AY922, A NOVEL HSP90 INHIBITOR EFFECTIVE AGAINST ABC-DLBCl AND MALT LYMPHOMA CELLS HARBORING GENETIC ALTERATION-ASSOCIATED NF-κB ACTIVATION

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Purpose: Recurrent genetic alterations that are frequently observed in activated B cell subtype of diffuse large B cell lymphoma (ABC-DLBCl) and mucosa-associated lymphoid tissue type lymphoma (MALT lymphoma), such as mutation of MYD88, CD79a, CD79b and CARD11 in the former and t(11;18), t(1;14) and t(14;18) in the latter, are usually associated with NF-kB activation and confer resistance to therapy. In this study, we investigate the therapeutic efficacy and molecular mechanisms of AUY922, a novel HSP90 inhibitor, on representative cell lines - OCI-Ly3 (ABC-DLBCl with CARD11 and MYD88 mutations) and MA-1 (MALT lymphoma cells with t(14;18) translocation).

Methods: OCI-Ly3 and MA-1 cells were treated with various concentration of AUY922 or 17-AAG for 48 to 72 hrs, and then subjected for WST1 assay for determining cell viability and IC50. After demonstrating the growth inhibition efficacy, the cells were treated with fixed dose of AUY922 or 17-AAG for 0 to 48 or 72 hrs and subjected for annexin V/propidium iodide apoptotic assay, cell cycle analysis, and Western blot analysis to evaluate the expression levels of total and some phosphorylated forms of PI3K/Akt/GSK3α/b/mTOR/EPI/P70S6, cyclin D1, Raf-B/MEK1/2/MAPK, NK-kB p100/p52, Mcl-1, Bcl-2, Bax, BIk, BID, Bak, Bad, PARP, caspase-3, caspase-9, α-actinin, GAPDH, and HSP70.

Results: Our results showed that AUY-922, in contrast to 17-AAG, effectively inhibited the proliferation and induced apoptosis of OCI-Ly3 and MA-1 cells with IC50 of 20-30 nM. AUY922 also significantly downregulated the expression of molecules of multiple signaling pathways, including PI3K/AKT/GSK3α/b/mTOR, Raf/MEK/MAPK, JAK/STAT3, and NF-kB as well as mitochondrial apoptotic pathway-related anti-apoptotic Bcl-2 family proteins, in both cell lines.

Conclusions: The results highlight that AUY-922, but not 17-AAG, can effectively against the two B-cell lymphoma cell lines with genetic alteration-associated NK-kB activation, the OCI-Ly3 and MA-1 cells. The findings indicate the potential use of AUY922 in resistant or refractory B-cell lymphoma patients and deserves further clinical investigation.