A Phase I/II trial of weekly paclitaxel in combination with ganetespib in patients with recurrent or persistent, platinum-resistant ovarian, fallopian tube or primary peritoneal cancer

Supported by *Fox Chase Cancer Center*

Principal Investigator:

Gina M Mantia-Smaldone, M.D.
Fox Chase Cancer Center
333 Cottman Avenue
Philadelphia, PA 19111
Phone: 215-728-3175
Fax: 215-214-1590
Email: Gina.Mantia-Smaldone@fccc.edu

Co-Investigators:

Mark A. Morgan, MD
Jordan Center for Gynecologic Cancer
Abramson Cancer Center
Perelman Center for Advanced Medicine,
West Pavilion, 3rd Floor
3400 Civic Center Boulevard
Philadelphia, PA19104
1-800-789-PENN (7366)

Statistician:

Samuel Litwin, PhD.
Fox Chase Cancer Center
333 Cottman Avenue
Philadelphia PA 19111
Phone 215-728-2724Email: Samuel.litwin@fccc.edu

Elizabeth Handorf
333 Cottman Avenue
Philadelphia PA 19111
Email: Elizabeth.Handorf@fccc.edu
Phone: 215-728-4773

Translational Investigator:

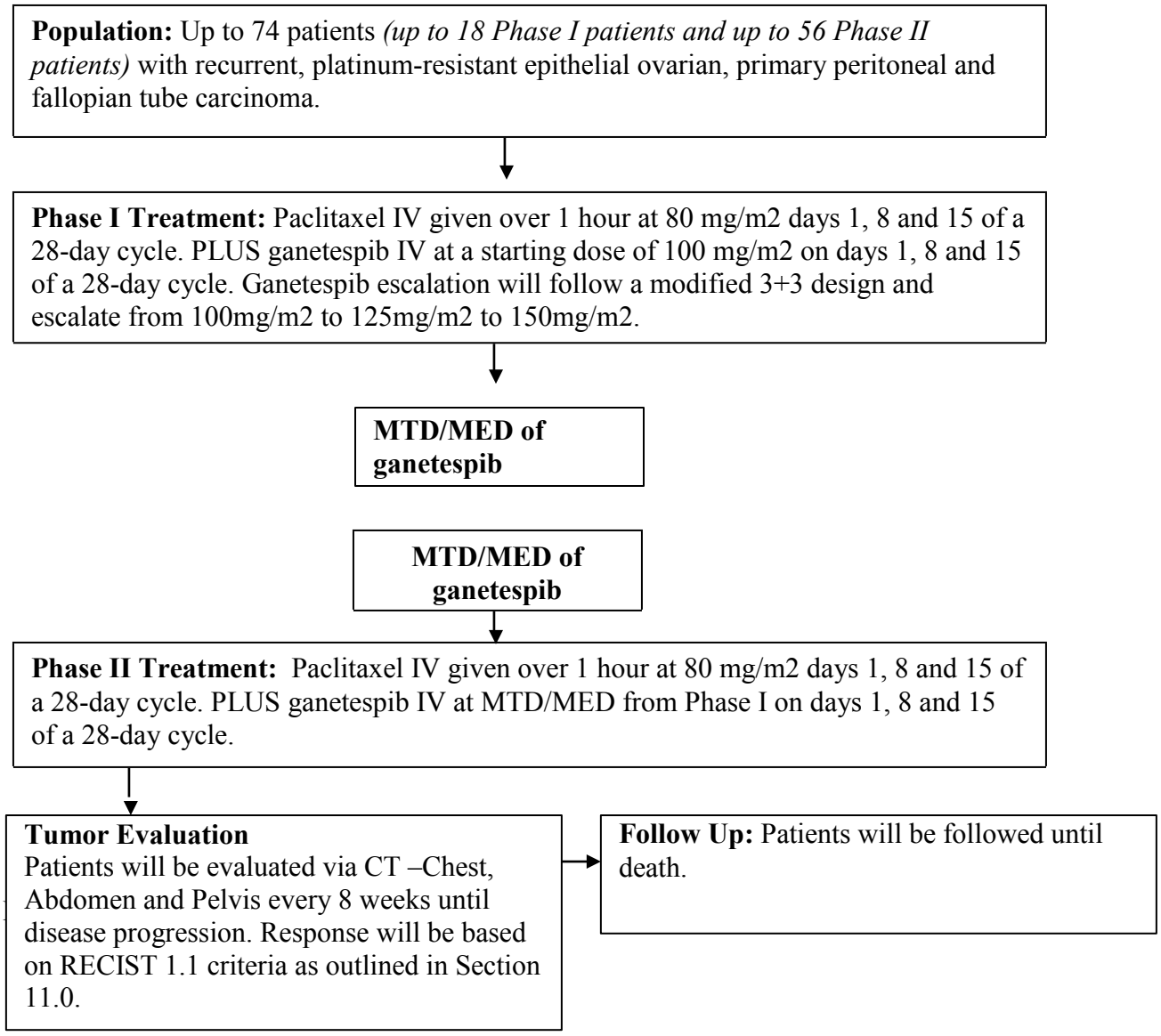
Denise Connolly, PhD.
Fox Chase Cancer Center
333 Cottman Avenue
Philadelphia PA 19111
Phone 215-728-1004
Email: denise.connolly@fccc.edu

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

Version Date: November 27, 2013 Amendment 1
October 20, 2014 Amendment 2
July 11, 2018 Amendment 3
IND# 120407

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

Schema



Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

Table of Contents

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

1.0 Introduction

1.1 Study Disease

Cancer of epithelial ovarian, fallopian tube or primary peritoneal origin (hereafter referred to as EOC) continues to be a leading cause of death from cancer in women. It is the eighth most common cancer in women in the U.S., and the fourth leading cause of death from cancer with 22,280 cases per year diagnosed and 15,500 deaths predicted for 2012.[1] In the majority of women, disease is diagnosed at an advanced stage and will respond well to initial treatment, but up to 80% of patients with a diagnosis of Stage III or IV EOC will experience a recurrence of their disease, which causes significant morbidity and ultimately death. The goal of treatment of recurrent disease is palliative, as there is no realistic chance of curing patients whose disease has recurred. In light of this observation, quality of life, prolongation of survival, and control of symptoms related to the cancer are the primary goals of treatment of recurrent disease. Median survival after diagnosis of recurrence is two years, but survival can range from months to years. The majority of patients with disease recurrence will receive a series of different regimens over the course of their disease, and in light of the limited benefit of the currently available treatments, there is a need for new therapies that are effective in treating recurrent EOC, particularly in patients who have developed early resistance to standard chemotherapy.

The treatment-free interval is predictive of both the expected response to treatment as well as the overall prognosis for the patient. The Gynecologic Oncology Group (GOG) has defined platinum resistant disease as recurrence seen less than 6 months from completion of front-line platinum-based therapy, and platinum sensitive disease as recurrence that occurs 6 or more months from completion of front-line platinum-based therapy, based on several retrospective studies.[2-5] A third category of platinum-refractory disease refers to disease which progresses during front-line platinum-based therapy. Even within the group of patients with platinum sensitive disease, the duration of the front-line treatment-free interval is predictive of the likelihood of benefit from second-line platinum-based therapy.[2-5] In patients with platinum sensitive recurrent disease there is a survival benefit from combination therapy.[6] For those patients with platinum-sensitive disease who are eligible based on performance status and organ function, the current standard of care would include a combination of a platinum agent with either a taxane, gemcitabine or liposomal doxirubicin. The most commonly used chemotherapeutic agents for treatment of platinum-resistant recurrent EOC include paclitaxel, docetaxel, pegylated liposomal doxorubicin (PLD), topotecan, oral etoposide and gemcitabine.

1.2 Agents under

Investigation

GANETESPIB

Ganetespib) is a novel, injectable, synthetic small molecule being developed by Synta Pharmaceuticals Corporation. Ganetespib inhibits Hsp90 chaperone activity by binding to its N-terminal adenosine triphosphate (ATP) pocket. Hsp90 inhibition causes its client proteins to adopt aberrant conformations, which are then targeted for ubiquitination and degradation

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

by the proteasome. Hsp90 is a molecular chaperone that regulates the post-translational folding and stability of its protein substrates (client proteins), which have crucial roles in cellular growth control, differentiation and survival.[7] In cancer, many Hsp90 client proteins are essential for signal transduction pathways known to play critical roles in cancer initiation and progression including HER2, BRAF, EGFR, AKT, MET, EML4-ALK, and steroid receptors. Inhibiting the ATPase activity of Hsp90 with small-molecule compounds such as ganetespib leads to client protein degradation and inhibition of tumor growth by inducing cell-cycle arrest and apoptosis.[8,9] In vitro, ganetespib is a potent inducer of cell death in many cancer cell lines, and in vivo, it inhibits the growth of human tumor cell lines in mouse xenograft models.

Ganetespib has been given to over 600 patients in clinical trials [http://www.syntapharma.com/PrdHsp90.aspx]. It is well tolerated, with the most common side effects including fatigue, diarrhea/constipation, nausea/vomiting, anorexia and abdominal pain. Single agent clinical activity has been seen in patients with advanced breast cancer, NSCLC, GIST, CRC and melanoma. Following completion of a Phase I trial demonstrating safety, ganetespib (150 mg/m2 q 15 days) is now undergoing Phase II evaluation in patients with NSCLC in combination with docetaxel (75 mg/m2). Based on our strong pre-clinical data in epithelial ovarian cancer (EOC) models and these early clinical successes, this Phase I/II trial will evaluate the efficacy of ganetespib in combination with paclitaxel in EOC patients. Briefly, we have demonstrated dose-dependent sensitivity of a panel of EOC cell lines to ganetesipib, with significant inhibition of cell viability, induction of apoptosis and reduction of the levels and activation of several Hsp90 client proteins (e.g., JAK2, STAT3, STAT5, CDK1, PKA, PKE and SRC) evident at low nanomolar doses of drug. In addition, single agent activity of ganetespib was demonstrated in two independent orthotopic models of EOC xenografts(unpublished data Connolly et al.). Moreover, in vivo tumor growth inhibition was enhanced when ganetespib was combined with weekly paclitaxel. In vivo fluorescent molecular imaging analysis of tumor bearing mice showed significant inhibition of tumor-associated matrix metalloproteinase activity, and analysis of tumor protein lysates demonstrated inhibition of several Hsp90 clients (as noted above) in mice treated with ganetespib.

1.2.1 ***Preclinical experience***

Anti-tumor Activity

Ganetespib is a highly potent Hsp90 inhibitor that selectively accumulates in tumors and induces long-lasting client protein degradation and subsequent tumor growth inhibition in a lung cancer xenograft model. Ganetespib displays potent activity across a broad spectrum of cancer cell lines, with an average IC50 value (the drug concentration that inhibits cell growth by 50%) 20-fold lower than 17-allylamino-17-demethoxygeldanamycin (17-AAG), another Hsp90 inhibitor currently in clinical trials for cancer.[8] Similar potency was observed in a panel of NSCLC cell lines with diverse genetic alterations common to the disease. This compelling activity of ganetespib is due to the degradation of Hsp90 client proteins and subsequent inactivation of their signaling effectors. Reverse phase protein arrays performed on lysates from four KRAS mutant NSCLC cells lines treated with ganetespib for 24 hours showed diminished expression of numerous receptor kinases (including EGFR, MET, HER2), signaling intermediates (CRAF, Src, STAT3, MAPK, GSK3), and kinases involved in protein synthesis and growth (AKT/mTOR), resulting in the activation of apoptotic mediators and cell cycle arrest.[10]

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

Tumor neoangiogenesis is a hallmark of cancer development and progression, from an in situ lesion to invasive and metastatic disease, hence targeting angiogenic pathways is an important strategy for treating cancer. Hypoxia inducible factor 1 alpha (HIF-1α) plays an important role in angiogenesis by controlling the expression of multiple angiogenic factors including VEGF, SDF1 and PGF.[11] Inhibition of HIF-1α activity dramatically inhibits tumor vascularization in animal models, and the transcription factor is a known client protein of Hsp90.[12] A single bolus exposure of ganetespib greatly reduced the expression of HIF-1α in NSCLC tumor xenografts, as far as 150 μm from the nearest blood vessel, suggesting that ganetespib can penetrate deep into the hypoxic regions of tumor tissue.[13] As a result, ganetespib had a marked effect on the tumor vasculature, reducing CD31 (endothelial cell marker) expression by 39%, coordinate with a reduction in cell proliferation and rise of both apoptosis and hypoxia.

Pharmacokinetics

The PK profiles of ganetespib were evaluated in mice, rats, and monkeys following IV administration. Ganetespib displayed dose proportional PK in all species over the dose ranges tested. Ganetespib was highly cleared in mice and rats, and moderately cleared in monkeys. No marked sex differences were observed in the PK of ganetespib in either rats or monkeys. Ganetespib does not appear to accumulate after multiple dosing.

Distribution

Ganetespib was highly distributed into various tissues in rats and mice.

Tissue Distribution

After a 1-hour IV infusion of [^{14}C]-ganetespib in Sprague-Dawley (albino) rats, [^{14}C]-ganetespib-derived radioactivity was widely distributed to all tissues by the first collection time point (approximately 1 hour following the start of infusion), with the exception of the CNS [Synta report, 6901-286, 2007]. Radioactivity was preferentially distributed into glandular tissues and organs of elimination. Radioactivity concentrations were highest in GI tract contents, indicating biliary excretion of [^{14}C]-ganetespib-derived radioactivity. The tissues showing the highest maximum concentrations of radioactivity, excluding the GI tract, were lymph nodes (iliac), liver, and adrenal gland in males and lymph nodes (iliac), adrenal gland, and pancreas in females. Radioactivity was eliminated from most tissues by 24 hours post dose but was still measurable in lymph nodes (iliac) by 168 hours post dose in both male and female rats.

[^{14}C]-ganetespib also showed systemic distribution to a wide variety of tissues, with the exception of the CNS, after a 1-hour IV infusion in male Long-Evans (pigmented) rats [Synta report, 150N-1202 (DDPS12-055), 2012]. Similarly to Sprague-Dawley rats, radioactivity was preferentially distributed into glandular tissues and organs of elimination and radioactivity concentrations were highest in GI tract contents, indicating biliary excretion of [^{14}C]-ganetespib-derived radioactivity. The tissues showing the highest maximum concentrations of radioactivity, excluding the contents of the GI tract, were cecum, small intestine, and adrenal gland cortex. Radioactivity was eliminated from most tissues by 671 hours post dose but low concentrations were observed in adrenal gland cortex, thyroid, adrenal gland medulla, spleen, kidney cortex, bone marrow, and liver at 671 hours post-dose (last time point). Relatively low concentrations of radioactivity in uvea and skin (pigmented) suggest that binding of ganetespib to melanin is minimal.

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

In another study, female severe combined immunodeficiency (SCID) mice were implanted with NCI H1975 cells. Subsequently, mice that developed tumors were administered an IV bolus injection of 125 mg/kg ganetespib. Results show that ganetespib was rapidly distributed to liver and lung; C_{max} in the liver and lung occurred at the first collection time point (approximately 5 minutes post dose) while C_{max} in the tumor occurred at approximately 30 minutes postdose [Synta report, DMPK09-185, 2009]. The concentrations of ganetespib in plasma, liver, and lung readily declined in a multi-exponential manner to below the quantitation limit (2.5 nM) within 24 to 48 hours post dose. The mean $t_{1/2}$ value in plasma, liver, and lung was 3.0, 5.6, and 5.4 hours, respectively. In contrast, the concentrations of ganetespib in tumor remained relatively constant throughout the study period (144 hours post dose), with the mean $t_{1/2}$ value of 58.3 hours. The highest exposure of ganetespib was observed in tumor (295 h μg/mL), followed by plasma (145 h·μg/mL) and liver (128
h·μg/mL). The exposure to lung (69.1 h·μg/mL) was the lowest among the tissues tested in this study.

Blood-to-Plasma Distribution Ratio
Mean blood: plasma radioactivity concentration ratios in rats were 0.586-1.11 [Synta report, 6901-286, 2007]. The ratio became close to 1 at later collection time points. Mean blood:plasma radioactivity concentration ratios in monkeys were 0.546-0.892.

Plasma Protein Binding

Ganetespib was highly bound to plasma proteins in mice (99.6%-99.7%), rats (97.5%-98.5%), dogs (98.3%-98.6%), monkeys (99.3%-99.4%), and humans (98.6%-98.7%) [Synta report, DMPK07-0036, 2007].

Drug Interactions
In preclinical studies evaluating distribution, biotransformation, and elimination, ganetespib exposure (peak plasma concentration and total systemic exposure) increased in an approximately dose proportional manner. Ganetespib was highly protein-bound and highly distributed throughout tissues, with the exception of the central nervous system (CNS). Fecal elimination via bile was the major route of excretion. Ganetespib was extensively metabolized in the liver to mainly glucuronide conjugates.

In vitro, ganetespib is an inhibitor of cytochrome P450 2C19 (CYP2C19) and cytochrome P450 3A4 (CYP3A4) (midazolam specific), but is not an inducer of cytochrome P450 (CYP) or uridine diphosphate (UDP)-glucuronosyltransferase (UGT) enzymes. Ganetespib is a substrate of P-glycoprotein (P-gp) but is not a substrate of breast cancer resistance protein (BCRP)-mediated transporter. Ganetespib has no inhibitory activity against organic anion transporter 1 (OAT1), organic cation transporter 2 (OCT2), organic anion transporting polypeptide 1B3 (OATP1B3), bile salt export pump (BSEP), and BCRP- mediated transport of the probe substrates, and has weak inhibitory activity against organic anion transporter 3 (OAT3), organic cation transporter 1 (OCT1), organic anion transporting polypeptide 1B1 (OATP1B1), and P-gp-mediated transport of the probe substrates under the experimental conditions.

<u>Preclinical Toxicology</u>

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

Preclinical GLP-compliant toxicology studies conducted with ganetespib include single-dose (acute) toxicity in rats, rising-dose toxicity studies in cynomolgus monkeys, a 5-day repeat-dose toxicity study in rats, a three-times-weekly repeat-dose toxicity study in rats, and twice weekly and once weekly repeat dose toxicity studies in rats and cynomolgus monkeys. Three-month dosing studies have been conducted in rats and cynomolgus monkeys. Additionally, genotoxicity and developmental toxicity studies, an ocular toxicity evaluation, a catheter compatibility study, and a local tolerance study were conducted. Studies were conducted in accordance with GLP regulations. Evaluation for ganetespib-related effects was based on mortality and morbidity, clinical signs, body weight, food consumption, hematology, serum chemistry, coagulation, urinalysis, ophthalmology, electrocardiographic examinations, and anatomic and microscopic pathology.

Rats survived a single 30 mg/kg dose of ganetespib, but doses of 85 or 250 mg/kg elicited moribundity and mortality. Rats given 10 or 30 mg/kg twice weekly for 4 weeks survived and were in good clinical condition. In contrast, rats given 100 mg/kg (reduced to 85 mg/kg beginning with the third dose) had pronounced clinical signs of systemic toxicity such as emaciation and decreased activity. Several of these animals died or were euthanized early. For 100/85 mg/kg rats assigned to a 14-day recovery evaluation, most changes returned to normal or improved. Male rats given 10, 30, 75, or 100 mg/kg once weekly for 4 weeks had no abnormal clinical findings; dose-related gross and microscopic changes occurred at 30, 75, and 100 mg/kg.

The maximum tolerated single-administration dose in cynomolgus monkeys was 11 mg/kg. When administered on 2 consecutive days, up to 3 mg/kg/day was well tolerated. Cynomolgus monkeys tolerated a 1 mg/kg dose of ganetespib, administered twice weekly for 4 weeks. A monkey given 3 mg/kg was euthanized moribund; the dose was reduced to 1 mg/kg and remaining monkeys given the reduced dose were clinically normal. Monkeys given 6 mg/kg (reduced to 4 mg/kg) or 11 mg/kg (reduced to 9 mg/kg) exhibited clinical signs consistent with GI tract changes observed pathologically. Two monkeys given 11/9 mg/kg were euthanized moribund. The incidence of histopathologic findings (in stomach and/or large intestine, adrenal gland, pancreas, and thymus) was lower in 11/9 mg/kg and 6/4 mg/kg monkeys assigned to a 2- to 4.5-week recovery evaluation.
In 3-month studies, ganetespib was administered on Days 1 and 15 of four 21-day cycles. Rats receiving that regimen tolerated 20 mg/kg/dose of ganetespib, the NOAEL. Transient decreases in weight gain occurred at 50 and 100 mg/kg/dose, and early deaths occurred at 100 mg/kg/dose. Cynomolgus monkeys in that regimen tolerated doses up to 7 mg/kg/dose, the NOAEL. Transient diarrhea occurred at 2, 4, and 7 mg/kg/dose, with reversible microscopic pathologic changes occurring at 7 mg/kg/dose.
Ganetespib was considered to be well tolerated by cynomolgus monkeys when administered by 1-hour infusion twice weekly for 4 weeks via an implanted silicone venous catheter.
When pregnant female rats were given ganetespib daily by infusion during organogenesis, doses up to 1 mg/kg/day did not elicit effects on maternal or fetal parameters. Maternal toxicity (clinical signs, decreased weight gain and food consumption) and developmental toxicity (postimplantation loss) occurred at doses of 3 mg/kg/day and higher.
As with the negative-control compound, 17-AAG (which has not been associated with ocular toxicity in clinical patients), ganetespib was rapidly eliminated from retinal tissue and did not cause photoreceptor cell apoptosis. Unlike 17-DMAG and AUY922, ganetespib was not associated with ocular toxicity in the rat model, suggesting that profiles of retina/plasma

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

exposure and retinal elimination rate play crucial roles in the onset of ocular toxicity. The ratio of the concentration of drug in retina and plasma, as well as the speed with which drug in the retina is cleared from that tissue, differ among the drugs tested, and is predictive of ocular toxicity.

In Vivo Activity of Ganetespib in Combination with Paclitaxel

Hsp90 inhibitors such as 17-AAG have been reported to enhance the activity of the microtubule stabilizer paclitaxel.[14] Similarly, the combination of ganetespib plus paclitaxel was highly active in the NCI H1975 NSCLC xenograft model, which expresses an activated and erlotinib resistant form of the epidermal growth factor receptor. Single-agent treatments of either 50 mg/kg ganetespib or 7.5 mg/kg paclitaxel dosed once per week were moderately efficacious, with %T/C values of 38 and 55, respectively. However, treatment with both drugs dosed at the same time was dramatically more efficacious, (%T/C = 7, $p<0.05$). This effect was not due to a pharmacokinetic (PK) interaction between ganetespib and paclitaxel, since no change in either agent's plasma exposure level was observed when they were combined. Similar combinatorial activity was observed when ganetespib was combined with docetaxel in this model and 5 other NSCLC xenograft models.[15]

1.2.2 ***Clinical experience***

Ganetespib is being studied in 10 Synta-sponsored clinical trials. Studies include: four Phase 1 studies, one Phase 1/2 study, four Phase 2 studies, and one Phase 2b study. Ganetespib is also being studied in 15 ISTs, the majority of which are proof-of-concept studies across a variety of tumor types. The ISTs include: two Phase 1/2 studies, three Phase 1 studies, and ten Phase 2 studies.

As of 20 September 2012, 630 patients have received at least 1 dose of IV ganetespib in one of these 25 studies. A total of 472 patients have been treated in 1 of the 10 Synta-sponsored studies, with the majority treated in single-agent studies (322 patients in Study 9090-01 through Study 9090-06 and 2 patients in Study 9090-09). The remaining patients (148/472) have been treated in Synta-sponsored combination therapy studies. In addition to these 472 patients, 158 patients have been enrolled in the ISTs.

Two Synta-sponsored Phase 1 studies evaluated the safety, tolerability, and preliminary activity of ganetespib in patients with solid tumors: Study 9090-01 (n=70) and Study 9090-02 (n=53). The recommended Phase 2 doses for single-agent ganetespib in this population are 200 mg/m² once weekly and 150 mg/m² twice weekly (72-hour interval between doses).

Two Synta-sponsored studies have evaluated the safety, tolerability, and preliminary antitumor activity of ganetespib in patients with hematologic malignancies: Study 9090-03 (n=31) and Study 9090-04 (n=29). In these studies, single-agent doses ranged from 120, 150, and 200 mg/m^2 (n=29) once weekly, and from 14 to 110 mg/m^2 (n=31) twice weekly. Unlike the solid tumor studies, no rest week was incorporated into the dosing schedule. Patients received ganetespib once or twice weekly for 4 consecutive weeks of a 4 week cycle. The doses selected for further study in this population were 200 mg/m^2 once weekly and 90 mg/m^2 twice weekly.

The Phase 2 program was designed to evaluate the antitumor activity of ganetespib in a variety of solid tumors. This includes 2 single-agent, proof-of-concept studies sponsored by Synta: Study 9090-05 (n=27) in GIST and Study 9090-06 (n=112) in NSCLC. In addition, Study 9090-06 was amended to offer combination therapy to a subset of NSCLC patients after treatment with single-agent ganetespib.

The Phase 2 program was expanded to evaluate ganetespib in combination with docetaxel in patients with solid tumors. In Study 9090-07 (n=27), the recommended combination dose is

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

150 mg/m^2 ganetespib on Days 1 and 15 and 75 mg/m^2 docetaxel on Day 1 in a 21-day cycle in patients with solid tumors.
Following identification of the recommended combination dose for Phase 2 in Study 9090- 07, a Phase 2b/3 Study 9090-08 was initiated in order to evaluate the safety and activity of ganetespib in combination with docetaxel vs. docetaxel alone in NSCLC.
The Phase 3 portion of the original Phase 2B/3 9090-08 study will be conducted as a standalone Phase 3 study, 9090-14. Studies 9090-09 and 9090-11 are additional single-agent Phase 2 studies that will examine different patient populations.

Preliminary signals of clinical activity of ganetespib as a single agent have been observed in ongoing clinical studies at different dose levels and schedules in patients with solid malignancies. In patients with hematological malignancies, some evidence of clinical activity has been observed in these heavily pre-treated patients. Preliminary safety findings in patients treated with ganetespib ± docetaxel show a pattern of adverse events (AEs) and incidence of special events that is similar to that of patients treated with single-agent ganetespib. Diarrhea is the most significant AE associated with the use of ganetespib. Diarrhea management guidelines are provided in Appendix III.

Pharmacokinetics in Humans
The PK of ganetespib, administered at various doses on a weekly or twice-weekly schedule, are under investigation in three Phase 1 trials. Preliminary data and calculated parameters are available from these trials in patients with solid and hematologic tumors and are summarized below.
Ganetespib PK shows distribution and elimination phases with concentrations declining by approximately 10-fold within the first hour and nearly 100-fold within 10 hours following infusion termination. Mean terminal half-lives have ranged from approximately 5 to 15 hours. Ganetespib plasma concentrations following the first and subsequent doses are comparable following either once or twice-weekly dosing, indicating the lack of drug accumulation. Ganetespib plasma concentrations are also comparable in the solid and hematologic tumor patients. C_{max} and AUC increase in approximate proportion to dose irrespective of dosing day with virtually identical dose-exposure ratios for doses given on different days, indicating linear PK (r2 = 0.7080 and 0. 7596 for C_{max} and AUC versus dose, respectively). Ganetespib C_{max} correlates well with AUC (r^2 = 0.9338). CL and V_d are approximately constant across doses.
Two ganetespib glucuronide metabolites were quantified in Study 9090-07: STA-12-0671 and STA-12-0672. Terminal half lives were unaffected by ganetespib dosage. At a ganetespib dose of 150 mg/m^2, the mean STA-12-0671 terminal half life was 11.9 hours (n=16) and at a dose of 200 mg/m^2 the terminal half life was 11.0 hours (n=4). For STA-12-0672, at a ganetespib dose of 150 mg/m^2, the mean terminal half life was 9.9 hours (n=16) and at a dose of 200 mg/m^2 the terminal half life was 9.4 hours (n=4). For both metabolites, T_{max} was typically at the end of the ganetespib infusion and PK parameters were consistent across sampling days (Days 1, 8, and 15).

Safety in Humans

Monotherapy Studies
The MTD for once-weekly dosing in solid tumors was established at 216 mg/m^2 ganetespib based on DLTs of asthenia and diarrhea at the highest tested dose level, 259 mg/m^2. The recommended once-weekly dose is 200 mg/m^2. The recommended dose for twice-weekly

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

dosing (72-hour interval between doses) in patients with solid tumors is 150 mg/m^2 and is based on current safety, tolerability, and preliminary activity data.
The doses selected for further study in patients with hematologic malignancies were 200 mg/m^2 once weekly and 90 mg/m^2 twice weekly.
Approximately 98% of the patients in the largest pooled data set (single-agent studies, n=322) experienced at least 1 AE; 90% experienced at least 1 treatment-related event. The most frequently reported AEs were related to GI toxicity, and included diarrhea (77%), nausea (42%), decreased appetite (28%), vomiting (24%), constipation (21%), and abdominal pain (21%). Non-GI related events that occurred frequently have included fatigue (53%), headache (19%), and anemia (22%). Two-thirds (66%) of these patients experienced an event that was a Grade ≥3; 29% experienced a Grade ≥3 treatment-related event. Thirty-nine percent experienced at least 1 serious adverse event (SAE); 8% of patients had at least 1 treatment-related SAE.

Combination Study

In the Phase 2b study in patients treated with ganetespib in combination with docetaxel, Study 9090-08, preliminary findings show a similar safety profile. In the combination arm (ganetespib + docetaxel), 92% of patients experienced at least 1 AE, 66% at least 1 treatment-related event. The most frequently reported AEs were related to GI toxicity and included diarrhea (41%), nausea (17%), decreased appetite (16%), vomiting (10%), constipation (6%), Non-GI related events that occurred frequently include neutropenia (31%), fatigue (27%), and anemia (22%).
Half (53%) of the 9090-08 patients treated with ganetespib and docetaxel had treatment-emergent AEs that were Grade 3 or Grade 4. Thirty-two percent had at least 1 SAE and 11%, at least 1 treatment-related SAE. The most common Grade 3 or 4 event in patients receiving the combination treatment was neutropenia (14% and 11%, respectively). In patients treated with docetaxel only, 12% of patients experienced a Grade 3 event of neutropenia and 8% experienced a Grade 4 event. The most common SAE was febrile neutropenia, experienced by 7% of those receiving the combination treatment compared to 5% of patients treated with docetaxel only.

Events of Special Interest

Events that may be a class effect of Hsp90 inhibition include diarrhea, ocular toxicities, and elevations in liver enzymes. Diarrhea is the most significant AE associated with the use of ganetespib. In Study 9090-08, 41% of patients treated with both ganetespib and docetaxel experienced at least 1 AE of diarrhea compared to 11% of patients treated with docetaxel alone. In single-agent studies, approximately 77% of ganetespib patients experienced this event. The postulated mechanism of action is inhibition of EGFR in cells that line the GI tract, leading to a transient secretory diarrhea, limited to 24 to 48 hours following ganetespib infusion. This AE is manageable with loperamide or Lomotil® (atropine diphenoxylate). Prophylactic use of loperamide can reduce the occurrence of diarrhea from >80% to approximately 40%.
Ocular toxicity, manifested as visual disturbances, has been reported for several Hsp90 inhibitors. Of the 443 patients treated with ganetespib (single-agent and combination treatment studies) as of 20 September 2012, 10 (2%) patients experienced an event of visual disturbance that was assessed as related. In Study 9090-08, a visual disturbance of blurred vision was experienced by 2% of patients treated with ganetespib in combination with docetaxel. There were no such treatment-emergent events in the group treated with

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

docetaxel alone. In studies using single-agent ganetespib, visual disturbances included: blurred vision (4%), visual impairment (2%), and dry eye, reduced visual acuity, chromatopsia, night blindness, scotoma, and vitreous floaters (all <1%). The mechanism of visual disturbances is linked to induction of apoptosis in cells in the outer nuclear layer of the retina, which occurs following treatment with 17-DMAG or AUY922.[16] In contrast, ganetespib did not elicit induction of apoptosis in preclinical studies using rodent models, consistent with the very low number of reported visual disturbance cases in the clinic. Hepatocellular injuries are usually detected by enzyme elevations in serum aminotransferases (ATs), total bilirubin, and alkaline phosphatase. In the combination treatment arm of Study 9090-08, AEs of elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were reported in 3% and 2%, of patients, respectively. An AE of elevated alkaline phosphatase was reported in 3% of patients and an AE of elevated bilirubin was reported in <1% of patients. Grade 3 elevations of AST and ALT were reported in <1% and 2% of patients, respectively. In the pooled data from 322 patients who received single-agent ganetespib, AEs of elevated AST and ALT were reported in 14% of patients. An AE of elevated alkaline phosphatase was reported in 16% of these patients and an AE of elevated bilirubin was reported in 6%. Grade ≥3 elevations of AST and alkaline phosphatase were reported in 4% of patients and Grade ≥3 elevations of ALT and bilirubin in 3% of patients. None of the patients reported concomitant elevations of ATs ≥3X the upper limit of normal (ULN) and bilirubin ≥2X ULN. Liver toxicity in the 1st-generation geldanamycin-derivative Hsp90 inhibitors is an off-target effect. According to a study by Cysyk et al, the presence of benzoquinone moiety in the molecule is the suspected cause of liver toxicity.[17] Ganetespib does not contain the benzoquinone moiety and, therefore, liver toxicity is not expected. This correlates with the safety information collected to date.

Electrocardiogram Intervals Analysis Findings

Synta Pharmaceuticals conducted a thorough QT study, Protocol 9090-13, "A Randomized, Partially Double-blind, Placebo- and Positive-Controlled, 3-Arm, Crossover Study to Assess the Effect of Ganetespib (STA-9090) on Electrocardiogram Parameters in Healthy Volunteers, a Thorough ECG/QT Study". In Protocol 9090-13, healthy volunteers were administered a single dose of 200 mg/m^2 ganetespib which is the therapeutic dose for monotherapy studies and 33% higher than the ganetespib dose in combination studies. Analyses of the ECG data revealed a placebo-corrected modest change in QTcF from baseline of 20.9 msec at 24 hours post-dose. No increase in QTcF was observed at the time of ganetespib C_{max} (at the end of ganetespib infusion). This observation of a prolonged QTc interval is consistent with an indirect effect of ganetespib on cardiomyocyte repolarization, since the QTc prolongation occurred at a time when plasma concentrations of ganetespib are less than 0.5% of the C_{max} concentrations.

At this point, in the clinical development program there have been 362 patients treated with ganetespib as a single agent and 218 treated with ganetespib plus docetaxel (total 580 patients). Seven patients (1.2%) had prolonged QT interval reported as an adverse event, and none had *torsades de pointes or other ventricular arrhytmias* on any ECG recording. Eight deaths (8/580, 1.4%) potentially resulting from cardiovascular SAEs have been reported and were described by investigators as cardiac arrest (n=3), sudden cardiac death (n=2), sudden death (n=1), cardiopulmonary failure (n=1) and cardiovascular insufficiency (n=1). The incidence of deaths on treatment with ganetespib due to cardiovascular SAEs does not seem excessive for this advanced cancer patient population.

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

In addition, the randomized Phase 2b/3 study 9090-08, the frequency of cardiovascular SAEs resulting in death is comparable in patients treated with ganetespib plus docetaxel relative to the docetaxel-only control arm. In the ganetespib plus docetaxel arm there were 4 cardiovascular deaths reported among 191 patients (2.1%) vs. 5 cardiovascular related deaths reported among 192 patients (2.6%) in the docetaxel control arm.

Based on the data from Protocol 9090-13, the review of cardiac safety data from the 580 patient safety database, the apparent survival benefit seen in the interim analysis of the Phase 2b/3 9090-08 study in favor of the ganetespib plus docetaxel combination arm relative to the docetaxel control arm, and proposed modifications to ECG monitoring in our clinical protocols, we assess the benefit/risk for clinical trials of ganetespib as positive.

PACLITAXEL

1.2.3 ***Clinical experience***

Paclitaxel is an FDA approved chemotherapeutic agent that is one of the standard treatments available for patients with EOC. Paclitaxel was initially tested in patients with recurrent EOC every 3 weeks and response rates of 21-37% were seen, including response rates of 21-33% in patients with platinum resistant disease who had not previously received paclitaxel.[18,19]

In light of preclinical data suggesting improved efficacy from more frequent dosing of paclitaxel, a Phase I trial evaluating the weekly administration of paclitaxel in patients with platinum/paclitaxel resistant recurrent ovarian cancer was completed, and demonstrated responses.[20] Another Phase II trial confirmed the activity of weekly paclitaxel in patients whose disease had recurred or progressed on paclitaxel given at the higher dose every three weeks.[21] Additional clinical trials utilizing weekly paclitaxel have been performed, with response rates ranging from 21-54%.[22-26] Thus, paclitaxel has efficacy when given every 3 weeks as well as on a weekly schedule for patients with both platinum sensitive and platinum resistant disease, and when given on a weekly schedule, this agent has activity in patients with resistance to paclitaxel given every 3 weeks.[20,21,26]

In the trial conducted by the Gynecologic Oncology Group(GOG), 48 patients treated with weekly paclitaxel at a dose of 80 mg/m^2 were evaluable for safety. Hematologic toxicities were tolerable, with Grade 3 neutropenia seen in 2 patients (4%), and Grade 2 thrombocytopenia seen in 1 patient (2%). The most common toxicity was neuropathy, Grade 3 in 2 patients (4%) and Grade 2 in 10 patients (21%).[27]

1.3 Study Rationale

Rationale for Assessment of Treatment with Ganetespib with Weekly Paclitaxel

Heat shock protein 90 (Hsp90) is a highly conserved, ATP-dependent chaperone protein that regulates the post-translational folding of its protein substrates, Hsp90 client proteins, many of which are involved in signal transduction pathways important in the development and progression of cancer.[28] Its role in the regulation of multiple proteins important in malignant transformation and disease progression makes it an attractive target for cancer therapy. It is well tolerated, with the most common side effects consisting of GI toxicities. Weekly paclitaxel has been shown to be an effective treatment in patients with recurrent ovarian cancer and is also well tolerated, with the most common side effects consisting of

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

neuropathy. Preclinical data suggest synergy when paclitaxel is combined with Hsp90 inhibitors. (See Section 1.2). Based on our strong pre-clinical data in epithelial ovarian cancer models, we will proceed to a Phase I/II trial of this combination in patients with recurrent disease.

1.4 Correlative Testing

Laboratory correlative studies will be performed at FCCC and include: 1) analysis of patient pre- and post-drug treatment blood specimens (serum and peripheral blood mononuclear cells) for changes in the levels of expression of HSP70 and established HSP90 client proteins; 2) analysis of patient formalin fixed paraffin embedded (FFPE) tumor specimens for the expression and activation of established HSP90 client proteins; and 3) analysis of patient pre-treatment serum samples for the presence of secreted HSP90α. The goal of these correlative analyses is to determine patterns of HSP90, HSP70 and HSP90 client protein expression that may predict patient response to treatment and provide a rational basis for patient selection for this agent going forward.

2.0 Objectives

2.1 Primary

Objective Phase I

1) Determine the recommended Phase II dose of ganetespib with weekly paclitaxel.

Phase II

1) Probability of surviving progression-free for at least 6 months after initiating therapy.
2) Clinical response rate (partial and complete responses as defined by RECIST 1.1 criteria).

2.2 Secondary

Objectives Phase I

1) Determine the nature and degree of toxicity of ganetespib and weekly paclitaxel in this cohort of patients as measured by the frequency and severity of adverse reactions.

Phase II

1) Determine the nature and degree of toxicity of ganetespib and weekly paclitaxel in this cohort of patients as measured by the frequency and severity of adverse reactions encountered.
2) Duration of progression-free survival and overall survival.

3.0 Study Plan

3.1 Description of Study Design, Population and Duration of Study Therapy

This is an open-label study evaluating the combination of ganetespib with weekly paclitaxel. The study will commence with a Phase I dose escalation to evaluate up to 3 dose levels of ganetespib with weekly paclitaxel in adult women with epithelial ovarian, primary peritoneal and fallopian tube carcinoma. The lead-in phase I portion of this study will determine the recommended Phase II dose of the combination of weekly paclitaxel and weekly gaetespib for the second phase of the study. During the lead-in Phase I portion of the study, paclitaxel

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

will be dosed at 80 mg/m2 weekly for 3 weeks with of a 4 week cycle, and ganetespib will be given initially at 100 mg/m2 for 3 weeks of a 4 week cycle and escalated to 125 mg/m2 and 150 mg/m2 weekly as tolerated in subsequent cohorts. The maximum dose of ganetespib to be evaluated will be 150 mg/m2 weekly in combination with paclitaxel. The Phase I portion of the study will evaluate tolerance and safety of the combination of paclitaxel in combination with ganetespib to determine the recommended Phase II dose, and the Phase II portion of the study will evaluate efficacy of the combination in terms of response rates and the probability of 6-month progression-free survival and overall survival.

4.0 Patient Selection Inclusion & Exclusion

4.1 Inclusion Criteria

4.1.1 Patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancers who have received up to two prior treatment regimens.

4.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension in accordance with RECIST criteria v. 1.1 as described in detail in section 11.0.

4.1.3 Patients must have had one prior platinum-based chemotherapeutic regimen for management of primary disease containing carboplatin, cisplatin, or another organoplatinum compound. This initial treatment may have included intraperitoneal therapy, high-dose therapy, consolidation, or extended therapy administered after completion of initial chemotherapy. Patients who have received one prior regimen must be considered platinum resistant or refractory according to standard GOG criteria, i.e., have had a treatment-free interval following platinum of less than 6 months, have persistent disease at the completion of primary platinum-based therapy or have progressed during platinum-based therapy. Patients with greater than 6 month disease free interval after completion of primary therapy must have received a second platinum based regimen, and have persistent or progressive disease, or disease that recurs within 12 months of completion of second line platinum-based therapy. Patients who are unable to receive platinum-based therapy for recurrent disease would also be eligible.

4.1.4 Age $\geq$ 18 years.

4.1.5 ECOG performance status 0 -2.

4.1.6 Patients must have normal organ and marrow function as defined below:

- Hemoglobin $\geq$ 9 g/dL
- Leukocytes $\geq$ 3,000/mcL
- Absolute neutrophil count $\geq$ 1,500/mcL
- Platelets $\geq$ 100,000/mcL
- Total Bilirubin $\leq$ normal institutional limits
- AST/ALT (SGOT/SGPT) $\leq$ 2 times institutional normal limits
- Creatinine $\leq$ normal institutional limits

OR

- Creatinine Clearance $\geq$ 60 Ml/min/1.73 m^2 for patients

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

with creatinine levels above institutional normal

4.1.7 Ability and willingness to comply with scheduled visits, treatment plan, laboratory assessments and other study procedures.

4.1.8 Ability to understand and willingness to sign a written informed consent and HIPAA consent document.

4.2 Exclusion Criteria

4.2.1 Patients who have had surgery, chemotherapy or radiotherapy within 4 weeks prior to entering the study or those who have toxicity that has not recovered to ≤ Grade 1 from adverse events due to agents administered more than 4 weeks earlier (with the exception of alopecia). Patients may not be receiving any other investigational agents.

4.2.2 Histologic diagnosis of a benign or borderline tumor ('tumor of low malignant potential') or of a malignant tumor of non-epithelial origin (such as a germ cell tumor, sex-cord stromal tumor) of the ovary, fallopian tube or peritoneum.

4.2.3 Patients with known brain metastases.

4.2.4 History of allergic reactions to Cremophor EL, paclitaxel or its components.

4.2.5 Prior history of ≥ Grade 2 neurotoxicity or any other toxicity requiring discontinuation of taxane therapy that has not resolved to ≤Grade 1, with the exception of alopecia.

4.2.6 Diagnosis of another malignancy, with the exception of non-melanoma skin cancers within two years before the first dose, or previously treated for another malignancy with evidence of residual disease, with the exception of a synchronous endometrial cancer and non-melanoma skin cancers. Carcinoma in situ will not be considered as malignancy.

4.2.7 Patients with clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, active myocardial ischemia, or indwelling temporary pacemaker.

4.2.8 Patients with ventricular tachycardia or supraventricular tachycardia that requires treatment with a Class Ia antiarrhythmic drug or Class III antiarrhythmic drug.

4.2.9 Use of medications that have been linked to the occurrence of torsades de pointes

4.2.10 Complete left bundle branch block (LBBB)

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

4.2.11 History of long QT syndrome or a family member with this condition

4.2.12 Serum potassium, magnesium and calcium levels outside the laboratory's reference range.

4.2.13 Patients receiving QT prolonging medications (such as ondansetron).

4.2.14 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, known serious cardiac illness or psychiatric illness/social situations that would limit compliance with study requirements. Known serious cardiac illness or medical conditions include, but are not limited to:

i. History of documented congestive heart failure (CHF), New York Heart Association (NYHA) class II/III/IV (see Appendix II), with a history of dyspnea, orthopnea, or edema that requires current treatment with angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, beta blockers, or diuretics.
NOTE: Use of these medications for the treatment of hypertension is allowed

ii. Screening QTc (QT interval corrected for heart rate) >470 msec or history of QT (cardiac interval from start of Q wave to end of T wave) prolongation while taking other medications

iii. High-risk uncontrolled arrhythmias (ventricular arrhythmias, high-grade AV-block, supra-ventricular arrhythmias that are not adequately rate-controlled)

iv. Arrhythmias that require current treatment with the following anti-arrhythmic drugs: flecainide, moricizine, or propafenone

v. Current coronary artery disease with a history of myocardial infarction, angioplasty, or coronary bypass surgery within the preceding 6 months, or angina pectoris that has been symptomatic within the preceding 6 months

4.2.15 Known HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with ganetespib. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy.

4.2.16 Pregnant or breast feeding. Refer to section 4.4 for further detail.

4.3 Inclusion of Women and Minorities

Women, regardless of race, ethnic group or sexual orientation are eligible for this study.

4.4 Pregnancy

The effects of ganetespib and paclitaxel on the developing human fetus at the recommended therapeutic dose are unknown. For this reason and because anticancer agents as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential (WOCBP) and male sexual partners must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of treatment, and for at least 3 months after the completion of treatment. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

Prior to study enrollment, WOBCP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy.

All WOCBP must have a negative pregnancy test within 7 days of registration. If the pregnancy test is positive, the patient must not receive protocol treatment and must not be enrolled in the study.

WOCBP is defined as follows: Any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or a bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea $\geq$ 12 consecutive months, or women on hormone replacement therapy (HRT) with documented plasma follicle- stimulating hormone (FSH) level > 35 mIU/ml). Even women who are using oral, implanted, or injectable contraceptive hormones or mechanical products (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g. vasectomy), should be considered to be WOCBP. Patients of childbearing potential should agree to use dual forms of contraception.

4.5 Research Participant Registration

Eligible patients will be entered on study centrally by the Fox Chase Cancer Center QA Coordinator or their designee. Following registration, research participants must begin protocol treatment within 7 days of registration. Issues that would cause treatment delays must be discussed with the Principal Investigator. If a research participant does not receive protocol therapy following registration, the research participant will be replaced. The QA Coordinator must be notified as soon as possible if the research participant will not receive protocol therapy.

Research participants may be registered from 9:00 am to 5:00 pm excluding holidays by calling the QA Coordinator at 215-728-4770. The site's investigator or designee will then fax the completed registration form, entire, completed consent form,HIPAA authorization formand eligibility checklist to 215-214-1511. The QA Coordinator or designee will notify the site by fax when registration is confirmed and the sequence number has been assigned. Research participants must be registered and have received a sequence number assigned by the QA Coordinator prior to the initiation of treatment. The following forms must be completed at the time of registration:

- Signed and dated informed consent form
- Signed and dated HIPAA authorization form
- Registration form
- Signed eligibility checklist

Exceptions to the current registration policies will not be permitted including but not limited to:

- Late registrations (after initiation of treatment)
- Exceptions to eligibility requirements
- Participation by an institution/member not identified as eligible
- Non-Compliance with regulatory paperwork

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

5.0 Treatment Plan

Treatment will be administered on an outpatient basis. Treatment will be administered as described below. Dose delays and modifications should only be done following protocol guidelines described in section 6.0. If treatment delays are > 14 days study therapy will be discontinued.

5.1 Treatment Administration

Regimen description					
Agent	***Premedications, precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Paclitaxel	*Premedicate with dexamethasone, diphenhydramine, ranitidine and -prochlorperazine*	*80 mg/m^2*	*IV over 1 hr +/- 15 minutes*	*Days 1, 8, and 15*	*4 weeks (28 days)*
Ganetespib	*Loperamide*	*Starting at 100 mg/m2 to a maximum dose of 150 mg/m2*	*IV over 1 hr +/- 15 minutes*	*Days 1, 8, and 15*	

5.1.1 Paclitaxel During the Phase I and II portions of this study, paclitaxel will be administered IV over 1 hour +/- 15 minutes at 80 mg/m2 on days 1, 8 and 15 of a 28-day cycle. Paclitaxel is infused over 1 hour, however the infusion time may be modified if needed after review and agreement by the study PI. Patients will be premedicated as per institutional standards, with diphenydramine, dexamethasone, ranitidine and prochlorperazine. Modifications to the premedications are allowed upon review and agreement by the study PI, and will be documented.

The product label will be followed for additional details regarding paclitaxel administration.

5.1.2 Ganetespib During the Phase I portion of the study, ganetespib will be administered IV over 1 hour +/- 15 minutes at a starting dose of 100 mg/m2 on days 1, 8 and 15 of a 28-day cycle, in conjunction with, but not simultaneously, with paclitaxel, as described above, given on the same schedule. Patients will be premedicated with loperamide before each dose of ganetespib. The dose of ganetespib will be increased to 125 mg/m2 and then 150 mg/m2 in two subsequent cohorts if DLT is not observed. Doses of ganetespib will not exceed 150 mg/m2 and this will be the maximum dose evaluated and the recommended Phase II dose if DLT is not identified at any of the three dose levels evaluated.

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

The recommended Phase II dose will be administered at the same schedule during the Phase II portion of the study.

Cohort	*Paclitaxel weekly*	*Ganetespib weekly*
Cohort 1	*80 mg/m2*	*100 mg/m2*
Cohort 2	*80 mg/m2*	*125 mg/m2*
Cohort 3	*80 mg/m2*	*150 mg/m2*

5.2 Concomitant Medications, Supportive Care, Excluded Therapies and Restrictions

Patients should receive full supportive care therapies concomitantly during the study including transfusions of blood and blood products, antibiotics when appropriate.

Any disease progression requiring other forms of specific anti-tumor therapy will be cause for early discontinuation of study treatment.

Prohibited during the study:

- Use of anti-neoplastic or anti-tumor agents not part of the study therapy, including chemotherapy, radiation therapy (except as stated above), immunotherapy, and hormonal anticancer therapy, is not permitted while participating in this study.

- Use of concurrent investigational agents is not permitted.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events
- Treatment held > 14 days for toxicity
- Patient required > 3 dose reductions of either paclitaxel or ganetespib
- Patient becomes pregnant
- Patient decides to withdraw from the study or
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator.

Treatment may be postponed to the next treatment day due to weather emergencies, missed appointments, holiday or other unplanned events not related to toxicity.

5.4 Duration of Follow up

Patients will be followed after removal from treatment until death. Patients removed from study for unacceptable adverse events that are related to the study treatment will be followed

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

until resolution or stabilization of the adverse event.

5.5 Criteria for Discontinuation

Patients will be removed from study when any of the criteria listed in Section 5.3 applies. The reason for study removal and the date the patient was removed must be documented in the medical record and case report form.

6.0 Dose Modifications

6.1 General Principles

Dose modifications should be made based only on the guidelines described in Section 6.0. There are no dose re-escalations. Patients requiring > 3 dose reductions of paclitaxel or > 3 dose reductions of ganetespib must discontinue protocol treatment. Missed doses are not to be made up. Patients requiring treatment to be held > 14 days for recovery from toxicity must discontinue protocol treatment. Dose reduction should occur for Grade 4 non-hematologic toxicities including gastrointestinal toxicities and should be targeted to the drug most likely to cause the toxicity or both drugs if both are potential culprits. Dose reduction should occur for grade 4 neutropenia and febrile grade 3 or 4 neutropenia.

Dose reduction should not occur for grade 4 thrombocytopenia or grade 4 anemia if they are believed to be solely attributable to paclitaxel.

Toxicity will be evaluated according to the NCI CTCAE, Version 4.03, effective June 14, 2010, which are available at HTTP://ctep.cancer.gov/reporting/ctc.html.

Dose limiting toxicities will include the following events that are attributable to study treatment:

1. Grade 4 neutropenia or thrombocytopenia lasting more than 7 consecutive days
2. Grade 4 neutropenia associated with coincident fever (temp > 100.5°F)
3. Grade 3 or 4 thrombocytopenia with clinically significant bleeding, or a platelet count at any time of < 10,000/mm3
4. Grade 3 or greater nonhematologic toxicity, with the exception of:
    a. Nausea or vomiting occurring in the absence of optimal supportive therapy
    b. Diarrhea occurring in the absence of optimal supportive therapy
    c. Grade 3 or greater fatigue lasting less than a week
    d. Grade 3 or greater nonhematologic toxicity that can be controlled to ≤ Grade 2 with appropriate treatment
5. Grade 2 or greater nonhematological toxicity that is related to study treatment and requires a dose reduction in the opinion of the study PI
6. Delay of a subsequent of therapy by more than 7 days.

Only DLTs occurring during Cycle 1 of therapy will influence decisions regarding dose escalation and/or enrollment of additional patients to a dose level. Grade 4 anemia is not considered a DLT due to its known attribution to paclitaxel.

6.2 Dose Level Adjustment

6.2.1 Paclitaxel Paclitaxel may be reduced in 10 mg/m2 increments from the starting dose of 80 mg/m2. If the specific toxicity is related to myelosuppression, the treating physician may opt to drop the day 15 dose of paclitaxel and use

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

GCSF or a similar agent during subsequent cycles of therapy. Ganetespib may be continued on day 15.

6.2.2 Ganetespib Ganetespib may be reduced in increments of 25 m/m2 weekly from the starting dose. Patients enrolling in Cohort 1 of the Phase I portion of the study will be allowed no more than 2 dose reductions of ganetespib.

The decision regarding which study drug requires reduction will depend upon the specific toxicity. For example, paclitaxel has been shown to cause neuropathy, but neuropathy has not been associated with ganetespib. Diarrhea is known to be related to ganetespib and other Hsp90 inhibitors and is not commonly associated with paclitaxel. Therefore, paclitaxel will be reduced for dose-limiting neuropathy, while ganetespib will be reduced for dose limiting diarrhea, unresponsive to recommended prophylactic treatment for diarrhea.

Guidelines for Dose Modification or Dosing Delays due to Drug-Related Toxicities

Parameter	Paclitaxel administration	Ganetespib administration
Non-Hematologic Toxicity:		
Any Grade 3 or higher except : A. Nausea or vomiting occurring in the absence of optimal supportive therapy B. Diarrhea occurring in the absence of optimal supportive therapy C. Grade 3 or greater fatigue lasting less than a week D. Grade 3 or greater nonhematologic toxicity that can be controlled to ≤ Grade 2 with appropriate treatment	Delay until recovery Reduce Dose	Delay until recovery Reduce Dose
Unresolved Grade 4 toxicity exceeding 2 weeks beyond the planned administration date	Discontinue treatment	Discontinue treatment
QTc Prolongation - Grade 3 (≥ 501 ms on at least 2 separate ECGs) - Grade 4 or repeated Grade 3	 Delay until recovery	Reduce dose Discontinue
Hematologic Toxicity Neutropenia:- Grade 3: ANC < 1.0×10^9/L but ≥0.5×10^9/L Grade 4: ANC < 0.5×10^9/L Grade 3 or 4 neutropenia associated with fever >100.5^0F	 Delay until recovery Delay until recovery Delay until recovery Reduce Dose	 Maintain dose level Delay until recovery to at least Grade 3 Delay until recovery Reduce Dose

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

Hematologic Toxicity Thrombocytopenia Grade 4 Thrombocytopenia lasting more than 7 consecutive days	Delay until recovery Reduce Dose	Delay until recovery Reduce Dose
Grade 3 or 4 thrombocytopenia with clinically significant bleeding, or a platelet count at any time of < 10,000/mm3	Delay until recovery Reduce Dose	Delay until recovery Reduce Dose

In order for a patient to receive treatment, on day 1, 8 or 15 or at the start of a new cycle of therapy, the following criteria must be met:

ANC ≥ 1,000/mm3 (≥ 1,000 mm3 for the start of a cycle)
Platelet count ≥ 75,000/mm (≥ 100,000/mm for the start of a cycle)
All other toxicity consider related to therapy must have resolved to Grade 1 or as considered acceptable by the treating physician or to baseline (with the exception of alopecia).

In the event that a patient is not able to proceed to the next cycle of therapy based on the above criteria, and the toxicity is attributable to paclitaxel, a patient who is deemed to be achieving clinical benefit may be allowed to continue treatment with ganetespib, given on a weekly schedule for 3 weeks out of a 4 week cycle, after discussion with the study PI.

6.3 Specific Toxicities and Modifications (See also Appendix III)

Management of Gastrointestinal Adverse Events in Ganetespib-treated Patients

Many patients receiving ganetespib will experience diarrhea, and some patients may experience Grade 3 or 4 diarrhea. The following proactive and ongoing management principles are necessary to avoid more serious complications of diarrhea. However, guidelines such as these should never replace sound clinical judgment.

Experience suggests that diarrhea is an expected drug class effect for Hsp90 inhibitors and it typically starts 2 to 3 hours following administration of ganetespib in most patients. However, when appropriately managed with anti-diarrheal treatment, it is generally mild to moderate and its duration limited to 24 hours.

Diarrhea must be proactively managed for all patients treated with ganetespib to avoid complications or worsening of the patient's condition. Without appropriate prophylactic treatment, the diarrhea can be prolonged, severe, and lead to severe dehydration and other complications. Loperamide 2 mg must be given **prophylactically,** starting approximately 1 to 2 hours before ganetespib administration, to be repeated every 4 hours for the first 12 hours.

In the event of diarrhea, patients should take loperamide at an initial 4 mg dose, followed by 2 mg doses every 4 hours. In the presence of uncomplicated Grade 1 or 2 diarrhea, loperamide should be continued until the patient is free from diarrhea for 12 hours. The total daily dose may not exceed 16 mg (8 capsules).

For Grade 3 or 4 diarrhea or complicated Grade 1 or 2 diarrhea (severe cramping, severe nausea/vomiting, decreased performance status, fever, sepsis, Grade 3 or 4 neutropenia, frank bleeding, dehydration), IV fluids should be used as appropriate, as well as prophylactic antibiotics.

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

Management of Neutropenia

First occurrence of Grade 2, Grade 3, or Grade 4 neutropenia (ANC ≤ 1500/mm³) on **Day 1 (any cycle)**

- Delay dosing of both ganetespib and paclitaxel until neutrophil recovery to at least Grade 1.
- **Grade 2 and Grade 3 neutropenia (ANC 500 -1500/mm³) on Day 8 and 15 (any cycle)**
  - **Administer ganetespib without delay or dose modification**.
  - **Delay dosing of paclitaxel until neutrophil recovery to at least Grade 1.**

Management of Severe or Complicated Neutropenia

G-CSF prophylactic use is recommended during subsequent treatment cycles in case of neutropenia lasting more than 7 days, febrile neutropenia, or documented infection with neutropenia. In this case, the treating physician may opt to treat with paclitaxel and ganetespib on days 1 and 8 only during each cycle.

Ganetespib Premedication and Management of Hypersensitivity Reactions

Generally, ganetespib does not require premedication for hypersensitivity reactions. However, ganetespib contains a surfactant (polysorbate 80) that has been associated with hypersensitivity reactions in other medications administered by infusion. Symptoms have included pruritus, flushing, shortness of breath, chest tightness, dizziness, headache, increased systolic blood pressure, and heart rate.

If an infusion reaction is suspected, the following is provided as guidance only; treatment will be based on clinical presentation. Institution-specific premedication and/or treatment procedures and regimens may also be appropriate in lieu of these guidelines:

Mild or Moderate Symptoms:

Stop ganetespib administration.

Give IV dexamethasone 10 mg and diphenhydramine HCl 25 to 50 mg.

After recovery from symptoms, resume ganetespib infusion or re-schedule patient for re-treatment as soon as possible.

Use premedication for subsequent infusion drug administrations.

Severe Symptoms (such as hypotension requiring pressor therapy or IV fluids, angioedema, respiratory distress requiring bronchodilator therapy, or generalized urticaria):

Stop ganetespib administration.

Give IV dexamethasone 10 mg and diphenhydramine HCl 25 to 50 mg, as above.

Add adrenaline (1:1000) or bronchodilators, as indicated.

If severe symptoms recur with optimal premedication, treatment with ganetespib must be discontinued.

Example of infusion premedication regimen:

Dexamethasone 12 mg PO and diphenhydramine HCl 25-50 mg PO approximately 12 to 24 hours prior to the next dose of study drug

Repeat dexamethasone 12 mg PO and diphenhydramine HCl 25 to 50 mg PO approximately 4 to 6 hours prior to the re-challenge

7.0 Study Agent Information

7.1 ***Study Drug Paclitaxel***

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

7.1.1 Paclitaxel is an FDA- approved cytotoxic therapy. Please refer to the FDA-approved package insert for product information, preparation instructions and a list of adverse events.

7.1.2 Commerically available paclitaxel will be used throughout this study.

7.1.3 Solution preparation: Paclitaxel must be diluted prior to administration. Dilution will be as per institutional standards and within the package insert.

7.1.4 Storage requirements: Vials should be stored at controlled room temperature in the original package to protect from light and will be used up until the expiration date on the vial. Refrigeration does not adversely affect stability.

7.1.5 Stability: Intact vials are stable when stored as per Section 7.2.3 until the expiration date. Diluted solutions are stable for up to 27 hours at room temperature under normal room lighting.

7.1.6 Route of administration: Paclitaxel will be administered via intravenous infusion over 1 hour (+/- 15 minutes) as per institutional standards.

7.2 Study Drug Ganetespib

7.2.1 Product description

The current ganetespib investigational product is a concentrate for solution for infusion provided in a single-use vial containing 300 mg of ganetespib, as described in the Pharmacy Manual. The concentration of ganetespib is 25 mg/mL in a polyethylene glycol 300 (PEG 300), polysorbate 80 (Tween-80) and dehydrated alcohol non-aqueous solvent system. The drug product is a clear, colorless-to-pale-yellow solution, essentially free of visible particles.

Ganetespib Drug Product, 25 mg/mL, 300 mg/vial (identified with a dark blue color cap and applicable product label): Each vial contains 12 mL of deliverable volume (12.84 mL total including an overage per USP requirements) equivalent to 300 mg of ganetespib at a concentration of 25 mg/mL in a PEG 300, polysorbate 80, and dehydrated alcohol non-aqueous solvent system. The drug product, as noted, is a clear, colorless-to-pale-yellow solution.

The amount of ganetespib administered will depend upon the patient's body surface area. The drug product is diluted before infusion.

Container/Closure

The ganetespib drug product is provided in a 30 mL type I amber glass vial fitted with a 20 millimeter stopper and sealed with an aluminum crimp and flip-off cap.

7.2.2 Availability

Ganetespib will be supplied by Synta Pharmaceuticals Corp.

7.2.3 Solution preparation

Ganetespib must be diluted prior to administration. **The appropriate drug administration**

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

instructions per the preparation guidelines must be carefully followed prior to use. Refer to the Pharmacy Manual for detailed ganetespib preparation guidelines.

7.2.4 Storage requirements

Store the infusion solution at room temperature until use, avoiding direct exposure to light. Upon completing the infusion solution preparation, the 1-hour administration of the infusion solution must be completed within 4 hours. The time needed to prepare the dosing solution does not count against the 4-hour limit. There is no need to protect the IV bag from ambient light during the infusion.

Caution: Do not refrigerate the infusion solution.

Caution: The 1-hour administration must be completed within 4 hours of finishing the infusion solution preparation.

7.2.5 Route of administration

Set up the infusion pump to deliver the 500mL ganetespib infusion solution over 60 minutes.
Note: Use of Vascular Access Devices:
Based on preclinical data, use of vascular access devices (VADs) (such as ports and peripherally-inserted central catheters [PICCS]) containing silicone catheters are permitted.

Use of VADs with catheters made of any material other than silicone is not allowed. Following ganetespib administration through a VAD, care should be taken to flush the line after each dose of study drug. Please follow routine clinical practice for care of patients utilizing VADs.

At the end of the infusion, the IV tubing **must be flushed with D5W** to ensure complete delivery of the required dose of ganetespib. The infusion rate of the D5W flush should be at the same rate as the drug infusion.

7.3 Drug Ordering, Storage and Handling

Ganetespib will be supplied by SyntaPharmaceuticals, Corp.
Following submission and approval of the required regulatory documents, participation in the study initiation meeting and receipt of the site activation letter from the CTO Regulatory Coordinator, the initial order may be placed. Drug order forms and ordering procedure will be presented at the site initiation meeting.

7.4 Destruction of Drug

At the time of study closure, the unused, used and expired study drug will be destroyed at the site per Institutional SOPs unless otherwise specified.

7.5 Records to be kept at Site; Dispensing and Accountability

It is the responsibility of the Investigator to ensure that a current record of investigational product (ganetespib) disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs (supplied by CTO) must comply with applicable regulations and guidelines, and should include:

7.5.1 Number of vials received and placed in storage area.

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

7.5.2 Number of vials currently in storage area.

7.5.3 Label ID number or batch number.

7.5.4 Dates and initials of person(s) responsible for each investigational product

7.5.5 inventory entry/movement.

7.5.6 Number of vials dispensed to and returned for each patient, including unique patient identifiers.

7.5.7 Number of vials transferred to another area for dispensing or storage after ensuring adequate storage and accountability procedures are in place.

7.5.8 Non-study disposition (e.g., lost, wasted, broken).

8.0 Correlative /Special Studies

8.1 Study Correlative #1

Analysis of patient pre- and post-ganetespib blood specimens (serum and peripheral blood mononuclear cells) for changes in the levels of expression of HSP70 and established HSP90 client proteins.

Rationale: The standard correlative studies performed in conjunction with HSP90 inhibitors include analysis of pre- and post-drug treatment blood specimens for biomarker analysis in PBMCs [29]. Specifically, levels of relevant biomarkers, including HSP90, HSP70 and established HSP90 client proteins (e.g., HER-2, STAT3/pSTAT3, RAF-1, CDK1/pCDK1, etc.) are evaluated by immunoblot analysis of protein lysates isolated from PBMCs from pre- and post-treatment blood specimens. Treatment with HSP90 inhibitors commonly results in increased levels of HSF1 which result in induction of HSP70 (reviewed in [30]). More recent studies suggest that HSP70 is secreted and that detection and quantification of HSP70 levels in serum is a potentially valuable correlative measure to indicate response to ganetespib [31,32].

Outcome measure: Alterations (significant increase or decrease) in protein biomarker level in post-treatment specimens (PBMCs and/or serum) compared to pre-treatment specimen.

Assessment, method, timing: Biomarker levels in PBMCs will be assessed by the standard method of immunoblot analysis followed by densitometry of the blots comparing biomarker levels to standard loading controls and/or purified protein standards [29]. In addition to immunoblot analyses, levels of HSP90, HSP70 and HSP90 client proteins (e.g., AKT/pAKT,pSTAT3, etc.) in PBMC's will be assayed by ELISA using commercially available kits (Enzo Life Sciences, MesoScale Discovery). Levels of secreted HSP70 and HSP90 and secreted HSP90 clients (soluble HER-2 and IGFBP-2) present in pre- and post-drug treatment serum specimens will be assayed by ELISA using commercially available kits (Enzo Life Sciences, MesoScale Discovery).

Data recording, method, timing: Analyses will be performed after patient accrual to the clinical trial and specimen collection is complete.

8.1.1 Collection of specimen- Blood specimens (two 10 ml tubes of blood) will be collected prior to treatment with ganetespib and paclitaxel on day # 1 of Cycle # 1 and on Day # 15 of Cycle # 1 and Day # 1 of Cycle # 2.and Day #15 of Cycle #2

8.1.2 Handling of specimen- After collection, blood specimens will be transferred to the

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

FCCC protocol support laboratory where they will be logged in and processed for collection and storage of PBMCs and serum.

8.1.3 Shipping of specimen- None

8.1.4 Site(s) performing correlative study- FCCC

8.2 Study Correlative #2

Analysis of patient formalin fixed paraffin embedded (FFPE) tumor specimens for the expression and activation of established HSP90 client proteins

Rationale: In addition to the analysis of HSP90-related biomarkers in PBMCs and serum, we will also analyze levels of expression and/or activation of HSP90 client proteins in patient primary tumor specimens by immunohistochemistry (IHC). The goal of this analysis is to survey patient tumor specimens for activation of HSP90 clients to determine if overall levels of client activation or activation of specific clients are associated with response to drug therapy. In the event that there are patients that experience PR or CR, we may further analyze the tumor specimen by high throughput genomic techniques (microarray, array comparative genomic hybridization, and/or DNA/RNA sequencing analyses) in order to discover the mechanistic basis of response to therapy.

Outcome measure: High levels of expression and/or activation of HSP90 client protein level in primary tumor tissue compared to archives specimens of normal ovary and fallopian tube tissue.

Assessment, method, timing: HSP90 client protein biomarker levels in tumor tissue will be assessed by IHC using standard methods. Analysis of the stained sections will be performed using the Aperio image analysis instrument and accompanying software analysis package. Staining levels will be compared in patient samples using archived specimens (available through the FCCC-UPenn Ovarian Cancer SPORE Pathology Core Facility). HSP90, HSP70 and HSP90 client proteins (e.g., JAK2, pSTAT3, pSTAT5, CDK1/pCDK1, S6K/pS6K, c-MYC, EGFR, HER-2, pAUR, AKT/pAKT, and others) will be detected using commercially available antibodies that are suitable for IHC. Levels of client expression and/or activation will be compared to normal ovarian and fallopian tube tissue. In addition, levels of expression/activation of clients will be analyzed in the context of response to therapy. If necessary, high throughput genomic analyses (microarray, array comparative genomic hybridization, and/or DNA/RNA sequencing) will be performed using standard methodologies available through the FCCC Genomics Facility or the Cancer Genome Institute.

Data recording, method, timing: Analyses will be performed after patient accrual to the clinical trial and specimen collection is complete.

8.2.1 Collection of specimen- Banked tumor tissue (FFPE tumor tissue specimens) will be obtained from a previous resection or biopsy that was done as part of the patient's standard care from the Pathology Department at FCCC, or in the case of patients who have undergone prior surgery at an outside institution, from the Pathology Department of the respective institution.

8.2.2 Handling of specimen- FFPE specimens will be transferred to the FCCC protocol support laboratory where they will be logged in and stored until all specimens for the trial are accrued and ready for testing.

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

8.2.3 Shipping of specimen- None

8.2.4 Site(s) performing correlative study- FCCC

8.3 Study Correlative #3:

Analysis of patient pre-treatment serum samples for the presence of secreted HSP90α

Rationale: Recent studies have shown increased levels of HSP90α in the serum of patients with prostate (PC), colorectal (CRC) and hepatocellular (HCC) carcinomas compared to normal controls [33-35]. To investigate whether patients with EOC similarly exhibit elevated levels of secreted HSP90α in serum, we will use banked serum specimens collected from EOC patients and age matched donors to compare levels of HSP90α detected by ELISA. The aforementioned studies in PC and HCC identified significant differences in HSP90α levels using relatively small numbers of serum specimens from cancer patients and controls ($N \leq 20$ specimens each of cancer compared with controls). We predict that analysis of similar sized cohorts of EOC patient serum and normal controls (n = 20-25) will determine whether HSP90α levels are significantly elevated in EOC patients. De-identified serum specimens for this analysis have been obtained from the FCCC-UPenn Ovarian Cancer SPORE Pathology Core Facility for this analysis.

Outcome measure: Determine if EOC patients exhibit elevated levels of serum HSP90α and if increased levels of serum HSP90α correlate with response to drug therapy.

Assessment, method, timing: Assessment of HSP90α levels will be performed by ELISA using a commercially available (Enzo Life Sciences) or custom-built assay (MesoScale Discovery chemiluminescent ELISA assay platform).

Data recording, method, timing: Analyses will be performed after patient accrual to the clinical trial and specimen collection is complete.

8.2.1 Collection of specimen- Pre-treatment serum specimens (collected for Study Correlative #1) will be used for the ELISA assay.

8.2.2 Handling of specimen- As in Study Correlative #1

8.2.3 Shipping of specimen- None

8.2.4 Site(s) performing correlative study- FCCC

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

9.0 Study Calendar

	Pre-Study[b]	C1 D1[b]	C1 D2	C1 D8	C1 D15	C1 D22	C2 D1	C2 D8	C2 D15	C2 D22	C3 D1	C3 D8	C3 D15	C3 D22	Day 1 of all subsequent cycles	Off Study[g]
Informed consent & HIPAA[a]	X															
Medical history	X															
Physical exam[(b)]	X	X					X				X				X	X
Concurrent meds[(b)]	X		X----------X													
Vital signs (T, P, R, BP)[(b)]	X	X					X				X				X	X
Height	X															
Weight[(b)]	X	X					X				X				X	X
Performance status[(b)]	X	X					X				X				X	X
CBC w/diff, plts[(b)]	X	X		X	X	X	X	X	X		X	X	X		X	X
Serum chemistry[(b,c)]	X	X		X	X	X	X				X				X	X
ECG [(b,h)]	X	X									X				X[(h)]	
Adverse event evaluation			X----------X												X	
Tumor measurements (CT- Chest, Abd. & Pelvis)	X		Tumor measurements are repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.													X[g]
β-HCG	X[d]															
Correlate Blood/Serum Draw		X[e]			X		X		X							
Collection of FFPE tumor tissue	X[f]															
Ganetespib		X		X	X		X	X	X		X	X	X			
Paclitaxel		X		X	X		X	X	X		X	X	X			

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

a: Informed consent must be signed within 30 days of registration. If signature is outside that window the patient must sign a new consent

b: Pre-study H&P and all labs must be ≤ 14 days prior to registration. Tumor measurements and radiologic evaluations must be ≤ 30 days prior to registration. Pre-study assessments may be used for C1D1 assessments if completed ≤ 7 days from day one of treatment.

c: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. Will be performed weekly during cycle 1, and then Day 1 for cycles 2 and beyond.

d: Serum pregnancy test (women of childbearing potential) must be completed ≤ 7 days before registration.

e: Two 10 ml tubes of blood to be drawn pretreatment on C1,D1; C1, D15; C2,D1 and C2,D15.

f: In the event of any biopsies or collection of ascites required for appropriate medical care of the patient throughout the course of the study, samples not needed for medical care will be collected and used for further analysis as per correlative aim #2.

g. Off-study evaluation. If PD documented during scheduled on-study assessment, tumor measurements and radiologic staging do not need to be repeated. Follow up for PD, resolution of treatment related toxicities should be conducted every 3 months for 2 years, every 6 months for 2 years, annually until death.

h. ECG must be performed prior to treatment on day 1 of every odd cycle.

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

10.0 Adverse Events

10.1 Definitions

10.1.1 Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, treatment or procedure regardless of whether it is considered related to the medical treatment or procedure *(NCI CTEP Guidelines March 28, 2011)*

10.1.2 Serious Adverse Event (SAE) is an AE that is fatal or life threatening, requires inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours), persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly/ birth defect, or results in any important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the above outcomes. A "life-threatening" adverse event places the patient at immediate risk of death in the judgment of the investigator or sponsor.

10.1.3 Severity Rating

The investigator will evaluate the severity of each adverse event. NCI Common Terminology Criteria for Adverse Events (CTCAE v.4.0) or study specific toxicity tables provided in the protocol define severity. If not included in CTCAE v.4.0, severity is expressed in numerical grade using the following definitions:

1. Grade 1: Mild-asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2. Grade 2: Moderate-minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.
3. Grade 3: Severe-severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
4. Grade 4: Life-threatening consequences; urgent intervention indicated.
5. Grade 5: Death related to AE

10.1.4 Attribution/Relationship to study drug

1. Definite – clearly related
2. Probable – likely related
3. Possible – may be related
4. Unlikely – doubtfully related
5. Unrelated – clearly not related

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

10.1.5 Expectedness

An Expected Adverse Event is one where the specificity or severity is consistent with the current information available from the resources.

An Unexpected Adverse Event is one where the nature, severity, or frequency of the event which occurs during participation in the research is not consistent with either:

1. The known or foreseeable risk of adverse events associated with the investigational product(s) or procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts: or
2. The expected natural progression of any underlying disease, disorder, or condition of the subject (s) experiencing the adverse event and the subjects(s) predisposing risk factor profile for the adverse event. (OHRP Guidance on reviewing unanticipated problems 2007)

10.2 Recording and Reporting Responsibilities

10.2.1 Investigative site recording responsibilities:

1. Upon identification of an AE or SAE, the site investigator will utilize the above definitions to properly classify the event. Each category listed above must be recorded for each event.
2. All AEs and SAEs will be recorded in the "AE case report forms" (CRF) and in progress reports with details about the grade and attribution of each episode, action taken with respect to the study drug, and the patient's outcome will be recorded in the CRF. All events will be recorded on case report forms for the duration of the study until they resolve.
3. All SAEs will be recorded on the FDA MedWatch form 3500a. After submitting the initial report it may be necessary to submit follow up reports to the CTO, Sponsor and the FDA should the event require further investigation.
4. SAE reporting will begin after the research participant has received their first dose of drug unless the SAE was due to a study specific test or procedure.

10.2.2 Investigative site reporting responsibilities:

1. The investigator/ site is responsible for reporting all SAEs to the QA Specialist / Study Monitor within 24 hours of becoming aware of the event. A written report must follow within 48 hours.
2. Each investigator is responsible for reporting all AEs/SAEs to

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

their local IRB following guidelines set by that IRB. The FCCC CTO reserves the right to request an event be reported to the IRB at their discretion. Copies of events reviewed by the IRB must be sent via fax to the CTO Regulatory Coordinator at (215) 728-2914

3. If the investigator or IRB feels the event warrants a revision to the informed consent that was not already initiated by the CTO, draft revisions will be made in track changes and submitted to the CTO for consideration. Any consent revisions must receive CTO approval **prior** to submission to the IRB.
4. Any investigator who is in doubt of whether a particular AE needs to be reported is directed to call the QA Specialist / Study Monitor for confirmation with the Principal Investigator
5. If the results of an investigator or CTO investigation show an adverse event not initially determined to be reportable is so reportable, the investigator will report the event following the above guidelines based on the date the determination is made.
6. Copies of all related correspondence and reporting documents must be submitted to the CTO Regulatory Coordinator and will be maintained in a regulatory file.

The participating site should report events to:

QA Specialist / Study Monitor
Fox Chase Cancer Center Clinical Trials
Operations 333 Cottman Avenue
Philadelphia, PA 19111
Telephone: 215-214-3704
Fax: 215-214-1511
Email: beth.adaire@fccc.edu

10.2.3 ERP Reporting Responsibilities:

1. Adverse events which meet all of the following criteria must be reported to all participating institutions for IRB submission within 2 weeks of notification of the event.
   i. Unexpected (in terms of nature, severity, or frequency) given (a) the investigational product that is described in the protocol-related documents, such as the Investigational Brochure, IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
   ii. Possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the one or more of the procedures involved in the research); and
   iii. Serious (refer to above definition) or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.
2. If the adverse event requires modification of the study protocol and

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

informed consent, these changes will be provided to all participating institutions in the form of an amendment from the CTO for each site's IRB of record along with the report of the adverse event.

3. Copies of all related correspondence and reporting documents will be maintained in a centralized regulatory file for this study at CTO.
4. SAEs that are related, unexpected, fatal, or life-threatening are reportable through the Food and Drug Administration (FDA) MedWatch program by telephone or fax no later than 7 calendar days after initial receipt of the information. Further information on the timing of submissions are as directed by FDA guidelines (http://www.fda.gov/medwatch/index.html). Serious, unexpected events that suggest significant clinical risk will be submitted to within 15 calendar days after initial receipt of this information.
5. Synta Pharmaceuticals as the manufacturer of ganetespib is responsible for all SAEs in patients using its products. All SAE MedWatch forms, regardless of expectedness or relationship to the study drug must be submitted to TELERX within 24 hours of the investigator's (or designee's) becoming aware of the event. MedWatch forms should be faxed to:

TELERX at 1-888-975-2207
All transmission confirmations must be maintained with the submission documents.

Food and Drug Administration:
Telephone 1-800-FDA-1088
Fax 1-800-FDA-0178
http://www.fda.gov/medwatch/report.htm

Mandatory Drug Reporting:
Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

Office of Post-Marketing Drug Risk Assessment (HFD 730)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

(301) 827-3169 for any further questions regarding where to send drug mandatory reporting forms

10.4 Pregnancy

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

All WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

In the event of a confirmed pregnancy in a patient participating in the study, the Investigator must immediately notify the Fox Chase Cancer Center QA Specialist / Study Monitor who will notify the study PI.

All pregnancies occurring during the study must be reported to Synta within 24 hours of investigator/site awareness of the pregnancy. Pregnancies should be followed for outcome, including early termination of any kind as well a delivery details in the event of complications and to report fetal outcome. In the event of fetal demise, Synta may request additional information.

11.0 Measures of Effect

Response Evaluation Criteria in Solid Tumors (RECIST)

The Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria will be used for objective tumor response assessment. Assessments will be performed after every 8 weeks of treatments. Once protocol treatment has been completed research participants will be assessed every three months or sooner as indicated and judged by treating physicians.

11.1 Definitions

Evaluable for adverse events: All research participants will be evaluable for adverse events from the time of their first treatment with paclitaxel and ganetespib.

Evaluable for objective response: Only those research participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These research participants will have their response classified according to the definitions stated below. (Note: Research participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Research participants who have lesions present at baseline that are evaluable but do not meet the definitions of

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded for solid tumors) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan or MRI, or ≥10 mm with calipers by clinical exam.

Note: Tumor lesions that are situated in a previously irradiated area might or would not be considered measurable unless there is documented disease progression prior to commencement of the study treatment.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size, be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions,

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. If CA-125 is initially elevated, it must decrease to normal for patient to be considered to have a CR. Patients with resolution of visible disease by imaging whose CA-125 remains elevated will be considered to have a PR. CA-125 elevation or increase alone will not be considered sufficient evidence of disease progression in the absence of worsening clinical symptoms or visible progression on imaging analysis.

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.4 Response Criteria

Evaluation of Target Lesions

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

For Patients with Measurable Disease (i.e., Target Disease)

Target	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD /not evaluated	No	PR	
SD	Non-CR/Non-PD /not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
**Only for non-randomized trials with response as primary endpoint.
***In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11.7 Response Rate

Response rate is defined as the proportion of patients with a best response of CR or PR.

12.0 Statistical Considerations

12.1 Study Design/Endpoints

Dose escalation will follow a modified 3+3 design (Table 1). If doses in Cohort 1 are tolerable, Dose Level 1 will proceed to Dose Level 2. If Dose Level 2 doses are tolerable, dosing will proceed to Dose Level 3 and this cohort will be expanded to a total of 6 patients; if 1 or 0 patients experience a dose-limiting toxicity (DLT), this will be the chosen regimen for the Phase II trial. If≥2 patients experience a DLT, dose expansion will proceed at the next lower Dose Level, and an additional 3 patients would be evaluated at the lower dose level. If one patient of the first 3 experiences a DLT in any cohort, that cohort will be expanded to enroll, in sequence, an additional 3 patients. If 1 additional patient experiences a DLT, enrollment will proceed at the next lower Dose Level for expansion to 6 patients. We will enroll an additional 6 patients at the MTD or the maximum evaluated dose (MED), which is Dose Level 3, level to gather additional safety and toxicity information prior to proceeding with a Phase II trial. There will be no escalation beyond Dose Level 3, even in the absence of DLTs. DLTs will include grade 4 neutropenia lasting longer than 7 days, neutropenic fever, grade 4 thrombocytopenia or any Grade 3 non-hematologic toxicity lasting greater than 7 days, not controlled with optimal medical management.

Table 1

Ganetespib weekly dose:	Paclitaxel 80 mg/m2 weekly
100 mg/m2	Cohort 1
125 mg/m2	Cohort 2
150 mg/m2	Cohort 3

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

For the Phase II portion of the study we will test the composite null hypothesis that the chance of response to the combination therapy is at most 25% and the chance of PFS at 6 months is at most 30%. The alternative for which power is computed is that the chance of response is at least 40% OR the chance of PFS at 6 months is at least 50%. We used the design of Sill and colleagues.[36] This flexible double end-point design evaluates the first 29, 30 or 31 (n1) patients, (which, depending on control of patient accrual). If 7/29, or 7/30 or 7/31 (cr1/n1) respond or if 10/29, or 11/30 or 12/31 (cs1/n1) are PF at 6 months then recruitment will be continued until 54, 55 or 56 (n2) patients are on available for study. Final decision rules (cr2 and cs2) to reject the null are given in the tables below.

On the assumption of independence of response and PFS at 6 months the study will have at least 80% power and at most 9.5% type I error. Average power under all 9 possible combinations of early and final sample numbers is 82% with 9.1% average type I error. The chance of early stopping under the null is at least 42% and at most 6.6% under any alternative.

Statistics under the most extreme forms of dependence are also tabulated below. In all cases the average performance of the design gives at least 80% power and at most 10% type I error.

pr(null) 0.250 pr(alt) 0.400 Response
ps(null) 0.300 ps(alt) 0.500 PFS

n1: 29 30 31
cr1: 7 7 7
cs1: 10 11 12

cr2

n1\n2	54	55	56
29	18	18	18
30	18	18	18
31	18	18	18

cs2

n1\n2	54	55	56
29	22	23	24
30	22	23	24
31	22	23	24

---

independence case

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

pr	ps	min power	ave power	max power	min pes	ave pes	max pes
0.250	0.300	0.0882	0.0911	0.0953	0.4222	0.4279	0.4324
0.250	0.500	0.8152	0.8481	0.8814	0.0379	0.0520	0.0664
0.400	0.300	0.8019	0.8271	0.8523	0.0295	0.0367	0.0439
0.400	0.500	0.9726	0.9744	0.9764	0.0039	0.0043	0.0046

---

fullest dependence case: p11=min(pr,ps)

pr	ps	min power	ave power	max power	min pes	ave pes	max pes
0.250	0.300	0.0665	0.0745	0.0841	0.4719	0.5091	0.5444
0.250	0.500	0.7814	0.8218	0.8638	0.0656	0.0934	0.1220
0.400	0.300	0.7928	0.8212	0.8496	0.0330	0.0445	0.0570
0.400	0.500	0.8891	0.8939	0.9003	0.0278	0.0310	0.0333

---

fullest dependence case: p11=max(0,pr+ps-1)

pr	ps	min power	ave power	max power	min pes	ave pes	max pes
0.250	0.300	0.0891	0.0923	0.0963	0.3811	0.3887	0.3931
0.250	0.500	0.8657	0.8903	0.9145	0.0102	0.0148	0.0198
0.400	0.300	0.8225	0.8423	0.8623	0.0177	0.0196	0.0212
0.400	0.500	0.9998	0.9999	0.9999	0.0000	0.0000	0.0000

---

nb: Output from dblep19.doc

Testing for excess toxicity:

We will consider 15% or lower as reasonable for the chance of DLT. 33.3%, or 1/3 will be considered excessive. If the number of DLTs among the first 15 patients ever reaches 6, the study will be terminated for excess toxicity. Similarly if ever 9 of the first 29 patients experience DLTs the study will be stopped early for excess toxicity. Finally, if ever 14 patients experience DLTs the treatment will be considered too toxic.

The chance of finding the treatment too toxic when the true rate of DLT is 1/3 is 92%. The chance of declaring it too toxic when the true rate of DLT is 15% is 4.73%. The table below gives the chance of declaring the study too toxic under null or alternative and at each early and the final sample number. The 15 and 29 rules may be applied before the efficacy early stopping point is reached. Similarly, if the study accrues 55 or 56 patients, the 54 rule is to be applied

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.
Protocol version date: 10/20/2014

whenever 54 patients are accrued. The stopping numbers are fixed even though the early and final sample numbers are not known. In all 9 combinations of early and final sample numbers the chance of declaring the study too toxic when it is at least 90%. The type I error is at most 6.12% over these same combinations.

p(declare tox | ptox = 0.150000000000000): 4.730297624299153E-002
p(early stop) at 15 patients: 1.681008604795003E-002
p(early stop) at 29 patients: 1.521020715756849E-002
p(final stop) at 54 patients: 1.528268303747300E-002

p(declare tox | ptox = 0.333333300000000): 0.918379342938625
p(early stop) at 15 patients: 0.381628054489728
p(early stop) at 29 patients: 0.310791894575327
p(final stop) at 54 patients: 0.225959393873570
---
nb: output of tox3.f, see tox3b.out for complete listing.
tox3.f and tox3b.f both on stats.

12.2 Sample Size/Accrual Rate

The Phase I portion of the study will include no more than 18 patients, and the Phase II portion of the study will include no more than 56 patients.

12.3 Stratification Factors

N/A

12.4 Analysis of Correlative Endpoints

For the correlative studies, as described in Section 8.0, evaluations will be as follows:
For correlate 8.1: We will compare protein biomarker pre-treatment levels to their post-treatment levels. With 54 patients we will test the null hypothesis that the two levels do not differ. This corresponds to the hypothesis that the post-treatment levels exceed pre-treatment levels with probability 0.5. We expect 27 such exceedences under the null. If this number is at least 35 or at most 19 we will reject the null and conclude that pre and post-treatment levels differ. The test will have 84% power and 4% two-sided type-I error.

For correlate 8.2: We will compare Hsp90 expression or activation levels in our patients to those in 54 archived specimens of normal ovary and fallopian tube tissue. We will classify all 108 specimens as high or low level IHC staining. We will submit this doubly dichotomized data to Fisher's exact test which will have at least 80% power and at most 5% type I error to test the null hypothesis that patient and control staining levels are the same versus that patients tissues

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

experience higher staining levels and patients are at least 24% more likely to be in the higher staining category.

For correlative study 8.3: We will compare patient pre-treatment serum samples of secreted Hsp90-alpha to serum from age-matched normal controls. With 25 such differences we will test the null hypothesis of no difference, i.e. the chance that patient exceeds control is one-half, versus the hypothesis that the chance that patient levels exceed the control levels is at least 75%. This test of the binomial proportion will have 85% power and 5.4% type-I error to detect such a difference.

12.5 Reporting and Exclusions

12.5.1 Evaluation of toxicity: All patients who have received any amount of study drug will be evaluable for toxicity. All patients will be evaluated for safety.

12.5.2 Evaluation of response: All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

13.0 Data and Safety Monitoring Plan

13.1 Monitoring Plan

The QA Specialist/Study Monitor will monitor the medical and study records of each participant accrued throughout the course of the study. In addition, the CTO will collect and report data to the study Principal Investigator who will review these data on a regular basis at a rate dependent on subject accrual. All serious adverse events (SAEs) will be reviewed on a real time

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

basis first by the study site PI and subsequently study PI.

13.2 Extramural Data Safety Monitoring Committee

Interim analysis of toxicity, outcome and ongoing scientific investigations may be performed every 6 months by the Extramural Data Safety Monitoring Committee (EDSMC). In this capacity the EDSMC will serve as an advisory committee to the PMEC. The EDSMC will review those aspects of this trial that are outlined in the responsibilities section of the Extramural Data and Safety Monitoring Plan (DSMP). If the committee decides that changes should be made to this trial, it will make recommendations in writing to the Study PI, the Extramural Research Committee and Division Medical Director, which, in turn, have the authority to approve or disapprove these recommendations. These changes will be discussed with the Study Principal Investigator before they are implemented. These changes may include early termination of accrual. Other changes might include altering the accrual goals or changing the eligibility criteria for the trial.

14.0 Administrative

This study will be conducted in accordance will local, state and Federal regulations and according to accepted good clinical practice guidelines.

14.1 Data Reporting

The FCCC QA Specialist / Study Monitor will request case report form submission upon resolution of outstanding queries. Participating sites are responsible to respond to queries prior to the next scheduled monitoring visit. Participating sites are responsible for submitting case report forms to the QA Specialist / Study Monitor within two weeks of request.

The QA Coordinator is responsible for compiling and submitting data to the study PI and statistician on an ongoing basis for monitoring as described in the data safety monitoring plan and reporting to the Extramural Data and Safety Monitoring Committee.

All patient information will be stored on an electronic Microsoft Office Excel Spreadsheet on a drive accessible only to the study team members for the purpose of entering, reviewing and analyzing data. Any paper records, such as case report files, produced will be stored in locked file cabinets with limited access.

The CTO Regulatory Coordinator is responsible for distributing and tracking review of all IND Action Letters, Safety Reports, study specific Serious Adverse Events

14.2 Retention of Records

Time points for the retention of records are described in detail in the contract between the grantor and the CTO and passed on to the participating site. Please refer to the study specific terms for specific time points. In all cases

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

the QA Specialist / Study Monitor must be notified of any plans to move records to an offsite location prior to doing so.

14.3 Study Agents

Any study agent supplied through the CTO from the manufacturer or a third party distributor may not be used for any purpose outside the scope of this protocol. The agent may not be transferred to any party not participating in the clinical trial.

14.4 Informed Consent

The IRB approved informed consent documents must be signed by the patient, or the patient's legally authorized representative, before his or her participation in the study. The case history for each patient shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent documents must be provided to the patient or the patient's legally authorized representative. If applicable, they will be provided in a certified translation of the local language.

Original signed consent forms must be filed in each patient's study file or medical record with a copy in the study file.

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

15.0 References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10-29.
2. Markman M, Reichman B, Hakes T, et al. Responses to second-line cisplatin-based intraperitoneal therapy in ovarian cancer: influence of a prior response to intravenous cisplatin. J Clin Oncol 1991;9:1801-5.
3. Gore ME FI, Wiltshaw E, Dawson T. Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compounds. Gynecol Oncol 1990;36:207-11.
4. Blackledge G LF, Redman C, Kelly K. Response of patients in phase II studies of chemotherapy in ovarian cancer: implications for patient treatment and the design of phase II trials. Br J Cancer 1989;59:650-3.
5. Dizon DS, Dupont J, Anderson S, et al. Treatment of recurrent ovarian cancer: a retrospective analysis of women treated with single-agent carboplatin originally treated with carboplatin and paclitaxel: The Memorial Sloan-Kettering Cancer Center experience. Gynecol Oncol 2003;91:584-90.
6. Orlando M, Costanzo MV, Chacon RD, Tajer CD. Randomized trials of combination chemotherapy (combo) versus monotherapy (mono) in relapsed ovarian carcinoma (ROC): A meta-analysis of published data. J Clin Oncol (Meeting Abstracts) 2007;25:5524-.
7. Whitesell L, Lindquist SL. HSP90 and the chaperoning of cancer. Nature reviews Cancer 2005;5:761-72.
8. Ying W, Du Z, Sun L, et al. Ganetespib, a unique triazolone-containing Hsp90 inhibitor, exhibits potent antitumor activity and a superior safety profile for cancer therapy. Mol Cancer Ther 2012;11:475-84.
9. Proia DA, Foley KP, Korbut T, et al. Multifaceted intervention by the Hsp90 inhibitor ganetespib (STA-9090) in cancer cells with activated JAK/STAT signaling. PloS one 2011;6:e18552.
10. Acquaviva J, Smith DL, Sang J, et al. Targeting KRAS-mutant non-small cell lung cancer with the Hsp90 inhibitor ganetespib. Mol Cancer Ther 2012;11:2633-43.
11. Semenza GL. Hypoxia-inducible factors: mediators of cancer progression and targets for cancer therapy. Trends Pharmacol Sci 2012;33:207-14.
12. Lee K, Zhang H, Qian DZ, Rey S, Liu JO, Semenza GL. Acriflavine inhibits HIF-1 dimerization, tumor growth, and vascularization. Proc Natl Acad Sci U S A 2009;106:17910-5.
13. Shimamura T, Perera SA, Foley KP, et al. Ganetespib (STA-9090), a nongeldanamycin HSP90 inhibitor, has potent antitumor activity in in vitro and in vivo models of non-small cell lung cancer. Clin Cancer Res 2012;18:4973-85.
14. Nguyen DM, Lorang D, Chen GA, Stewart JHt, Tabibi E, Schrump DS. Enhancement of paclitaxel-mediated cytotoxicity in lung cancer cells by 17-allylamino geldanamycin: in vitro and in vivo analysis. The Annals of thoracic surgery 2001;72:371-8; discussion 8-9.
15. Proia DA, Sang J, He S, et al. Synergistic activity of the Hsp90 inhibitor ganetespib with taxanes in non-small cell lung cancer models. Invest New Drugs 2012;30:2201-9.

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

16. Zhou D, Teofilovici F, Liu Y, et al. Associating retinal drug exposure and retention with the ocular toxicity profiles of Hsp90 inhibitors. ASCO Meeting Abstracts 2012;30:3086.
17. Cysyk RL, Parker RJ, Barchi JJ, Jr., Steeg PS, Hartman NR, Strong JM. Reaction of geldanamycin and C17-substituted analogues with glutathione: product identifications and pharmacological implications. Chem Res Toxicol 2006;19:376-81.
18. McGuire WP RE, Rosenshein NB, Grumbine FC, Ettinger DS, Armstrong DK, Donehower RC Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms Ann Intern Med 1989;111:273-9.
19. Thigpen JT, Blessing JA, Ball H, Hummel SJ, Barrett RJ. Phase II trial of paclitaxel in patients with progressive ovarian carcinoma after platinum-based chemotherapy: a Gynecologic Oncology Group study. J Clin Oncol 1994;12:1748-53.
20. Fennelly D, Aghajanian C, Shapiro F, et al. Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. J Clin Oncol 1997;15:187-92.
21. Markman M, Hall J, Spitz D, et al. Phase II Trial of Weekly Single-Agent Paclitaxel in Platinum/Paclitaxel-Refractory Ovarian Cancer. J Clin Oncol 2002;20:2365-9.
22. Dunder I BB, Atabekoglu C, Bilgin T. Preliminary experience with salvage weekly paclitaxel in women with advanced recurrent ovarian carcinoma. Eur J Gynaecol Oncol 2005;26:79-82.
23. Ghamande S LS, Marchetti D, Baker T, Odunsi K. Weekly paclitaxel in patients with recurrent or persistent advanced ovarian cancer. Int J Gynecol Cancer 2003;13:142-7.
24. Kita T, Kikuchi Y, Takano M, et al. The effect of single weekly paclitaxel in heavily pretreated patients with recurrent or persistent advanced ovarian cancer. Gynecol Oncol 2004;92:813-8.
25. Le T, Hopkins L, Baines KA, Rambout L, Al Hayki M, Kee Fung MF. Prospective evaluations of continuous weekly paclitaxel regimen in recurrent platinum-resistant epithelial ovarian cancer. Gynecol Oncol 2006;102:49-53.
26. Markman M, Blessing J, Rubin SC, Connor J, Hanjani P, Waggoner S. Phase II trial of weekly paclitaxel (80 mg/m2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: A Gynecologic Oncology Group study. Gynecol Oncol 2006;101:436-40.
27. Markman M, Blessing J, Rubin SC, Connor J, Hanjani P, Waggoner S. Phase II trial of weekly paclitaxel (80 mg/m2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. Gynecol Oncol 2006;101:436-40.
28. Young JC, Agashe VR, Siegers K, Hartl FU. Pathways of chaperone-mediated protein folding in the cytosol. Nature reviews Molecular cell biology 2004;5:781-91.
29. Hubbard J, Erlichman C, Toft DO, et al. Phase I study of 17-allylamino-17 demethoxygeldanamycin, gemcitabine and/or cisplatin in patients with refractory solid tumors. Invest New Drugs 2011;29:473-80.
30. Powers MV, Jones K, Barillari C, Westwood I, van Montfort RL, Workman P. Targeting HSP70: the second potentially druggable heat shock protein and molecular chaperone? Cell Cycle 2010;9:1542-50.

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

31. Dakappagari N, Neely L, Tangri S, et al. An investigation into the potential use of serum Hsp70 as a novel tumour biomarker for Hsp90 inhibitors. Biomarkers 2010;15:31-8.
32. Zhang H, Chung D, Yang YC, et al. Identification of new biomarkers for clinical trials of Hsp90 inhibitors. Mol Cancer Ther 2006;5:1256-64.
33. Burgess EF, Ham AJ, Tabb DL, et al. Prostate cancer serum biomarker discovery through proteomic analysis of alpha-2 macroglobulin protein complexes. Proteomics Clin Appl 2008;2:1223.
34. Chen JS, Hsu YM, Chen CC, Chen LL, Lee CC, Huang TS. Secreted heat shock protein 90alpha induces colorectal cancer cell invasion through CD91/LRP-1 and NF-kappaB-mediated integrin alphaV expression. J Biol Chem 2010;285:25458-66.
35. Sun Y, Zang Z, Xu X, et al. Differential proteomics identification of HSP90 as potential serum biomarker in hepatocellular carcinoma by two-dimensional electrophoresis and mass spectrometry. Int J Mol Sci 2010;11:1423-33.
36. Sill MW, Rubinstein L, Litwin S, Yothers G. A method for utilizing co-primary efficacy outcome measures to screen regimens for activity in two-stage Phase II clinical trials. Clinical trials 2012;9:385-95.

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

Appendices:

Appendix I New York Heart Association Classification
Functional Class Description

0	No cardiac disease or limitations
I	Patients with cardiac disease but without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnea or palpitation.
II	Patients with cardiac disease that results in slight limitations of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea or angina.
III	Patients with cardiac disease that results in marked limitation of physical activity. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.
IV	Patients with cardiac disease that results in an inability to carry on physical activity without discomfort. Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

Appendix II Management of Events of Special Interest

Management of Gastrointestinal Adverse Events

Many patients will experience diarrhea, and some patients may experience Grade 3 or 4 diarrhea. The following proactive and ongoing management principles are necessary to avoid more serious complications of diarrhea. However, guidelines such as these should never replace sound clinical judgment.

Experience suggests that diarrhea is an expected drug class effect for Hsp90 inhibitors and it typically starts 2 to 3 hours following administration of ganetespib in most patients. However, when appropriately managed with anti-diarrheal treatment, it is generally mild to moderate and its duration limited to 24 hours.

Diarrhea must be proactively managed for all patients treated with ganetespib to avoid complications or worsening of the patient's condition. Without appropriate prophylactic treatment, the diarrhea can be prolonged, severe, and lead to severe dehydration and other complications. Loperamide 2 mg must be given **prophylactically,** starting approximately 1 to 2 hours before ganetespib administration, to be repeated every 4 hours for the first 12 hours.

In the event of diarrhea, patients should take loperamide at an initial 4 mg dose, followed by 2 mg doses every 4 hours. In the presence of uncomplicated Grade 1 or 2 diarrhea,

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.

loperamide should be continued until the patient is free from diarrhea for 12 hours. The total daily dose may not exceed 16 mg (8 capsules).

For Grade 3 or 4 diarrhea or complicated Grade 1 or 2 diarrhea (severe cramping, severe nausea/vomiting, decreased performance status, fever, sepsis, Grade 3 or 4 neutropenia, frank bleeding, dehydration), IV fluids should be used as appropriate, as well as prophylactic antibiotics.

Ganetespib Premedication and Management of Hypersensitivity Reactions

Generally, ganetespib does not require premedication for hypersensitivity reactions. However, ganetespib contains a surfactant (polysorbate 80) that has been associated with hypersensitivity reactions in other medications administered by infusion. Symptoms have included pruritus, flushing, shortness of breath, chest tightness, dizziness, headache, increased systolic blood pressure, and heart rate.

If an infusion reaction is suspected, the following is provided as guidance only; treatment will be based on clinical presentation. Institution-specific premedication and/or treatment procedures and regimens may also be appropriate in lieu of these guidelines:

Mild or Moderate Symptoms:

- Stop ganetespib administration.
- Give IV dexamethasone 10 mg and diphenhydramine HCl 25 to 50 mg.
- After recovery from symptoms, resume ganetespib infusion or re-schedule patient for re-treatment as soon as possible.
- Use premedication for subsequent infusion drug administrations.

Severe Symptoms (such as hypotension requiring pressor therapy or IV fluids, angioedema, respiratory distress requiring bronchodilator therapy, or generalized urticaria):

- Stop ganetespib administration.
- Give IV dexamethasone 10 mg and diphenhydramine HCl 25 to 50 mg, as above.
- Add adrenaline (1:1000) or bronchodilators, as indicated.

If severe symptoms recur with optimal premedication, treatment with ganetespib must be discontinued.

Example of infusion premedication regimen:

- Dexamethasone 12 mg PO and diphenhydramine HCl 25-50 mg PO approximately 12 to 24 hours prior to the next dose of study drug

Repeat dexamethasone 12 mg PO and diphenhydramine HCl 25 to 50 mg PO approximately 4 to 6 hours prior to the re-challenge

Copyright© 2013 Fox Chase Cancer Center® Clinical Trials Operations. All rights reserved.