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Axl, a prognostic and therapeutic target in acute myeloid leukemia mediates paracrine crosstalk of leukemia cells with bone marrow stroma

Isabel Ben-Batalla*, Alexander Schultze*, Mark Wroblewski, Robert Erdmann, Michael Heuser, Jonas Waizenegger, Kristoffer Riecken, Mascha Binder, Denis Schewe, Stefanie Sawall, Victoria Witzke, Miguel Cubas-Cordova, Melanie Janning, Jasmin Wellbrock, Boris Fehse, Christian Hagel, Jürgen Krauter, Arnold Ganser, James B. Lorens, Walter Fiedler, Peter Carmeliet, Klaus Pantel, Carsten Bokemeyer & Sonja Loges
**contributed equally*

ABSTRACT: Acute myeloid leukemia (AML) represents a clonal disease of hematopoietic progenitors characterized by acquired heterogenous genetic changes that alter normal mechanisms of proliferation, self-renewal and differentiation. Although 40-45% of patients younger than 65 years can be cured with current therapies, only 10% of older patients reach long-term survival. As only very few novel AML drugs were approved in the last two decades there is an urgent need to identify novel targets and therapeutic strate-gies to treat underserved AML patients. We here report that Axl, a member of the Tyro3, Axl, Mer receptor (TAMR) tyrosine kinase family, represents an independent prognostic marker and therapeutic target in AML. AML cells induce expression and secretion of the Axl ligand growth arrest-specific gene 6 (Gas6) by bone marrow-derived stromal cells (BMDSCs). Gas6 in turn mediates proliferation, survival and chemoresistance of Axl-expressing AML cells. This Gas6-Axl paracrine axis between AML cells and BMDSCs establishes a chemoprotective tumor cell niche, which can be abrogated by Axl-targeting ap-proaches. Axl inhibition is active in FLT3-mutated and -wt AML, improves clinically relevant endpoints and depends on presence of Gas6 and Axl. Axl-inhibition alone or in combination with chemotherapy might represent a novel therapeutic avenue for AML.

STATEMENT: *Our study indicates that the receptor tyrosine kinase Axl represents an independent prognostic factor and a therapeutic target in acute myeloid leukemia (AML). We could uncover that AML cells educated bone marrow stroma cells to produce growth arrest-specific gene 6 (Gas6) which promoted AML growth and chemoresistance. The small molecule Axl inhibitor BGB324 blocked this vicious circle and inhibited growth of Axl+ AML cells in primary AML samples. Furthermore, treatment with BGB324 improved clinically relevant endpoints in preclinical AML models.Thus our data provide a rationale for testing clinical efficacy of BGB324 in AML patients in whom novel treatment approaches are urgently needed. Furthermore. they highlight importance of leukemia-stroma interactions as therapeutic targets and in AML pathobiology*

BACKGROUND: This work was performed in the Max Eder group headed by Sonja Loges at the II. Medical Clinic and the Institute of Tumor Biology. Experiments were conducted by Isabel Ben-Batalla and Alexander Schultze. The study was performed in collaboration with UKE scientists at the Research Department Cell and Gene Therapy and the Institute of Neuropathology. Studying the Gas6-Axl axis in AML is funded by the DFG (grant LO1863) and by BerGenBio. The research interests of Sonja Loges are the investigation of tumor-stroma interactions in hematologic and solid cancers with a focus on bone marrow niches.