NVP-BEZ235 exerts anti-tumor activity in Waldenstrom Macroglobulinemia

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Background. The PI3K/Akt and mTOR pathways play a pivotal role in initiation and progression of malignancies. Therefore, it is critical to examine therapeutic agents that explicitly target these pathways, in tumors that harbor activation of PI3K/Akt/mTOR pathway, such as WM.

Aims. 1) To evaluate expression level of PI3K/Akt and mTOR in primary WM cells. 2) To evaluate the anti-tumor activity of dual PI3K/Akt and mTOR inhibitor in WM cells in the context of bone marrow milieu.

Methods. Primary-CD19+ bone-marrow(BM)-derived WM cells; BM stromal cells; WM and IgM secreting low-grade lymphoma cell lines; primary normal CD19+ peripheral-blood-derived (CD19+PB) cells were used. Cytotoxicity/DNA synthesis/cell cycle/apoptosis were measured by thymidine uptake/MTT/PI staining/Apo2.7 and flow cytometry analysis, respectively. Cell signaling and apoptotic pathways were delineated by Western Blot and immunofluorescence. In vivo homing has been assessed by in vivo flow cytometry.

Results. Primary BM-derived-WM cells present with lower expression of PTEN; higher expression of pospho(p)-Akt, p-mTOR, rictor, raptor, as compared to normal CD19+PB cells. We tested the dual PI3K/Akt and mTOR inhibitor NVP-BEZ235, which induced cytotoxicity and inhibited DNA synthesis in primary WM cells, and in IgM-secreting-cell-lines; without cytotoxicity on CD19+PB cells. NVP-BEZ235 inhibited p-Akt/p-mTOR; and downstream-Akt-targeted-proteins (GSK3alpha/beta;p-S6R;p-p70S6). NVP-BEZ235 also inhibited Akt and mTOR in vitro kinase activities; as well as rictor and raptor, thus abrogating the rictor-induced-Akt-phosphorylation in WM cells. NVP-BEZ235 also induced significant cytotoxicity in WM cells through targeting forkhead-box-transcription-factors. Finally, NVP-BEZ235 targeted WM cells in the context of BM microenvironment by inhibiting migration, adhesion in vitro and homing in vivo.

Conclusion. These studies therefore show that WM cells harbor activation of the PI3K/Akt/mTOR cascades; and dual targeting of the PI3K/Akt/mTOR pathways represents a promising therapy for WM.