentinib has anti-leukemic activity in refractory AML and MDS patients. Bemcentinib is well tolerated in elderly and heavily pre-treated AML and MDS patients. Several potentially predictive biomarker candidates for response to bemcentinib were identified.

Conclusions

Bemcentinib induces diversification of the T-cell receptor repertoire in AML patients. Bemcentinib has anti-leukemic activity in refractory AML and MDS patients. Bemcentinib is well tolerated in elderly and heavily pre-treated AML and MDS patients. Several potentially predictive biomarker candidates for response to bemcentinib were identified.

References

- Loges S, The immunomodulatory activity of bemcentinib (BGB324) – a first-in-class selective, oral AXL inhibitor in patients with relapsed/refractory Acute Myeloid Leukemia or Myelodysplastic Syndrome. (Loges S1
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