The Dual IAP Antagonist, ASTX660, Increases The Anti-tumor Activity of Paclitaxel in TNBC Preclinical Models In Vivo

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INTRODUCTION
Paclitaxel-mediated secretion of inflammatory mediators, including TNFα, potentiates creates paracrine and autocrine loops that can contribute to survival and reduction of paclitaxel-induced apoptosis in cancer cells. One of the mechanisms of cancer cell survival is the expression of inhibitor of apoptosis proteins (IAPs). Cellular IAP (cIAP) is involved in inflammatory pro-survival NF-kB activation, blocking the activation of the effector caspases 3 and 7, while XIAP (X-linked IAP) indirectly binds to the effector caspases 3, 7 and 8, inhibiting the full activation of the apoptosis pathway.

ASTX660, a fragment-derived small molecule that is orally bioavailable, is a dual antagonist of cIAP and XIAP (Chesnut 2016). Its inhibitory activity has been demonstrated in preclinical models of melanoma and other types of cancer, in which inflammation was present. It is currently being investigated in a single agent Phase I clinical trial in patients with advanced solid tumors and lymphomas (NCT02305423). Here, we characterize the activity of ASTX660 in preclinical models of triple-negative breast cancer (TNBC) as a single agent and in combination with paclitaxel whose inflammatory properties are hypothesized to sensitize the cells to ASTX660.

ASTX660 derived from fragment-based drug discovery

EFFECTS OF ASTX660 ON TNBC CELL LINES IN VITRO

ASTX660 Treatment reduces viability of TNBC cells

In vitro cell line-screening

HCC1806 cells treated with ASTX660, paclitaxel and TNFa combination study

In vivo anti-tumor activity of ASTX660 in TNBC models

In vivo anti-tumor activity of ASTX660 in TNBC MODELS

Figure 3: Degradation of cIAP in HCC1806 and HCC38 cells after 1 hour incubation with ASTX660 and XIAP were detected by Western blotting, demonstrating IAP antagonistic activity of ASTX660.

Figure 4: In vivo anti-tumor activity of ASTX660 in TNBC xenograft in BALB/c nude mice. Tumors were treated with ASTX660 monotherapy and ASTX660 in combination with paclitaxel. ASTX660 monotherapy inhibited tumor growth in vivo (p = 0.008; Veh. Ctr.). Combination of ASTX660 and paclitaxel enhanced tumor growth inhibition (p = 0.006). Combination of ASTX660 and paclitaxel also prolonged survival (p = 0.006). Combination of ASTX660 and paclitaxel increased paclitaxel accumulation in tumors (p = 0.01). Treatment of ASTX660 monotherapy or ASTX660 in combination with paclitaxel led to a decrease in circulating levels of inflammatory cytokines TNFα and IL-1β (p = 0.006). Combination of ASTX660 and paclitaxel resulted in a decrease in circulating levels of inflammatory cytokines TNFα and IL-1β (p = 0.006).

CONCLUSIONS

• ASTX660 is effective against 40% of TNBC cell lines in vitro in the presence of TNFα. TNBC cells treated with ASTX660 in the presence of TNFα undergo apoptosis via caspase cleavage following IAP antagonism.

• TNBC tumors that have infiltrated inflammatory environment might be susceptible to ASTX660 in vivo.

• Paclitaxel not only has anti-tumor activity but also increases systemic inflammatory markers. Combination of ASTX660 and paclitaxel resulted in enhanced tumor growth inhibition over paclitaxel alone.

• Combining IAP antagonist with another therapeutic agent that provides inflammatory tumor microenvironment could be a valid therapeutic approach.

• ASTX660 is currently in Phase II clinical trial in patients with advanced solid tumors and lymphomas (NCT02305423).