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Ganetespib, a Novel Hsp90 Inhibitor in Patients With KRAS Mutated and Wild Type, Refractory Metastatic Colorectal Cancer

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Abstract

Seventeen patients with refractory KRAS mutated and wild type metastatic colorectal adenocarcinoma received single agent ganetespib in a single institution phase II study. The drug was well tolerated but did not yield any responses, although two patients achieved durable stable disease.

Background—Heat shock protein 90 (Hsp90) is a cellular chaperone that is required for the maturation and stability of a variety of proteins that play key roles in colon cancer initiation and progression. The primary objective of the current study was to define the safety and efficacy of ganetespib, a novel, selective small-molecule Hsp90 inhibitor, in patients with refractory metastatic colorectal cancer.

Patients and Methods—The study was a single-arm, Simon 2-stage, phase II trial for patients with chemotherapy-refractory, metastatic colorectal cancer. Patients received ganetespib 200 mg/m² intravenously. Tumor tissue was collected before treatment and 48 hours after treatment for changes in expression of Hsp90 client proteins and other potential pharmacodynamics markers. V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS), v-Raf murine sarcoma viral oncogene homolog B, and phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) mutational status was also determined.

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Disclosure

Dr. Proia is an employee of Synta Pharmaceuticals. All other authors declare no conflicts of interest.

Results—Seventeen patients were treated (median age, 58; range, 44–79 years). No patients demonstrated objective regression of disease. Two patients had stable disease of 6.8 and 5.1 months duration. Serious adverse events that were potentially attributable to ganetespib included diarrhea (12%, n = 2), fatigue (17%, n = 3), and increased aspartate aminotransferase/alanine aminotransferase (12%, n = 2) and alkaline phosphatase (6%, n = 1) levels. Of the 17 evaluable patients, 9 (53%) including patients with stable disease as best response, had KRAS-mutant tumors.

Conclusion—In this first phase II investigation of an Hsp90 inhibitor in colorectal cancer, ganetespib as a single agent did not demonstrate activity in chemotherapy-refractory metastatic colorectal cancer. However, on the basis of the drug's promising preclinical combination data and the relatively mild toxicity profile, further clinical investigation of this agent in combination with standard cytotoxic agents is planned.

Keywords

Ganetespib; HSP 90; Metastatic colorectal cancer; KRAS; Single agent

Introduction

Heat shock protein (Hsp) 90 belongs to a class of molecular chaperone proteins that help modulate cellular responses to environmental stress by supporting stabilization, folding, and function of many oncogenic proteins, and other proteins responsible for cancer cell growth and survival. Cancer cells upregulate Hsp90 in response to stress,^{1–3} allowing critical Hsp90-bound proteins to escape proteolytic degradation, and thereby promote cellular proliferation.^{4,5} Additionally, Hsp90 expression has been shown to enable the tumor cells to escape apoptosis.⁶

A number of treatment regimes are available for patients with metastatic colorectal cancer (CRC) including chemotherapies with 5-fluoracil–based regimens, irinotecan, oxaliplatin, and targeted therapies such as anti-vascular endothelial growth factor (VEGF) treatment with bevacizumab and anti-epidermal growth factor receptor (EGFR) treatment with cetuximab or panitumumab (for patients with V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) wild type tumors). Unfortunately, eventually metastatic CRC becomes unresponsive to medical therapy. Currently, there is no effective standard treatment for this refractory patient population and no known drug for which the response rate would be expected to be greater than approximately 0% to 1%. Therefore, new approaches are needed.

KRAS Kirsten and Neuroblastoma RAS viral oncogene homolog-activating mutations have been shown to result in resistance to anti-EGFR–targeted therapies in CRC, and recent data have also shown similar resistance in tumors with mutated v-Raf murine sarcoma viral oncogene homolog B (BRAF),⁷ and in patients with mutations in the PI3K/protein kinase B (Akt) pathway.⁸ The attempt to identify a single driver mutation has been disappointing thus far, as evidenced by the still relatively low response rate of approximately 20% to 25% in RAS wild type tumors to anti-EGFR therapy and the lack of response to the BRAF inhibitor vemurafenib (PLX4032) in BRAF V600E-mutated cells.⁹ Thus, it is becoming increasingly more evident that the biology of CRC is different from malignancies in which there is a

clear-cut driver mutation, such as HER2-mutated breast cancer or EGFR-mutated non-small-cell lung cancer. Hsp90 inhibition enables the simultaneous blockade of multiple oncogenic transduction pathways and tumor–stroma interactions, thereby potentially inhibiting cancer cell growth and survival. Thus, Hsp90 inhibition represents an attractive potential therapeutic target in CRC.

Ganetespib is a novel second small molecule Hsp90 inhibitor. It is a resorcinol-containing triazole compound that binds to the N-terminus of Hsp90 and is structurally unrelated to the geldanamycin class of Hsp90 inhibitors. Preclinical and phase I studies appear to demonstrate less toxicity (including lack of ocular and hepatic toxicity) than the earlier Hsp90 inhibitors and effective downregulation of key oncogenic proteins in CRC cell lines.^{10,11} In the phase I study, single-agent ganetespib was well tolerated and a patient with metastatic CRC achieved a partial response.¹²

Because of this response, favorable toxicity profile, and compelling preclinical data, we hypothesized that ganetespib as a single agent would have clinically meaningful activity in refractory metastatic CRC.

Patients and Methods

Study Population

Patients were required to have pathologically confirmed CRC with measurable metastatic disease according to Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) criteria and documentation of previous progression during at least 1 chemotherapeutic regimen. Patients were further required to have an Eastern Cooperative Oncology Group performance status of 0 or 1, age 18 or older, and have an estimated life expectancy of > 3 months. Adequate kidney and bone marrow function were required and adequate hepatic function, defined as a total bilirubin $\leq 1.5 \times$ the upper limit of normal. Patients with compromised cardiac function (ejection fraction < 45%) or a history of arrhythmia were excluded. Patients were required to agree to undergo tumor biopsies before and after treatment.

Treatment and Evaluation

Patients received 200 mg/m² of ganetespib during a 1-hour intravenous infusion, for 3 consecutive weeks followed by a 1-week dose-free interval. Treatment was continued until progression of disease or unacceptable toxicity or the patient withdrew consent. Adverse events were graded based using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3. All Grade 3 toxicities required dose modification if optimal prophylactic measures were unsuccessful. In patients who developed Grade 3 or 4 toxicity, treatment was held until the toxicity returned to baseline or Grade 1. Ganetespib was then restarted at a 25% dose reduction. Grade 3 electrocardiogram abnormalities required withdrawal from the study. For Grade 2 drug-related diarrhea, neutropenia, or other toxicity believed by the investigator to be drug-related and to warrant dose reduction, treatment was held until that toxicity was Grade 1. Treatment was then resumed with a 25% dose reduction.

Imaging with computed tomography scans or magnetic resonance imaging scans of measurable lesions were obtained at baseline and every 8 weeks. Responses were categorized according to standard RECIST criteria. Response and progression were determined by a reference radiologist (M.G.). The primary objective of the study was to define the RECIST objective response rate. Secondary end points included progression-free survival (PFS) and overall survival (OS). Tumor biopsies were obtained from all patients before and 48 hours after the initial dose of ganetespib.

Correlative Laboratory Analyses of Tumor Tissue Samples

Immunohistochemical Analyses—Immunohistochemistry (IHC) was performed using formalin-fixed, paraffin-embedded tumor tissue to quantitate the expression of phospho extracellular signal-regulated kinases (pErk) (XP rabbit monoclonal antibody [mAb] from Cell Signaling Technology, Inc), Cyclin D1 (rabbit mAb from Lab Vision Corp), phospho protein kinase B (pAkt) (XP rabbit mAb from Cell Signaling), hypoxia inducible factors (HIF)-1 α (mouse mAb from Novus Biologicals), VEGFr2 (rabbit mAb from Cell Signaling), p70S6 (rabbit mAb from Cell Signaling), and Hsp70 (rabbit polyAb from Cell Signaling) were determined before and after treatment with drug. Staining was scored based on intensity (0–3 or more) and the percentage of tumor cells stained.

Tumor Genotyping—To ensure adequate tumor content for genomic analysis, hematoxylin and eosin stained slides were reviewed by a reference pathologist (E.V.) before DNA extraction. Sections were cut (5–6 mm thick) from paraffin-embedded tumor samples were available for 16 of 17 patients and were evaluated for v-Ki-ras2 *KRAS*, *BRAF*, and *PIK3CA*. The mutational status was determined using a chip-based, matrix-assisted, laser desorption-time-of-flight mass spectrometry-based assay (Sequenom, San Diego, CA) and confirmed using Sanger sequencing. The details of this assay have been published previously.¹³

Statistical Analyses

The primary end point was objective response rate (defined as complete + partial responses). The study was a single-arm Simon optimal 2-stage phase II trial. The study was power-based on a null response rate of 1% (because there is no known drug for which the response rate would be expected to be > approximately 0%–1% in CRC patients in whom standard treatment has failed) and an alternative of 15% and with type I error (falsely accepting a non-promising therapy) and type II error (falsely rejecting a promising therapy), both set to 10%. On this basis, we planned to enroll 15 patients in the first stage. If no patients experienced an objective response, the study was to be terminated; if 1 or more confirmed responses were observed, 18 additional patients were to be enrolled (for a total of 33 patients in the 2 stages). At the end of stage 2, the regimen would be declared worthy of further study if 2 or more patients of the total 33 were to achieve an objective response. OS and PFS was calculated from the date of initial therapy until the time of death (for OS) or until the date of either disease progression or death, whichever came first (for PFS). Patients removed from the study because of toxicity before determination of progression were treated as an event for PFS at the off-study date. Patients who were alive at the time of study completion were censored at the time the patient was last known to be alive. OS and PFS were estimated

using the Kaplan–Meier method. Exploratory IHC analyses as outlined herein were planned to test for associations between the marker activation, objective tumor response, and toxicity using a McNemar test. In the event that no responses were seen, only descriptive results were to be reported.

Results

Patient Characteristics

Seventeen patients were enrolled and treated in this trial between June 2010 and November 2011. The median age was 58 years (range, 44–79 years). Patient characteristics are summarized in Table 1. All patients had received previous chemotherapy as required for study eligibility with most having received 3 or more previous regimens. All patients with KRAS wild type tumors had received previous anti-EGFR therapy. Two patients were removed from the study because of events unrelated to treatment (both for progression of disease). Thus, in total, 17 patients were treated and evaluated.

Toxicity

All 17 patients were evaluable for toxicity. One developed symptomatic brain metastases, after 2 months during the study. These were believed in retrospect to have been present before enrolling in the study because of their size (4 cm). A second patient who received only 1 dose of ganetespib developed a bowel obstruction which was attributed to disease progression.

Grade 3/4 toxicities believed to be possibly, probably, or definitely related to ganetespib were diarrhea in 2 patients (12%), increased aspartate aminotransferase/alanine aminotransferase levels in 2 (12%) patients, increased alkaline phosphatase in 1 patient (6%), and fatigue in 3 patients (17%). One patient developed a Grade 2 allergic reaction. In Table 2 are outlined the most common Grade 1/2 toxicities that were probably or definitely attributable to ganetespib.

Efficacy

None of the patients achieved an objective response: RECIST overall response rate was 0/17 (0%; 95% confidence interval [CI], 0%–15%). Two patients had stable disease of > 4 months as best response, 1 for 6.8 months, and a second for 4.7 months. The median PFS was 1.6 months (95% CI, 1–2.8 months). All 17 patients died at the end of the follow-up. The median OS was 5.1 months (95% CI, 3.45–8.58 months) and 6-month OS was 41% (95% CI, 19%–62%); PFS and OS curves are shown in Figures 1 and 2.

Correlative Assessments

Genotyping—KRAS mutations were detected in the tumors of 9 patients: 3 G12D, 4 G12V, 1 G12S, and 1 G12C. The 2 patients who achieved stable disease both had tumors that harbored KRAS G12V mutations. One patient did not have sufficient tissue for analysis. The PFS and OS outcomes as a function of mutational status are shown in Table 3.

Immunohistochemistry Analyses—Thirteen patients had sufficient tissue for IHC studies. No significant changes were noted in the expression level of p70S6, pErk, pAkt, Cyclin D1, HIF-1 α , VEGFr2, and Hsp70 (Figure 3).

Discussion

In this phase II study, the single-agent Hsp90 inhibitor ganetespib did not demonstrate meaningful antitumor activity in chemotherapy-refractory metastatic CRC.

The OS and PFS were consistent with refractory metastatic CRC. IHC analysis also did not reveal any significant differences in marker expression between 1 of the 2 patients with stable disease and the remaining 13 who had disease progression. Unfortunately, the patient with stable disease for 23 weeks did not have sufficient tissue for analysis.

We had hypothesized that the inhibition of Hsp90 by ganetespib would lead to the simultaneous degradation of many oncogenic client proteins (HIF-1 α , VEGF receptor, EGFR, Cyclin D1, v-Raf murine sarcoma viral oncogene homolog B, mutant p53) leading to deactivation of their downstream signaling pathways. The IHC results did not reveal any significant changes in protein expression from the tissue samples before and after ganetespib treatment. This might be because of intrinsic limitations of IHC analyses, in that they might be insufficiently sensitive and/or insufficiently quantitative in nature. Alternatively, our IHC results might indicate a failure to adequately hit the putative target, Hsp90, either because of drug metabolism or appropriate exposure. It was recently published that ganetespib is metabolized by the UDP-glucuronosyltransferase 1A (UGT1A) family of glucuronosyltransferase enzymes,¹⁴ which are known to be highly expressed in colon cancer.¹⁵ From personal communication with David Proia at Synta Pharmaceuticals, the developers of ganetespib, they have a manuscript recently accepted for publication that highlights the inactivation of ganetespib in colon cancer cells that express UGT1A.¹⁶ Therefore, it is conceivable that the drug was simply metabolized in many of our patients' tumors and thus this indication is ill appropriate for ganetespib and other Hsp90 inhibitors that are substrates for glucuronidation. In patients in whom the drug was not metabolized, it is possible that the effects of the drug were transient and that the timing of the biopsies (48 hours after dosage) was too long after drug administration to see an effective persistent decline in protein expression. In the phase I study, ganetespib reached maximum concentration within 1 hour of infusion termination and 1% of maximum concentration within 8 to 10 hours. Additional pharmacodynamic studies of ganetespib, however, concluded that Hsp70 was a good marker of biologic activity of the drug because it was increased for several days after exposure. We were unable to reproduce this result, as demonstrated by variable levels of Hsp70 after drug exposure. It is possible that a quantitative means of protein expression analysis (such as Western blot) would have been more informative; however, we were limited by the amount of tissue obtainable and therefore could not perform these analyses.

All patients had molecular analyses of the mitogen-activated protein kinases pathway on either archived or biopsied tissue. The frequency of KRAS mutations was 60%, which is greater than would be expected in metastatic CRC.^{17–19} This might have occurred because

patients with KRAS-mutated tumors have fewer standard treatment options and thus are more likely to enroll in clinical trials. Also, our trial numbers are small. The frequency of each mutation was, however, in general accordance with published data.

Interestingly, the 2 patients who experienced disease control both had KRAS G12V mutations. KRAS G12V mutations have been shown to incur a more aggressive phenotype and modulate genes implicated in cell cycle control, apoptosis, and angiogenesis.^{20,21} An analysis of outcomes in patients with KRAS mutations demonstrated that G12V KRAS mutations were associated with a significantly worse survival in patients with advanced CRC.²² If the more aggressive nature of G12V mutations is because of alterations in downstream effector molecules and upregulation of proteins responsible for angiogenesis, it is conceivable that an Hsp90 inhibitor, which has a broad mechanism of action, might affect some of these pathways and prevent tumor progression. An alternative explanation for the differential response from the other KRAS mutations is that KRAS G12V has been demonstrated to interact differently with downstream effects of the MAPK pathway than the more common KRAS mutation G12D.²³ We can only speculate, however, and 2 other patients with G12V mutations did not incur the same apparent benefit.

Because of the promising preclinical data of Hsp90 inhibition, why was there no evidence of antitumor activity? It is possible that the weekly dosing of ganetespib might have been too infrequent to effectively inhibit rebound (regeneration) of relevant oncogenes. This is supported by our IHC results, which did not show sufficient downregulation of proteins at 48 hours. Possibly more frequent or greater dosing would have led to better inhibition of client proteins. However, several responses in patients with non-small-cell lung carcinoma treated with single-agent ganetespib with the same dose and schedule as was used on our study have been reported. Molecular analyses confirmed that all of the responders in the lung study had KRAS wild type tumors and possessed anaplastic lymphoma kinase (ALK) translocations.²⁴ It is conceivable that the suppression of tumor growth by ganetespib in these patients was because of the dual inhibition of KRAS and ALK. In CRC it is possible that the suppression of client proteins was insufficient, which resulted in tumor escape from apoptosis.

One of the described mechanisms of Hsp90 inhibition is via upregulation of the cellular stress response via increased transcription of heat shock factor 1 and upregulation of Hsp70.^{25–27} We performed IHC analyses evaluating Hsp70 expression and did not note significant overexpression of the protein in any of our patients. This supports the idea that either the dosing was insufficient to result in upregulation, that other intracellular mechanisms prevented ganetespib from effectively hitting its target, or that the technique or timing of the IHC studies were not adequate in capturing the increase in protein expression.

Our data indicate that the drug was well tolerated with minimal side effects. There were no serious adverse events during the study and only 3 patients (20%) required dose reductions. Most patients developed diarrhea which was low-grade, transient, and manageable with supportive therapy.

Conclusion

Ganetespib alone did not demonstrate any meaningful antitumor activity in patients with refractory metastatic CRC. Single-agent ganetespib had a mild toxicity profile and was well tolerated. Preclinical studies suggest that Hsp90 inhibitors are able to enhance the efficacy of anticancer agents, and potentially overcome drug resistance.^{28–30} Several studies have been conducted with Hsp90 inhibitors in combination with cytotoxic chemotherapies including the GALAXY-I study of ganetespib with docetaxel in advanced non–small-cell lung cancer, which demonstrated improved OS with docetaxel with ganetespib compared with docetaxel alone as second line therapy.³⁰ These data, along with unpublished preclinical data suggesting strong synergy of ganetespib with platinum in CRC cell lines and xenografts support our plans for a combination study in metastatic CRC particularly in KRAS-mutated CRC where we believe Hsp90 might have the most potential benefit based on preclinical data. Such studies are currently planned.

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Clinical Practice Points

- Novel therapies for refractory metastatic colorectal cancer are desperately needed. This is particularly true in RAS mutated tumors where anti-EGFR therapy is not an option.
- Hsp 90 inhibitors help modulate a number of cellular responses and stabilize function in many oncogenic proteins responsible for cancer growth and survival.
- Ganetespib is a novel Hsp90 inhibitor.
- In a phase II study of single agent ganetespib, the drug was very well tolerated and resulted in disease stabilization in two of 17 patients. There were no responses.
- Based on synergistic preclinical data of platinum agents and ganetespib and the mild toxicity profile further combination studies in mCRC are warranted.

Figure 1.
Overall Survival (OS) From Start of Treatment (Months). Six-Month OS, 41% (95% CI, 19%–62%)

Figure 2.
Progression-Free Survival (PFS). PFS at 1 month, 76% (95% CI, 49%–90%); PFS at 3 months, 24% (95% CI, 7%–45%)

Figure 3. Immunohistochemistry (IHC) Analyses of p70s6, pERK, pAKT, Cyclin D1, VEGF-r2, HIF-1A, and Heat Shock Protein (Hsp) 70 Expression 24 to 48 Hours Before (PRE) and After (POST) Treatment With Ganetespib. Of the 17 Evaluable Patients, 13 Had Adequate Tissue Sampling For IHC Analyses. Two to 3+ and > 5% Staining Was Considered Positive.

Table 1

Patient Demographic Characteristics

Characteristic	Value
Sex	
Male	11
Female	6
Age, Years	
Median	58
Range	44–79
ECOG Performance Status	
0	3
1	14
Number of Previous Chemotherapies	
3	4
>3	13

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

Table 2

Grade 1/2 Toxicities (Total Patient n = 17)

Toxicity	Grade 1/2, n (%)
Diarrhea	14 (82)
Fatigue	9 (53)
Nausea	9 (53)
Vomiting	11 (65)
Anorexia	7 (41)
Headache	4 (24)
Alk Phos (↑)	8 (47)
AST (↑)	9 (53)
ALT (↑)	12 (70)
Amylase (↑)	5 (29)
Bilirubin	6 (35)

Abbreviations: Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Table 3

Patient Outcomes and Tumor Genotyping

PFS (Weeks)	OS (Weeks)	KRAS	BRAF	PIK3CA
5	26	WT	WT	WT
9	31	G12D	WT	WT
6	113	G12D	WT	E542K
6	15	WT	WT	WT
31	139	G12V	WT	E545K
4	16	WT	WT	WT
9	113	WT	WT	E542K
23	37	G12V	WT	WT
2	11	WT	WT	WT
4	14	G12D	WT	WT
6	14	G12V	WT	WT
7	18	G12S	WT	WT
12	22	G12C	WT	WT
15	63	WT	WT	WT
7	19	G12V	WT	WT
6	24	Q618	WT	WT

Abbreviations: OS = overall survival; PFS = progression-free survival; WT = wild type.