Original Study

# A Phase II Open-Label Study of Ganetespib, a Novel Heat Shock Protein 90 Inhibitor for Patients With Metastatic Breast Cancer

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## Abstract

**This phase II trial evaluated the role of single agent ganetespib, an Heat Shock Protein 90 (HSP90) inhibitor, in unselected Metastatic Breast Cancer (MBC). The study did not meet its prespecified criteria for overall response rate (ORR) in this heavily pretreated population. However, clinical activity was noted in HER2-positive and triple-negative breast cancer (TNBC), which warrants further study as part of rational combinations.**

**Background:** Ganetespib is a small molecule, nongeldanamycin HSP90 inhibitor with potent inhibitory effects on HSP90-dependent oncoproteins of relevance to breast cancer pathogenesis. We therefore tested ganetespib in an unselected cohort of patients with MBC. **Patients and Methods:** Patients were treated with single agent ganetespib at 200 mg/m$^2$ once weekly for 3 weeks, on a 28-day cycle. Therapy was continued until disease progression. The primary end point was ORR using Reponse Evaluation Criteria in Solid Tumors version 1.1. **Results:** Twenty-two patients were enrolled with a median age of 51(range, 38-70) years and a median Eastern Cooperative Oncology Group performance status of 0 (range, 0-1). Most patients had at least 2 previous lines of chemotherapy in the metastatic setting. Most common toxicities, largely grade 1/2, were diarrhea, fatigue, nausea, and hypersensitivity reaction. The ORR in this unselected population was 9%, with all responses coming from the subset of patients with HER2-positive MBC (2/13; 15%). One patient with TNBC had objective tumor regression in the lung metastases. The clinical benefit rate (complete response + partial response + stable disease > 6 months) was 9%, median progression-free survival was 7 weeks (95% confidence interval [CI], 7-19), and median overall survival was 46 weeks (95% CI, 27-not applicable). **Conclusion:** The study did not meet the prespecified criteria for ORR in the first stage of the Simon 2-stage model in this heavily pretreated unselected population of MBC. However, activity was observed in trastuzumab-refractory HER2-positive and TNBC. Ganetespib was well tolerated and responses in more targeted populations harboring specific HSP90-dependent oncoproteins justifies its further study, particularly as part of rational combinations.

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## Introduction

Heat Shock Protein 90 (HSP90) has been well established as a rational target for many cancers based on extensive preclinical work. The protein functions as an Adenosine triphosphate-dependent molecular chaperone that helps promote the maturation and stability of multiple cellular proteins known as "clients." Many of these clients are oncoproteins and are required for cellular proliferation, regulation of cell cycle progression, and apoptosis of cancer cells.[1]

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HSP90 inhibitors bind to the Adenosine triphosphate pocket in the N-terminus of HSP90, prevent stabilization of oncoproteins, and ultimately result in their degradation.[2] Preclinically, HER2 served as a remarkably sensitive client protein to HSP90 inhibition.[3] These findings were translated clinically with objective tumor regressions observed with the geldanamycin-derived HSP90 inhibitor (tanespimycin) when given in combination with trastuzumab to patients with human epidermal growth factor receptor 2-positive (HER2+) Metastatic Breast Cancer (MBC).[4,5] Numerous HSP90 inhibitors have followed the path designed for tanespimycin and have been or are being explored in combination with trastuzumab for HER2+ MBC.[6-8] This is despite not knowing the precise contribution of trastuzumab in this combination. However, we have not successfully reproduced similar objective responses with other HSP90 inhibitors in MBC perhaps because of suboptimal dosing or scheduling, increased toxicity, incomplete inhibition of the target, or lack of our ability to select patients that might best respond to these agents.[8,9]

Of the second-generation inhibitors, ganetespib (STA-9090), 5-[2,4-dihydroxy-5-(1 methyl ethyl)phenyl]-2,4 dihydro-4-(1-methyl-1*H* indol-5 yl)-3*H*-1,2,4 triazole-3-one, a novel triazolone heterocyclic HSP90 inhibitor, is of particular interest. It is structurally unrelated to geldanamycin-derived inhibitors. Preclinical studies with this compound when compared with the other first- and second-generation compounds reveal increased potency activity against a wide range of xenograft tumors, a more favorable safety profile, including lack of hepatotoxicity and ocular toxicity.[10,11] Compared with 17-AAG, ganetespib produced more potent antitumor activity in different breast cancer subtypes including triple-negative breast cancer (TNBC) in vitro and in vivo.[12-15]

In phase I and II clinical studies, single-agent ganetespib was well tolerated with the most common adverse events being fatigue and diarrhea that were easily manageable with no consistent hepatotoxicity and the rate of visual impairment was also substantially low (< 3%) compared with that reported with other HSP90 inhibitors.[16-18]

Therefore, supported by the preclinical data for ganetespib in various subtypes of breast cancer and to address the active role of trastuzumab in this combination, we conducted the first phase II trial of single-agent ganetespib in an unselected cohort of patients with MBC.

## Patients and Methods

### *Patient Selection*

Eligibility criteria included: age > 18 years, histologically confirmed breast cancer, and recurrent and/or metastatic disease, Eastern Cooperative Oncology Group (ECOG) performance status of < 2 and measurable disease according to Reponse Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria.[19] Patients with HER2+ disease must have received previous trastuzumab and those with hormone receptor-positive disease must have received previous endocrine therapy. Previous treatment with at least 1 and no more than 3 lines of chemotherapy and/or biologic therapy (except endocrine therapy) in the metastatic setting with last dose at least 3 weeks before enrollment (no washout period required for endocrine therapy) was allowed. Patients with adequate end organ function were eligible.

Patients were excluded for any of the following: surgery, radiation or lesion ablative procedure to the only area of measurable disease, or poor venous access. Study drug administration via indwelling catheters was allowed only if the catheter was made of silicone material. Pregnant or lactating women, previous HSP90 inhibitor therapy, history of previous severe (Grade 3 or 4) allergic or hypersensitivity reaction to excipients (eg, polyethylene glycol 300 and polysorbate 80), treatment with chronic immunosuppresants (eg, cyclosporine after transplantation), active central nervous system metastases, New York Heart Association class III/IV congestive heart failure requiring active treatment, left ventricular ejection fraction < 50% at baseline, history of current coronary artery disease, ventricular arrhythmia requiring antiarrhythmic agents, Grade 2 or greater left bundle branch block, baseline QTc interval of > 470 msec were excluded. Patients with uncontrolled illness/active infection including HIV-positive subjects receiving combination antiretroviral therapy, severe acute/chronic psychiatric condition, or laboratory abnormality that might interefere with study drug administration, or with the interpretation of study results in the judgement of the investigator, were excluded.

The study protocol was registered in clinicaltrials.gov (NCT01273896). Participants gave informed consent before they entered the study. The study was approved by the institutional research ethics board of Memorial Sloan-Kettering Cancer Center.

### *Study Treatment*

Patients were administered an intravenous infusion of ganetespib weekly at a dose of 200 mg/m$^2$ over 1 hour for 3 consecutive weeks of a 28-day cycle. The starting dose was derived from the maximum tolerated dose in a previous once weekly phase I study in solid tumors. Treatment with ganetespib continued until disease progression, unacceptable toxicity, or patient consent withdrawal.

### *Toxicity Assessments and Dose Reductions*

Patients were examined and assessed for toxicities during and prior to each cycle. Toxicity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3. For Grade 3 hematologic or nonhematologic toxicity (except Grade 3 alopecia and fatigue), ganetespib was held until the toxicity returned to baseline or decreased to Grade ≤ 1 within 14 days and then resumed with a 25 mg/m$^2$ dose reduction (ie, 175 mg/m$^2$). For Grade 3 nausea, vomiting, and diarrhea, dose modification was allowed only after optimal prophylactic measures had failed to control the symptoms adequately. A total of 2 dose reductions were allowed, ie, a total of 50 mg/m$^2$ (150 mg/m$^2$). Patients unable to tolerate the dose at 150 mg/m$^2$ or whose toxicity had not returned to Grade ≤ 1 were discontinued from the study. Electrocardiograms (ECGs) were obtained before and after ganetespib infusions on day 1 of each cycle. If an ECG showed QTc prolongation (> 470 msec), the ECG was repeated twice to obtain values in triplicate.

### *Assessment of Treatment Response*

Patients were evaluated for response initially after 2 cycles and then every 3 cycles thereafter using the international criteria proposed by the RECIST Committee.[19] All patients with partial response (PR) or complete response (CR) were required to have confirmation of response conducted 4 weeks or later after the criteria for response were first met. The best overall response was defined as the best response recorded from the start of treatment until disease progression or withdrawal from the study.