

Abstract #P3-17-05

Beyond HER2 and hormonal agents: the Heat Shock Protein 90 inhibitor ganetespib as a potential new breast cancer therapy.

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Background: Ganetespib is a fully synthetic and selective inhibitor of heat shock protein 90 (HSP90), a molecular chaperone recognized as a key facilitator of breast cancer initiation, progression and metastasis.

Methods: Preclinical activity of ganetespib across the four major breast cancer subtypes and inflammatory breast cancer was assessed in vitro and in vivo. Modulation of cell proliferation and viability was determined both in monolayer and three-dimensional cultures. HSP90 client protein expression and activity was monitored by Western blot and protein array. To recapitulate clinical dosing, kinetics of client protein destabilization were measured following short exposures to drug in vitro. Anticancer activity of ganetespib was further investigated in vivo using breast cancer xenografts.

Results: Ganetespib displayed potent, low nanomolar activity in luminal (A and B), basal (A and B) and inflammatory breast cancer cell lines grown as monolayers in vitro. BT-474 (HER2 amplified) luminal cells grown as mammospheres in 3D were equally as sensitive to ganetespib as those grown in monolayer. In luminal cells, ganetespib simultaneously disrupted multiple signaling components including the estrogen and progesterone receptor, several receptor and non-receptor tyrosine kinases, as well as the MAPK pathway. Further, ganetespib effectively inhibited AKT, PDK1 and SGK3 activity in PIK3CA mutant cells suggesting that HSP90 is essential for both AKT-dependent and AKT-independent signaling. Clinically relevant exposure times to ganetespib in vitro resulted in potent, long term destabilization of HER2. In the basal-like breast cancer cell line MDA-MB-231, enriched in CD44⁺CD24⁻ stem like cells that commonly display chemotherapeutic resistance and activated JAK2/STAT3 signaling, ganetespib (50 nM) induced significant degradation of JAK2 concordant with loss of both tyrosine and serine phosphorylation of STAT3, followed by cell death. The potent anticancer activity in vitro translated in vivo, where ganetespib was effective in modulating breast cancer xenograft growth as a single agent in both luminal and basal-like breast cancer models. Finally, ganetespib has demonstrated encouraging signs of clinical activity in breast cancer patients, including confirmed partial responses in both a triple negative breast cancer patient and a HER2 positive breast cancer patient.

Conclusions: Ganetespib is a highly potent HSP90 inhibitor that displays preclinical activity in breast cancer due to its ability to simultaneously perturb multiple oncogenic signaling pathways.