

A phase I dose-escalation study of the Hsp90 inhibitor ganetespib administered twice weekly in patients with solid tumors: updated report

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BACKGROUND

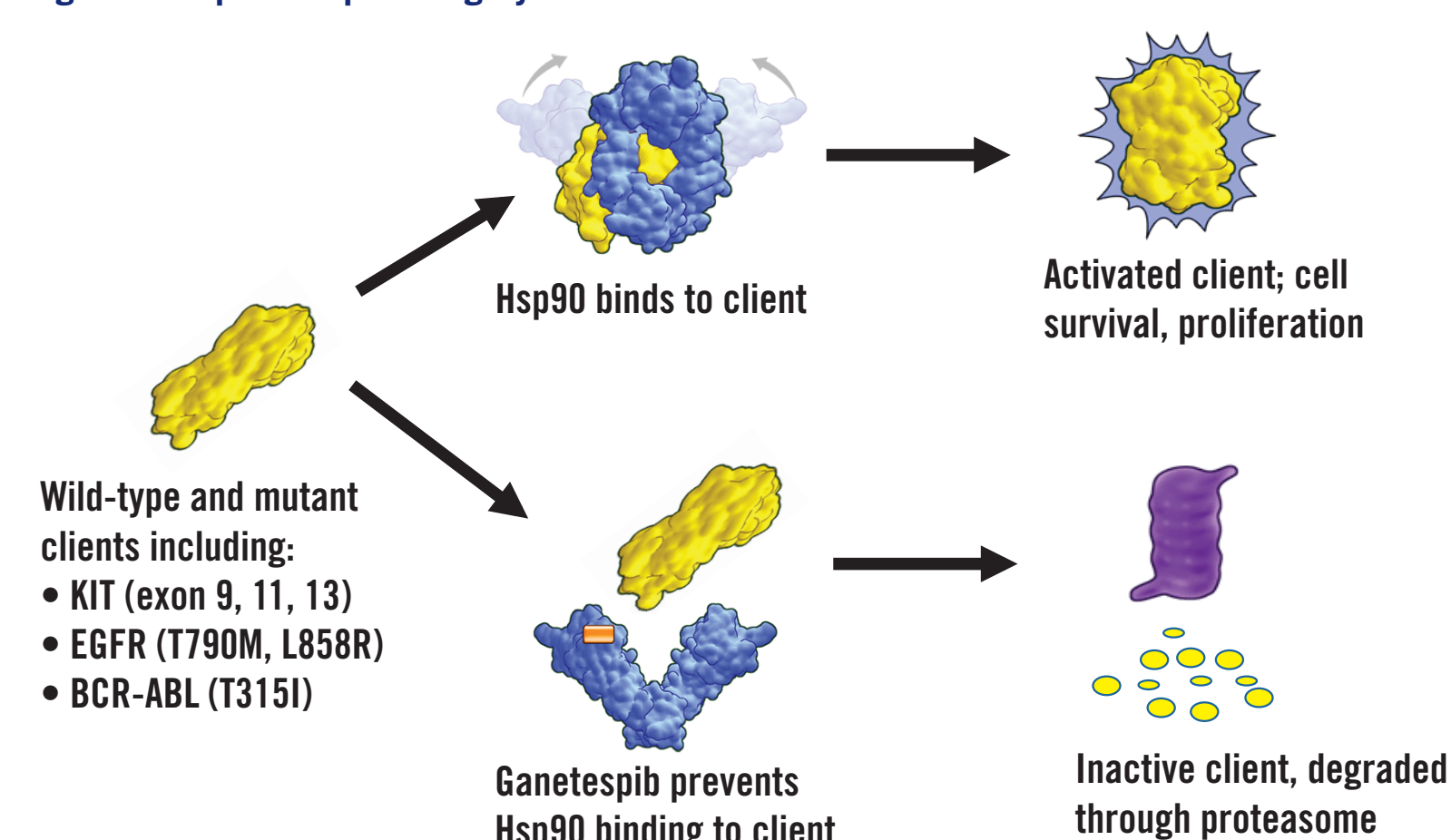
Hsp90 Inhibition

- Hsp90 is a chaperone protein that controls the folding and processing of proteins that drive tumor development and progression
- Hsp90 clients include many proteins that play a critical role in tumor pathophysiology such as EGFR, HER2, c-MET, AKT, BCR-ABL, RAF, CDK4, KIT, FLT3, and VEGFR
- Degradation of client proteins allows for simultaneous targeting of multiple oncogenic signaling pathways
- Kinase client proteins are generally dependent on Hsp90 regardless of mutational status - wild type, TKI-sensitive, TKI-resistant – which creates potential for use in multiple settings

Ganetespib Overview

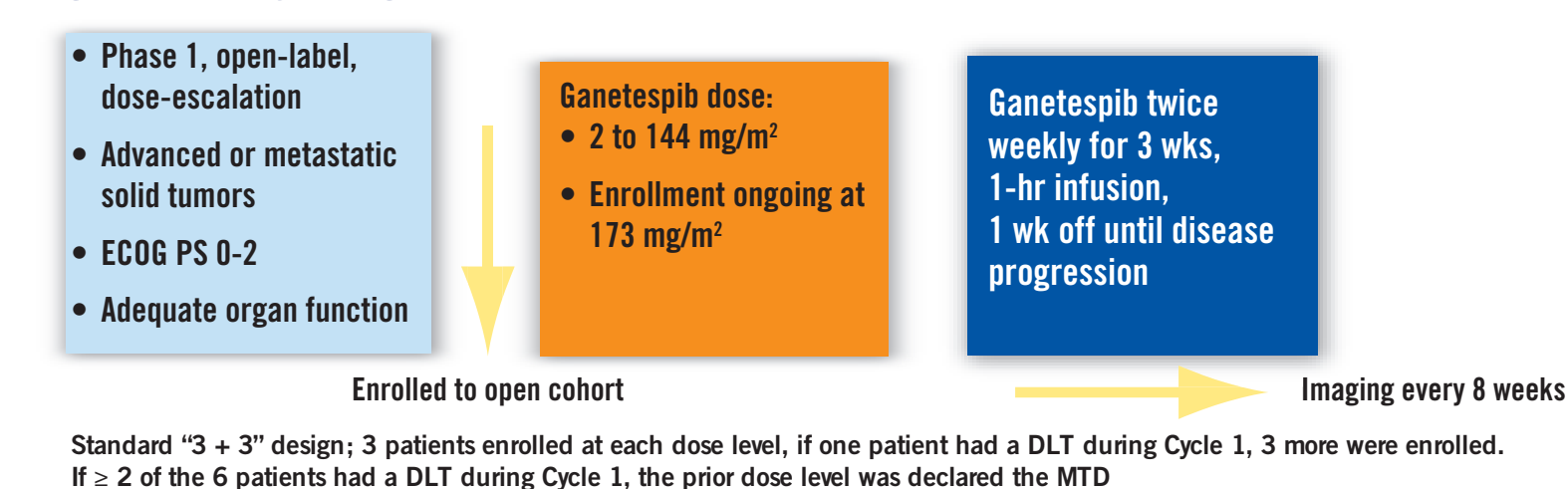
- Potent intravenous small molecule Hsp90 inhibitor¹⁻³
 - Structurally unrelated to first-generation Hsp90 inhibitors (such as 17AAG and IPI-504);
 - Up to 100 times more potent than first-generation Hsp90 inhibitors
- Strong preclinical results
 - Potently inhibits Hsp90 leading to the degradation of multiple clinically-validated oncogenic client proteins
 - Penetrates deeply into hypoxic tumors, inhibiting HIF-1 α
- Clinically well tolerated and has shown promising antitumor activity in early trials in multiple cancers
- Twice-weekly dosing may be needed in some tumor types
 - Preclinical data indicate that different client proteins show disparate expression kinetics upon Hsp90 inhibition.

Figure 1: Hsp90 Chaperoning Cycle



METHODS

Figure 2: Study Design



Study Objectives

- Primary Objectives:
 - To characterize the safety and tolerability of ganetespib in cancer patients
 - To determine the pharmacokinetics of ganetespib when administered by intravenous infusion
- Secondary Objectives:
 - To recommend the dose for future study using a twice-a-week schedule
 - To assess preliminary evidence of anti-tumor activity

RESULTS

Table 1: Demographics and Baseline Status

	2-50 mg/m ² (n=36)	100-120 mg/m ² (n=11)	144 mg/m ² (n=7)	Total (n=54)
Age Median	56	53	44	55
Sex				
Male	16	5	6	27
Female	20	6	1	27
Race				
White	32	8	6	46
Black	2	2	0	4
Asian	0	1	1	2
American Indian	1	0	0	1
Other	1	0	0	1
ECOG Status				
0	12	2	3	17
1	17	8	2	27
2	7	1	2	10
Tumor Type				
Lung	5	1	0	6
Breast	1	0	1	2
Genitourinary	1	1	0	2
Pancreas	2	0	0	2
Colon	7	4	2	13
Melanoma	7	1	0	8
Other	13	4	4	21

Table 2: Summary of Adverse Events

	2-50 mg/m ² (n=36)	100-120 mg/m ² (n=11)	144 mg/m ² (n=7)	Total (n=54)
Any AE	36 (100)	11 (100)	7 (100)	54 (100)
Any Grade 3 AE	24 (67)	6 (55)	5 (71)	35 (65)
Any SAE	14 (39)	2 (18)	2 (29)	18 (33)
Any DLT	1 (3)	0	1 (14)	2 (4)
AEs leading to treatment discontinuation	8 (22)	1 (9)	1 (14)	10 (19)
AEs with outcome of death	3 (8)	0	0	3 (6)

Table 3: Most Common Overall AEs (≥15% of all patients)

Number of patients (N, %)	2-50 mg/m ² (n=36)	100-120 mg/m ² (n=11)	144 mg/m ² (n=7)	Total (n=54)
Diarrhea	12 (33)	9 (82)	6 (86)	27 (50)
Fatigue	17 (47)	6 (55)	3 (43)	26 (48)
Nausea	13 (36)	5 (46)	3 (43)	21 (39)
Anemia	12 (33)	3 (27)	2 (29)	17 (32)
Headache	7 (19)	4 (36)	3 (43)	14 (26)
Constipation	5 (14)	6 (55)	2 (29)	13 (24)
Vomiting	8 (22)	3 (27)	1 (14)	12 (22)
Abdominal pain	7 (19)	3 (27)	1 (14)	11 (20)
Decreased appetite	9 (25)	1 (9)	1 (14)	11 (20)
Alkaline phosphatase increased	7 (19)	1 (9)	1 (14)	9 (17)
Weight decrease	6 (17)	1 (9)	2 (29)	9 (17)
ALT increased	4 (11)	2 (18)	2 (29)	8 (15)
AST increased	6 (17)	1 (9)	1 (14)	8 (15)
Hypokalemia	4 (11)	1 (9)	3 (43)	8 (15)

Table 4: Most Common Grade ≥3 Adverse Events (occurred in ≥2 patients)

Number of patients (N, %)	2-50 mg/m ² (n=36)	100-120 mg/m ² (n=11)	144 mg/m ² (n=7)	Total (n=54)
Diarrhea	3 (8)	3 (27)	1 (14)	7 (13)
Alkaline phosphatase increased	3 (8)	1 (9)	0	4 (7)
AST increased	2 (6)	0	1 (14)	3 (6)
Hypophosphatemia	1 (3)	0	2 (29)	3 (6)
Abdominal pain	2 (6)	0	0	2 (4)
ALT increase	1 (3)	0	1 (14)	2 (4)
Dehydration	1 (3)	0	1 (14)	2 (4)
Dyspnea	2 (6)	0	0	2 (4)
Hyperkalemia	1 (3)	1 (9)	0	2 (4)
Hyponatremia	2 (6)	0	0	2 (4)
INR increased	2 (6)	0	0	2 (4)
Pulmonary embolism	2 (6)	0	0	2 (4)
Renal Failure	0	1 (9)	1 (14)	2 (4)

Most Common Adverse Events:

- Gastrointestinal events (diarrhea, nausea, vomiting)
- Most events were transient, and mild or moderate in severity
- 13% of patients reported severe diarrhea, and one patient each reported severe nausea or vomiting (2%)

Serious Adverse Events:

- Reported by 33% of patients
- Events reported in more than one patient were dyspnea and pulmonary embolism (2 patients each)
- All other SAEs were reported in one patient each
- Three patients had an AE with an outcome of death

RESULTS

Table 5: AEs with Outcome of Death

# Pts	Dose level	Reason for DC of study	AE	Relationship	Days from last dose
1	10 mg/m ²	symptomatic deterioration	dyspnea and rales	Possibly related	12
1	25 mg/m ²	disease progression	pulmonary embolism	Not related	17
1	25 mg/m ²	symptomatic deterioration	progressive disease	Not related	7

- Adverse events leading to discontinuation of study drug:
 - Occurred in 10 (19%) patients
 - 3 patients with AEs related to study drug: ALT increase, infusion reaction and dyspnea/hypoxia/rales
- DLTs
 - ALT increase, grade 3: 1 at 10 mg/m²
 - ALT increase, grade 3: 1 at 144 mg/m²

Pharmacokinetics

- Ganetespib exposures are directly proportional to dose. This is shown in Figure 3 where the area under the curve (AUC) increases linearly with dose.
- Exposures on Day 1 and Day 15 are not statistically significantly different (p-value = 0.1885) (Figure 4).
- No drug accumulation is seen upon multiple dosing
- Ganetespib exhibits biphasic pharmacokinetics
- Concentrations rise rapidly during infusion. Concentrations decline rapidly upon infusion termination; by a factor of approximately 10 fold within 1 hour and approximately 100 fold within 8 to 10 hours.

Figure 3: Ganetespib AUC on Cycle 1

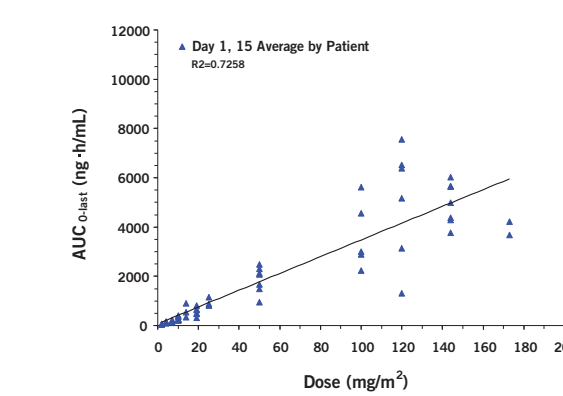
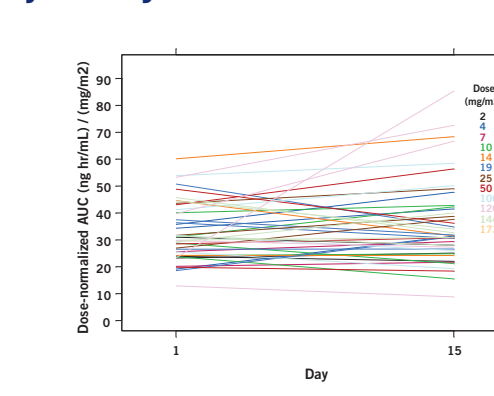


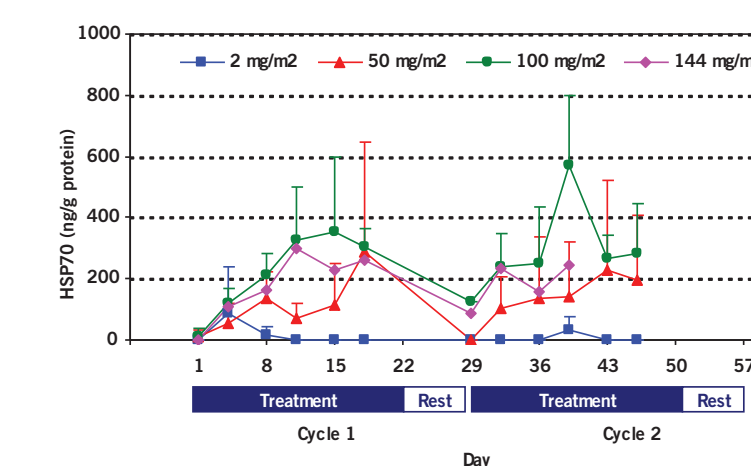
Figure 4: Ganetespib AUC, Days 1 and 15 by Subject (Cycle 1)



Hsp70 Plasma Protein

- Hsp70 plasma protein concentrations increased in response to ganetespib administration demonstrating ganetespib's biological activity in patients
- Hsp70 plasma protein levels were lower 2 weeks post-dose relative to 1 week post-dose, approaching baseline for lower doses
- There is no increased dose response at levels higher than 100 mg/m²
- During the second treatment cycle, biological responsiveness to ganetespib is retained

Figure 5: Hsp70 Plasma Protein Levels



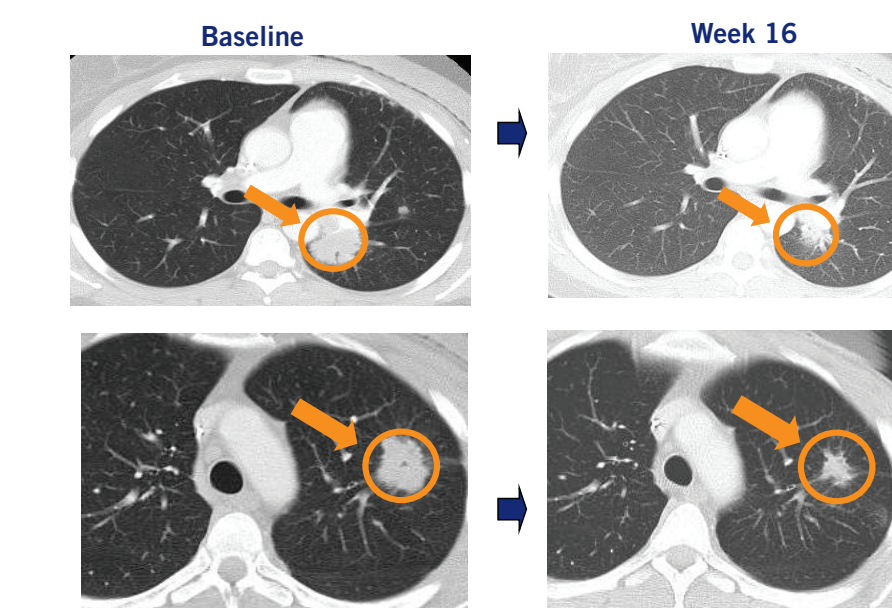
Clinical Activity per RECIST Criteria

- 41 of 54 enrolled patients were assessable for response as of the March 25, 2011 data cut-off date
 - 13 patients discontinued prior to the Week 8 response assessment
- Objective tumor responses
 - 1 partial response in a patient with melanoma
 - 1 partial response in a patient with triple negative breast cancer
- 15 patients achieved stable disease
- The maximum tolerated dose has not yet been reached; dose escalation continues

Ganetespib Case Study

- A 39-year-old white female with triple negative breast cancer
 - Initial diagnosis: March 2007, Stage III invasive ductal carcinoma
 - Progressed on 7 prior chemotherapeutic regimens
 - Enrolled in November 2010, ganetespib dosing at 144 mg/m² twice weekly
 - After 2 cycles, demonstrated stable disease per RECIST; 31% reduction in target lesion size documented after Cycle 4 (partial response)
 - Treatment interrupted due to brain metastases treated with whole brain radiation; ganetespib resumed in cycle 5
 - Treatment well tolerated with mild/moderate toxicities

Figure 6: Case Study CT Scans



CONCLUSIONS

- Ganetespib appears to be well-tolerated at the dose levels administered in this regimen of twice-weekly dosing to date (2-144 mg/m²)
- Enrollment in the study continues, with the objective of identifying the MTD and recommended Phase 2 dose for a twice-weekly schedule
- Encouraging signs of clinical activity – MTD has not yet been reached
- Ganetespib shows linear PK (exposures directly proportional to dose), shows no accumulation, and exposures are essentially identical on days 1 and 15 of dosing
- Phase 2 studies in NSCLC, GIST, colorectal cancer, gastric cancer, breast cancer, pancreatic cancer, prostate cancer, and ocular melanoma are ongoing

Acknowledgements

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Disclosures

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