#D02 Combination of the Hsp90 Inhibitor Ganetespib (STA-9090) With Docetaxel Displays Synergistic Anticancer Activity in Solid Tumor Cells

David A. Proia, Jim Sang, Jaime Acquaviva, Julie Friedland, Suqin He, Donald Smith, Chaohua Zhang, Ronald K. Blackman, Yumiko Wada

Synta Pharmaceuticals Corp., Lexington, Massachusetts USA

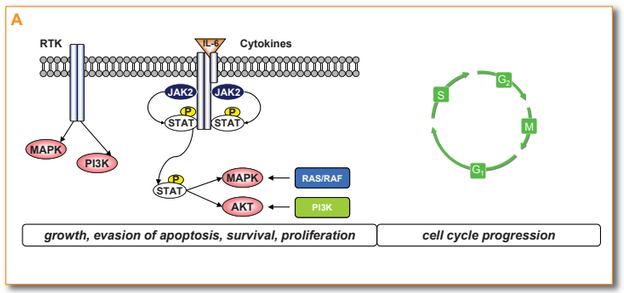
Abstract

Background: Ganetespib (STA-9090) is a synthetic, small-molecule inhibitor of Hsp90 that is currently in 11 Phase 2 trials for solid and hematologic malignancies. Recent results from a Phase 2 trial in non-small cell lung carcinoma (NSCLC) show that ganetespib is clinically active and is well tolerated in patients whose tumors are wild-type for EGFR and KRAS. Because of the accumulating evidence that Hsp90 inhibition sensitizes tumor cells to taxanes, we studied combinations of ganetespib with the taxane docetaxel in NSCLC, prostate and colon cancer cells.

Results: We observed potent single agent activity with ganetespib across a panel of NSCLC cell lines independent of EGFR status both *in vitro* and in mouse xenograft models. Similar activity was observed in patient-derived NSCLC tumor cells grown as tumor spheres *in vitro* or tumor grafts *in vivo*. Comparable results were demonstrated in prostate and colon cell lines regardless of androgen receptor or p53 status, respectively. To investigate the potential for therapeutic synergy, we measured the response of lung, prostate and colon cancer cells to the combination of ganetespib and docetaxel. By microscopy and proliferation assays, the combination resulted in enhanced cell death compared to either agent alone *in vitro*. Similarly, mouse xenograft models of NSCLC containing wild-type EGFR displayed greater efficacy with the combination of docetaxel and ganetespib than monotherapy.

Conclusions: Ganetespib is a highly potent Hsp90 inhibitor which displays nonclinical efficacy across a broad range of indications and genetic alterations, both in cancer cell lines as well as in primary human tumors. Combining ganetespib with docetaxel enhanced cell death in a synergistic fashion in multiple cancer cell types, and as a result, could expand the therapeutic potential of both drugs. A phase 2b/3 trial of ganetespib in combination with docetaxel is currently being initiated.

Introduction



Disruption of mitogenic signaling by ganetespib leads to growth arrest and apoptosis.

(A) Receptor (RTK) and non-receptor kinases play essential roles in mediating cell growth and survival via activation by cognate ligands and cytokines. Hyperactivation of these pathways is often associated with oncogenesis and uncontrolled cell division.

(B) Inhibition of the molecular chaperone Hsp90 by ganetespib leads to the destabilization of oncoproteins driving tumor initiation and progression, as well as several key kinases required to regulate the cell cycle, resulting in growth arrest and cell death.

Ganetespib is Potent in NSCLC Cells Independent of Genetic Status

A

Cell Line	IC50 (nM)	BRAF	EGFR	ERBB2	KRAS	MET	MYC	NRAS	PIK3CA	RB1	TP53
NCI-H1975	4	wt	mutant	wt	wt	wt	amp	wt	mutant	wt	mutant
NCI-H1355	5	wt	wt	wt	mutant	wt	wt	wt	wt	wt	mutant
NCI-H2228	7	wt	wt	wt	wt	wt	wt	wt	wt	mutant	mutant
NCI-H157	7	wt	wt	wt	mutant	wt	wt	wt	wt	wt	mutant
LC-2-ad	8	wt	wt	wt	wt	wt	amp	wt	wt	wt	mutant
SK-MES-1	9	wt	wt	wt	wt	wt	wt	wt	wt	wt	mutant
IA-LM	10	wt	wt	wt	mutant	wt	wt	wt	wt	wt	wt
NCI-H596	11	wt	wt	wt	wt	wt	wt	wt	mutant	mutant	mutant
HOP-62	11	wt	wt	wt	mutant	wt	wt	wt	wt	wt	Null
NCI-H727	13	wt	wt	wt	mutant	wt	wt	wt	wt	wt	mutant
NCI-H1648	13	wt	wt	wt	wt	amp	wt	wt	wt	wt	mutant
NCI-H2170	15	amp	wt	amp	wt	amp	amp	amp	wt	amp	mutant
NCI-H358	15	wt	wt	wt	mutant	wt	wt	wt	wt	wt	wt
LXF-289	15	wt	wt	wt	wt	wt	wt	wt	wt	wt	mutant
SK-LU-1	18	wt	wt	wt	mutant	wt	wt	wt	wt	wt	mutant
A549	19	wt	wt	wt	mutant	wt	wt	wt	wt	wt	wt
NCI-H1792	20	wt	wt	wt	mutant	wt	amp	wt	wt	wt	Null
CORL-23	22	wt	wt	wt	mutant, amp	wt	amp	wt	wt	wt	wt
CAL-12T	25	mutant	wt	wt	wt	wt	wt	wt	wt	wt	mutant
Calu-1	28	wt	wt	wt	mutant	wt	wt	wt	wt	wt	wt
NCI-1437	30	wt	wt	wt	wt	wt	wt	wt	wt	wt	mutant
NCI-H810	36	wt	wt	wt	wt	wt	wt	wt	wt	wt	mutant
NCI-H838	51	wt	wt	wt	wt	wt	wt	wt	wt	wt	mutant
NCI-H2122	53	wt	wt	wt	mutant	wt	amp	wt	wt	wt	mutant
NCI-H522	61	wt	wt	wt	wt	wt	wt	wt	wt	wt	mutant
LCLC-103H	62	wt	wt	wt	wt	wt	wt	wt	wt	wt	mutant
Calu-6	64	wt	wt	wt	mutant	wt	wt	wt	wt	wt	mutant

B

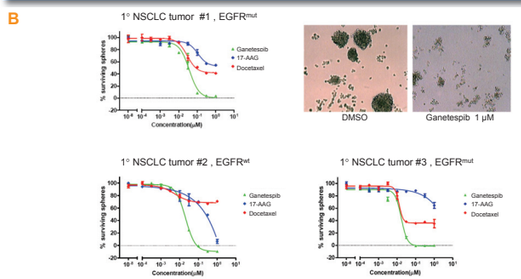


Figure 1. (A) Ganetespib has activity against a broad array of NSCLC cell lines independent of gene copy number amplification (amp), or mutations commonly associated with NSCLC. (B) Primary human tumor cells are highly sensitive to ganetespib. Human NSCLC tissue (obtained from 3 separate patients) was dissociated into single cells and exposed 1 day later to indicated compounds for 7 days.

Ganetespib Induces Caspase-Mediated Apoptosis and Cell Death

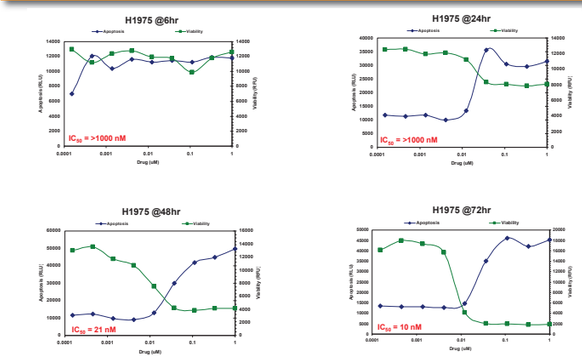


Figure 2. Ganetespib induces cell death in part through apoptosis. NCI-H1975 cells were exposed to increasing concentrations of ganetespib for 6 to 72 hr. Apoptosis was measured using activated caspase 3/7 levels and compared to cell viability.

In Vitro Synergy Between Ganetespib and Docetaxel in NSCLC

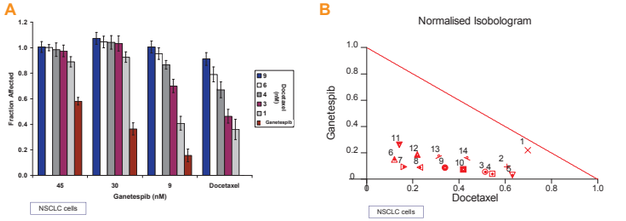


Figure 3. Synergy achieved by the combination of ganetespib and docetaxel in NSCLC cells. (A) NCI-H522 NSCLC cells were treated with ganetespib, docetaxel or the combination of the two for 72 hr. (B) Isobologram analysis of ganetespib/docetaxel combination. Data points below the red line in the isobologram indicate synergy (combination index <1), whereas data points above the red line indicate antagonism between the two drugs. Ganetespib was found to potently synergize with docetaxel.

In Vitro Synergy Between Ganetespib and Docetaxel in Prostate Cancer

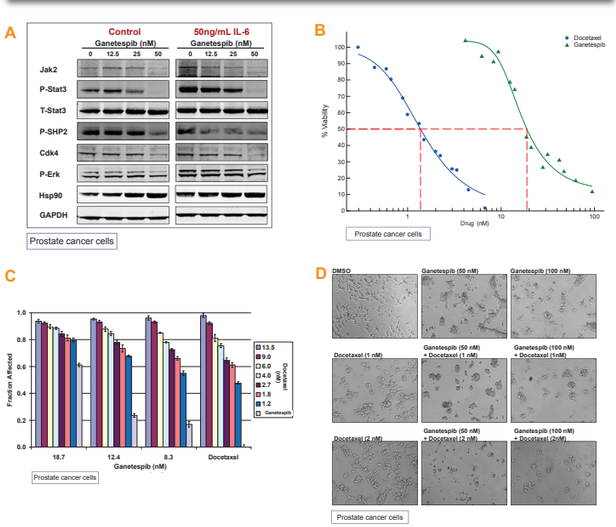


Figure 4. (A) Inhibition of Hsp90 by ganetespib disrupts intrinsic and cytokine mediated activation of the JAK/STAT pathway as well as mitogenic signaling in DU-145 prostate cancer cells. (B) Ganetespib and docetaxel display potent anticancer activity in DU-145 cells. (C) The combination of ganetespib and docetaxel in DU-145 prostate cancer cells leads to greater cell death than monotherapy. (D) Short exposure to both ganetespib and docetaxel displays considerably greater cell death than either agent alone. LNCaP cells were treated with ganetespib, docetaxel or the combination of the two for one hour on day one and day two. Twenty-four hours later, viability was assessed by microscopy.

In Vitro Synergy Between Ganetespib and Docetaxel in Colon Cancer

A

Cell Line	Ganetespib IC50 (nM)	17-AAG IC50 (nM)	Mutations
HCT-15	8	1800	APC, BRCA2, NRAS, MSH6, PI3K, p53
Colon205	14	17	APC, BRAF, SMAD4, p53
HCT-116	16	148	CDKN2A, CTNNB1, NRAS,MLH1, PI3K
SW620	17	29	APC, KRAS, MAPK, SMAD4, p53
SW480	21	210	p53, KRAS
Caco-2	37	4946	p53 null, SMAD4
HT-29	60	22	APC, BRAF, PI3K, SMAD4, p53
LoVo	66	3555	APC, KRAS

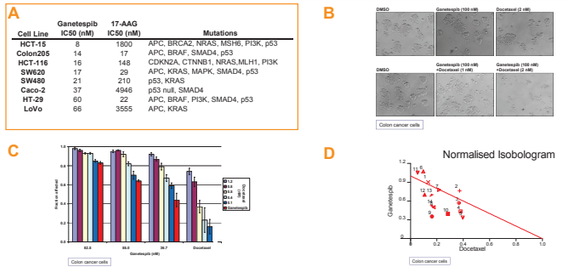


Figure 5. (A) Ganetespib has activity against a broad range of colon cancer cell lines independent of mutations commonly associated with the disease. (B-D) The combination of ganetespib and docetaxel in colon cancer cells leads to greater cell death than monotherapy.

In Vivo Synergy Between Ganetespib and Docetaxel in NSCLC Xenograft Models

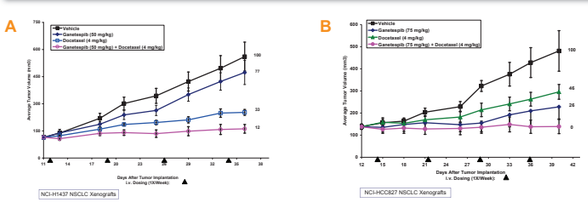


Figure 6. Combining ganetespib with docetaxel improves tumor growth suppression in NSCLC xenografts. (A) NCI-H1437 NSCLC xenografts were treated with ganetespib, docetaxel or the concurrent combination of the two compounds (1X/week, 3 weeks). The combination of ganetespib and docetaxel displayed greater efficacy than either single agent alone, with %T/C values of 12, 77 and 33, for the combination, ganetespib and docetaxel, respectively. (B) Similar results were observed in the NCI-HCC827 model, with %T/C values of 0, 26 and 46, for the combination, ganetespib and docetaxel, respectively.

Conclusions

- Ganetespib is a highly potent Hsp90 inhibitor displaying nonclinical efficacy across a broad range of NSCLC, prostate and colon cancer cell lines, as well as primary tumor cells, regardless of increased copy number or mutations in genes common to the respective diseases
- Combining ganetespib with docetaxel enhances cell death in a synergistic fashion in multiple cancer cell types *in vitro*
- Ganetespib improves the activity of docetaxel in NSCLC xenografts *in vivo*, and as a result, could expand the therapeutic potential of both drugs
- A Phase 2b/3 trial of ganetespib in combination with docetaxel is currently being initiated

SYNTA PHARMACEUTICALS®

Targeted Anticancer Therapies Meeting, 7-9 March 2011, Paris, France

For further information on Ganetespib: www.syntapharma.com