The identification of the AXL/Gas6 signalling axis as a key player of myelodysplastic syndrome (MDS) and the potential of the oral selective AXL inhibitor bemcentinib in the treatment of MDS

Background & Study Objectives

Myelodysplastic syndrome (MDS)

MDS is a stem cell disorder that is characterised by inefficient haemopoesis and a high risk of progression to acute myeloid leukaemia. MDS stem cells are defined as In-CD34-CD38- (MDS-SCs). We have previously shown that there is a strong dependency of MDS-SCs on disease-associated mesenchymal niche cells (MDS-MSCs). Compared to healthy cells, MDS-MSCs display de-regulation of several niche factors involved in intercellular communication, including GAS6, a high affinity AXL ligand.

Study objectives

In this study we explored the functional importance of GAS6/AXL axis in MDS pathogenesis using both in vitro and in vivo assays. We used bemcentinib (BG0204), a selective, orally bioavailable small molecule inhibitor of AXL, to demonstrate the potential therapeutic benefit of targeting GAS6/AXL axis in human MDS.

Bemcentinib, first-in-class, highly selective orally bioavailable AXL inhibitor in phase II human MDS.

Bemcentinib is being explored as a mono-therapy and in combination with immune-, target- and chemo-Therapy in AML, MDS, NSCLC, TNBC and melanoma across phase II clinical trials.

Molecular effects of bemcentinib on MDS cells in vivo

AXL is readily detectable in bone marrow trephine biopsies from lower-risk MDS & is only TMB closely expressed in MDS stem/progenitor cells ex vivo

Validation of GAS6 over-expression by qRT-PCR

Compared Gas6 levels were observed across all MDS risk categories.

GAS6 is upregulated in MDS-derived mesenchymal niche cells

Bemcentinib reduces the frequency, the proliferation and the clonogenic potential of CD34+ MDS stem (progenitor) cells ex vivo

Bemcentinib reduces MDS burden in a PDX model of MDS

Conclusions

- Gas6 is over-expressed in mesenchymal niche cells from lower-risk MDS patients.
-Comparable Gas6 levels were observed across all MDS risk categories.
- AXL, the high affinity GAS6 receptor is the only TAM receptor up-regulated in purified CD34+ MDS stem/progenitor cells.

References


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