HSP90 Inhibition is Effective in Breast Cancer: A Phase 2 Trial of Tanespimycin (17AAG) plus Trastuzumab in Patients with HER2-Positive Metastatic Breast Cancer Progressing on Trastuzumab

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TRANSLATIONAL RELEVANCE:

HSP90 is a ubiquitous protein that is commonly overexpressed in cancer cells where it is required to promote the proper folding of several oncoproteins. Without its chaperoning presence, these proteins are ubiquitylated and degraded, hence inhibiting HSP90 has the potential to disrupt multiple key survival pathways within cancer cells, making it an attractive target for drug development. Our phase I trial of 17-AAG plus trastuzumab (Modi S et al, J Clin Oncol 2007) was the first trial to show objective responses with 17-AAG in a solid tumor type. In building on this data, we now present the positive results for our phase 2 study of 17-AAG plus trastuzumab for patients with advanced HER2+ MBC refractory to trastuzumab. We believe the findings of this study represent a major advance in defining the role of HSP90 as a bonafide target in oncologic therapy and a validated target for HER2+ breast cancer.
ABSTRACT

Purpose: Hsp90 is a chaperone protein required for the stability of a variety of client proteins. 17-AAG is a natural product that binds to Hsp90 and inhibits its activity, thereby inducing the degradation of these clients. In pre-clinical studies, HER2 is one of the most sensitive known client proteins of 17-AAG. Based on these data and activity in a phase 1 study, we conducted a phase 2 study of 17-AAG (tanespimycin) with trastuzumab in advanced trastuzumab-refractory HER2 positive breast cancer.

Experimental Design: We enrolled patients with metastatic HER2+ breast cancer whose disease had previously progressed on trastuzumab. All patients received weekly treatment with tanespimycin at 450mg/m2 intravenously and trastuzumab at a conventional dose. Therapy was continued until disease progression. The primary endpoint was response rate by RECIST criteria.

Results: Thirty-one patients were enrolled with a median age of 53 years and a median KPS of 90%. The most common toxicities, largely grade 1, were diarrhea, fatigue, nausea and headache. The overall response rate was 22%, the clinical benefit rate (CR + PR + SD) was 59 %, the median progression-free survival was 6 months (95% CI: 4-9), and the median overall survival was 17 months (95% CI: 16-28).

Conclusions: This is the first phase 2 study to definitively show RECIST-defined responses for 17-AAG in solid tumors. Tanespimycin plus trastuzumab has significant anti-cancer activity in patients with HER2 positive, metastatic breast cancer previously progressing on trastuzumab. Further research exploring this therapeutic interaction and the activity of HSP90 inhibitors is clearly warranted.
INTRODUCTION:

Breast cancers with HER2 amplification form a distinct class that is dependent on this receptor and sensitive to its inhibition\(^1\). The anti-HER2 antibody, trastuzumab has activity in this tumor when given alone\(^2\), enhances survival and extends time to progression when combined with first-line chemotherapy for metastatic disease\(^1\), and increases survival in the adjuvant setting\(^3,4,5\). Despite trastuzumab, a substantial number of patients with HER2 amplified breast cancer experience recurrence or progression and the vast majority of those with metastatic cancer eventually succumb to their disease. The significant antitumor activity of lapatinib\(^6\), a HER2-tyrosine kinase inhibitor, in these patients, along with the activity of trastuzumab continued beyond progression\(^7,8\) and other novel anti-HER2 agents\(^9,10,11\), suggests that a significant fraction of these tumors may remain dependent on HER2 function. This implies that, as with other targeted therapies, resistance to trastuzumab may be relative or situational and only in part due to loss of its effectiveness in inhibiting the target. Many of these mechanisms could potentially be overcome by inhibition of HER2 with another therapeutic agent.

Hsp90 is an abundant protein chaperone that functions in refolding proteins in cells exposed to stress and in the conformational maturation of certain regulatory proteins\(^12\). Several natural products, including geldanamycin, bind selectively to an amino-terminal pocket in Hsp90 and inhibit its function\(^12\). These compounds cause the proteasomal degradation of Hsp90 client proteins, including a number of proteins involved in growth factor signaling. Of these clients, HER2 is one of the most sensitive targets\(^13\). Geldanamycin is hepatotoxic in vivo, but its derivative, tanespimycin (17AAG, 17-demethoxygeldanamycin; KOS-953) has reduced toxicity and can be administered to mice at concentrations that effectively inhibit Hsp90 function, as measured by its degradation of Hsp90 client proteins and induction of heat shock protein expression in vivo\(^14\). While 17-AAG has antitumor activity in several preclinical murine models including AR-dependent prostate cancer, V600E BRAF mutant melanoma and mutant...
EGFR-driven lung carcinoma, HER2-breast cancer xenografts and transgenics are especially sensitive to its effects, in some cases producing durable tumor regressions\textsuperscript{13,15,16,17}.

In 2006, we initiated a phase I study of 17AAG plus trastuzumab in advanced solid tumors. Among patients with HER2+, trastuzumab refractory metastatic breast cancer (MBC), we observed objective responses, including two confirmed partial responses and three minor responses\textsuperscript{18}. We hypothesized that 17AAG is active in these patients because HER2 is hypersensitive to its effects and, at the maximally tolerated dose, enough degradation is achieved to significantly affect the tumor. In order to confirm these results and to obtain a more precise estimate of activity, we conducted a phase II study of tanespimycin plus trastuzumab for patients with HER2+ MBC who had previously progressed on one line of trastuzumab-containing therapy.

PATIENTS AND METHODS

Patients

Eligibility criteria included: age $\geq$ 18 years, KPS $\geq$ 70%, HER2+ MBC (IHC 3+ or FISH ratio $\geq$ 2), measurable disease, progression on one line of prior trastuzumab therapy (including during/within 3 months of adjuvant trastuzumab), resolution of toxicities from other therapies to NCI CTCAE (v. 3.0) grade $\leq$ 2, and end organ function defined as: hemoglobin $\geq$ 8.5g/dL, ANC $\geq$ 1.5x10\(^9\)/L, platelets $\geq$ 75 x10\(^9\)/L, bilirubin $\leq$ 2 xULN, AST and ALT $\leq$ 2 xULN, and serum creatinine $\leq$ 2 xULN.

Patients were excluded for any of the following: prior hypersensitivity to Cremophor or trastuzumab of grade $\geq$ 3, pregnancy or breast-feeding, known active CNS metastases, other anticancer therapy within 14 days of study treatment (6 weeks for nitrosoureas) excluding trastuzumab, other malignancies unless free of recurrence for 5 years, dyspnea at rest requiring supplemental oxygen, NYHA class III or IV CHF, LVEF $<$ 50%, congenital QTc prolongation, baseline QTc $>$ 450 msec for men or $>$ 470 msec for women, medication known to prolong QTc, LBBB, history of uncontrolled dysrhythmias.
or a requirement for antiarrhythmics, MI or ischemic heart disease within 12 months, or prior radiation including the heart in the field (e.g., mantle). All patients were required to sign a written informed consent that was approved by the institutional IRB.

Treatment

All patients received trastuzumab as 2mg/kg iv over 30 minutes; if their last dose of trastuzumab was more than 21 days prior to the study they received an initial loading dose of 4mg/kg over 90 minutes. Following this, tanespimycin was administered (KOS-953 dissolved in 20% Cremophor EL) as 450mg/m² iv over 2 hours. Both drugs were given weekly on a continuous schedule. Given the potential for Cremophor-induced hypersensitivity, all patients received pre-medication with corticosteroids and an H2-antagonist as per the treating physician. After 21 patients had been enrolled, a second formulation of tanespimycin (a suspension formulation) without Cremophor was substituted into the study based on demonstrated equivalence in a randomized PK cross-over study comparing the two formulations (unpublished). This suspension formulation of tanespimycin contains 1% polysorbate 80, 0.25% lecithin, and 10% sucrose in a suspension-based formulation to a concentration of 50mg/ml, and was administered as an intravenous infusion over 60 minutes without pre-medications.

Efficacy and Safety Evaluation

All patients receiving at least one dose of study drug were included in the safety analysis. Patients were examined and assessed for toxicities during and prior to each cycle (4 weeks) and all adverse events and laboratory variables apart from cardiac failure (NYHA classification) were assessed according to the NCI CTCAE, version 3 grading system. Assessment of cardiac function via echocardiogram or MUGA was conducted every 8 weeks or sooner if clinically indicated and described. ECGs were obtained pre- and post-tanespimycin infusions on week 1 and week 4 of Cycle 1.
Re-treatment criteria included: ANC $\geq 1.0 \times 10^9$/L, platelets $\geq 75 \times 10^9$/L, Hemoglobin $\geq 8$ g/dL; additionally, patients must have met all eligibility criteria with respect to KPS, hepatic and renal function, and all toxicities considered related to study drug must have recovered to baseline or $\leq$ grade 2, excluding alopecia. Failure to meet these criteria resulted in treatment delay up to a maximum of 3 weeks, after which point patients were discontinued from the trial. For delays $\geq 2$ weeks but $\leq 3$ weeks, a dose reduction to $375\text{mg/m}^2$ was instituted. Any further delays $\geq 14$ days at this dose resulted in discontinuation from the trial.

For cardiac toxicities: any new $\geq$ grade 3 occurrence of sinus tachycardia or atrial dysrhythmia, QTc prolongation $\geq 500$ msec with life-threatening signs or symptoms (eg. arrhythmia, CHF, hypotension or shock), or development of torsade de Pointes resulted in a treatment suspension to allow a full cardiac evaluation. If the event resolved, patients could resume study treatment at the reduced $375\text{mg/m}^2$ dose level. If unresolved, patients were removed from the trial. For confirmed LVEF decrease to $\leq 40\%$ or ventricular arrhythmia (VT or VF) $\geq 3$ beats in a row, patients were discontinued from trial.

Tumor response was assessed via CT or MRI scans every 2 cycles; bone scans every 4 cycles. Response was defined using RECIST criteria\textsuperscript{19}. All patients with PR or CR were required to have confirmation of response performed $\geq 4$ weeks after the criteria for response were first met. In the case of stable disease, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks. The Best Overall Response was defined as the best response recorded from the start of treatment until disease progression or withdrawal from study. All cases of radiographic response were re-analyzed by independent radiologists through RadPharm.

Statistical Analysis
A Simon’s two-stage design methodology was used based upon testing the null hypothesis and alternative hypotheses of $\leq 5\%$ versus $\geq 20\%$. The associated power was 80% and significance level was 10%. The analysis was planned this way for evaluable patients only. Patients were considered non-evaluable for efficacy if they: (1) withdrew having received two or fewer infusions of tanespimycin without radiologic or clinical evidence of progression; (2) violated clinically significant inclusion/exclusion criteria of the protocol. Confirmed objective response rate, best tumor response rate, and the associated 80% and 90% Clopper-Pearson confidence intervals were computed. Kaplan-Meier estimates of duration of response and PFS with their confidence limits were also calculated with 90% two-sided confidence.

As part of the two-stage design, an interim analysis of response rate was done after the first 9 evaluable patients were accrued with a provision to stop the trial if no responses were observed in this group. Otherwise, accrual was planned for 24 evaluable patients.

RESULTS

Patient Characteristics
Thirty-one patients were enrolled with a median age of 53 years and a median KPS of 90%. Baseline patient characteristics are presented in Table 1. All patients had received one line of prior trastuzumab-based therapy, with the majority receiving this in the metastatic setting. Only three patients enrolled in the trial had progressed during or within 3 months of completing adjuvant. The majority of patients were receiving trastuzumab as part of their treatment for metastatic disease immediately prior to enrolling on the trial. Overall, the median number of prior chemotherapy regimens for metastatic breast cancer was 1 (range 0-5).

Efficacy
Of the 31 patients enrolled, 27 patients were evaluable for response based on protocol criteria; 4 patients were considered inevaluable/ineligible due to: non-compliance with protocol after one dose, withdrawal after one dose to resume care locally, withdrawal after one dose due to reaction to treatment, and treatment with greater than one line of prior trastuzumab based therapy. Of those evaluable, 6 patients had a confirmed partial response by independent review, for an objective overall response rate of 22% (Table 2). An additional 10 patients achieved stable disease as their best response, for a clinical benefit rate of 59%. The median duration of response was 147 days (range 109-203 days) and median progression free survival was 6 months (Figure 1a). Median overall survival was 17 months (Figure 1b). Results based on the two different formulations were similar (Table 3). Patients having a response to therapy on the Cremophor-based formulation maintained this response after cross-over to the suspension formulation. A waterfall plot (Figure 2) shows the overall clinical benefit observed.

Toxicity

All 31 patients were included for the safety analysis. Five patients withdrew from the study based on the following singly-occurring adverse events: grade 3 fatigue (was continuing with PR when she elected to withdraw), decline in EF (see below), depression (in SD when she withdrew), elevated liver enzymes after one dose (subsequently discovered to have rapid POD and wanted to have care locally), and an atypical reaction to therapy (grade 2 tremor and unresponsive to verbal stimuli). The most common side effects were: diarrhea, fatigue, nausea, headache and neuropathy; these were predominantly grade 1 or 2 and easily managed with pre-/supportive medications (Table 4). Grade 3 toxicities were minimal and there were no grade 4 toxicities. One patient developed an asymptomatic decline in left ventricular ejection fraction after 14 months on trial to 42% from a baseline of 60%. She was removed from the trial with stable disease. Because she had a previous similar decline in her EF with the combination of paclitaxel plus trastuzumab (also necessitating a suspension of her trastuzumab therapy – after which her cardiac function recovered), it was felt that the EF decline was not attributable to the study drug. There were no other cases of grade 2 or higher EF decline.
Additionally, there was no noted alopecia or significant bone marrow suppression. There were no treatment-limiting hypersensitivity reactions with the Cremophor-based formulation, however, one patient had an atypical reaction to the suspension formulation: a 67 yo man with a history of HTN, had a near-syncopal event one minute into his first infusion. The treatment was stopped and he recovered with no sequelae. He was successfully re-challenged with pre-medications but at the time of the subsequent infusion he developed tremors, dizziness and became verbally unresponsive. It was decided to discontinue further administration. Elevated transaminases were observed in some patients but in all cases were reversible with dose delays and dose reductions, or attributable to progression of disease in the liver.

DISCUSSION

The phase 2 data presented here confirm the anti-tumor activity of tanespimycin and validate Hsp90 as a therapeutic target for HER2-dependent breast cancer. These findings build upon the phase 1 results\textsuperscript{18} which documented the first objective RECIST responses for this HSP90 inhibitor in patients with HER2+ MBC. The current data reveal an overall response rate of 22% and clinical benefit rate of 59% for patients with HER2-positive MBC pre-treated and progressing on prior trastuzumab.

The rationale for the development of Hsp90 inhibitors was based on the identification of a wide spectrum of signaling oncoproteins that are degraded in their presence. They have, therefore, been called inhibitors of all of the major processes required for maintenance of the malignant phenotype, and thus are hypothesized to be active in a wide variety of cancers. Phase I trials with tanespimycin established a number of different schedules for administration, identified common dose limiting toxicities of reversible transaminitis, fatigue and diarrhea, and importantly, identified a number of tumor types where anti-cancer activity in the form of prolonged disease stabilization was achievable.\textsuperscript{20-25} Disappointingly, tumor-specific phase 2 studies in these cancer populations where
the target client proteins were known to be susceptible to HSP90 inhibition failed to show any complete or partial tumor responses beyond disease stabilization\textsuperscript{26-29}.

The lack of efficacy seen in these initial phase 2 studies of tanespimycin has largely been attributed to suboptimal inhibition of intended client proteins due most probably to insufficient dose of drug or infrequent schedule of administration, both of which are limited by treatment-related toxicities. In the phase 2 melanoma trial by Solit et al., evaluation of pre-and post-treatment tumor biopsies confirmed that there was incomplete degradation of B-Raf, in both wild type and mutated forms, when tanespimycin was given on a weekly schedule\textsuperscript{29}. A similar overall dose intensity of tanespimycin was delivered in the renal and prostate phase 2 studies although tumor biopsies were not obtained to evaluate the precise pharmacodynamic effects\textsuperscript{27, 28}.

Preclinical studies have suggested that client proteins rebound within 24-72 hours and that more frequent administration of therapeutic doses of HSP90 inhibitors is required to induce significant anti-tumor effects\textsuperscript{30}. Clinically, however, frequent dosing schedules have been prohibitively toxic in patients. It has therefore been postulated that only tumors driven by client proteins that are hypersensitive to HSP90 inhibition will be susceptible to the effects of these inhibitors at the currently deliverable doses and schedules. In this regard, HER2 has been demonstrated to be one of the most sensitive target proteins of HSP90 inhibition and we believe that the effectiveness noted in our current trial, unlike the other phase 2 studies, is due to the potent degradation of this target protein by tanespimycin at the weekly dose and schedule employed. It follows that up to this point, HER2 + breast cancer is the only solid tumor where RECIST responses to tanespimycin have been observed.

To overcome these toxicity-based constraints of tanespimycin, there have been significant efforts to develop novel inhibitors with improved pharmacologic and safety profiles. Second generation inhibitors, both geldanamycin-based (such as 17-DMAG, and IPI-504)\textsuperscript{31,32} and novel, synthetic non-ansamycin HSP90 inhibitors (such as BIIB021, SNX-5422, STA-9090, and NVP-AUY922)\textsuperscript{33-37} have entered into clinical testing. These
latter compounds are of particular interest as they have the potential for more frequent administration and increased maximum dose due to the availability of oral formulations and lack of significant hepatotoxicity which has hindered dose escalation with geldanamycin-based agents. With the advantage of a greater therapeutic index, these compounds have early evidence of activity in diverse tumor types including non-small cell lung cancer, leukemia, rectal cancer and melanoma and may herald an expanded role for HSP90 inhibition in cancer therapeutics.

Recent studies suggest that the continuation of trastuzumab beyond progression can be beneficial. We recognize that all patients in our study had previously progressed on trastuzumab and the role that continuing this antibody played in mediating the antitumor activity seen with the combination cannot be ascertained without a randomized trial. In preclinical models, trastuzumab is a modest inhibitor of HER2 signaling compared to 17-AAG but has a much longer half-life. It is possible that the combination of weak prolonged inhibition of signaling by trastuzumab and stronger shorter-lived inhibition of the expression of HER2 by tanespimycin combine to more effectively inhibit this pathway. Indeed in a BT474 HER2+ xenograft model, the combination of these two drugs together produces a superior anti-tumor effect compared to either drug given alone.

In addition, the observation of retained anti-tumor activity for HER2-targeted therapies, including trastuzumab, in the face of progression on trastuzumab, not only suggests continued dependence on this signaling by this receptor but also raises questions about the meaning and mechanism of such resistance. Emerging data suggests that a number of factors may be operational in the development of trastuzumab resistance including: expression of a truncated (P95) fragment of HER2 that lacks the trastuzumab-binding epitope, activation of other receptor tyrosine kinases including IGF-1 receptor, mutational activation of PI3K signaling due to PTEN loss or direct activating PI3K/AKT mutations. While trastuzumab may be too weak an antagonist to sufficiently diminish signaling in all cases, the multi-oncoprotein inhibition caused by Hsp90 inhibitors alone or in combination may be able to reverse or overcome this resistance. Of particular note,
Chandarlapaty et al. have identified that P95HER2 is an Hsp90 client and is degraded by Hsp90 inhibitors. Furthermore, trastuzumab-resistant models with high levels of p95HER2 are sensitive to Hsp90 inhibition and with chronic administration there is sustained loss of full length HER2 and p95-HER2 expression and inhibition of AKT activation, together with induction of apoptosis and complete inhibition of tumor growth.

In conclusion, this trial is the first phase 2 study to definitively show RECIST-defined responses for tanespimycin in solid tumors. The combination of tanespimycin plus trastuzumab in patients with HER2+ MBC previously progressing on trastuzumab is well tolerated and active. Moreover, these results are consistent with those seen using other novel HER2 targeting therapies in development including Trastuzumab-MCC-DM1, pertuzumab, and neratinib, among others. Given the unique mechanism of action of tanespimycin, the potential for novel combinations with this agent remains to be explored. While our findings support the use of HSP90 inhibitors to overcome or delay the initiation of resistance to trastuzumab, the development of tanespimycin as a cancer therapy has been suspended by the sponsor for non-clinical reasons. It remains to be seen whether the next generation of HSP90 inhibitors will produce similar results. While they appear to have some efficacy across a broader spectrum of tumor types, the safety profile and tolerability of these second generation drugs is yet to be fully established.
ACKNOWLEDGEMENTS:

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REFERENCES:


42. Electronic Press Release:
<table>
<thead>
<tr>
<th>Table 1. Patient Demographics (n=31)</th>
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<tr>
<td>Median age, years (range)</td>
</tr>
<tr>
<td>Gender, n</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>Median KPS, % (range)</td>
</tr>
<tr>
<td>Prior chemotherapy regimens for MBC:</td>
</tr>
<tr>
<td>median</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
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<tr>
<td>5</td>
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<tr>
<td>Prior trastuzumab therapy, n (%)</td>
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<tr>
<td>Adjuvant/Neoadjuvant</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; line MBC</td>
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<td>2&lt;sup&gt;nd&lt;/sup&gt; line MBC</td>
</tr>
<tr>
<td>≥3&lt;sup&gt;rd&lt;/sup&gt; line MBC</td>
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<tr>
<td>*Trastuzumab ongoing at time of study entry, n (%)</td>
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<tr>
<td>Tanespimycin formulation, n (%)</td>
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<tr>
<td>Cremophor</td>
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<tr>
<td>Cross-over from Cremophor to Suspension</td>
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<tr>
<td>Suspension</td>
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* includes one patient progressing within 3 months of last dose of adjuvant trastuzumab
Table 2. Efficacy Results

<table>
<thead>
<tr>
<th>Best Overall Tumor Response, n (%)</th>
<th>N=27</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Complete Responses</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Partial responses</td>
<td>6 (22%)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>10 (37%)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>11 (41%)</td>
<td></td>
</tr>
<tr>
<td>Response Rate</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Clinical benefit (CR + PR + SD)</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>Median progression-free survival</td>
<td>6 months</td>
<td>4 - 9</td>
</tr>
<tr>
<td>Median overall survival</td>
<td>17 months</td>
<td>16 - 28</td>
</tr>
<tr>
<td>Median duration of response</td>
<td>147 days (range: 109-203 days)</td>
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</table>
Table 3. Overall Response: Cremophor vs. Suspension Formulation

<table>
<thead>
<tr>
<th></th>
<th>Enrolled</th>
<th>Evaluable</th>
<th>Responses</th>
<th>Overall Clinical Benefit</th>
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</thead>
<tbody>
<tr>
<td><strong>Cremophor</strong></td>
<td>21&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18</td>
<td>3 PR (17%)</td>
<td>10 (56%)</td>
</tr>
<tr>
<td><strong>Suspension</strong></td>
<td>10</td>
<td>9</td>
<td>3 PR (33%)</td>
<td>6 (67%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>31</td>
<td>27</td>
<td>6 PR (22%)</td>
<td>16 (59%)</td>
</tr>
</tbody>
</table>

<sup>a</sup>4 patients (2 PRs, 2 SD) crossed over to Suspension; no change in response
Table 4. Most Common Adverse Events Observed in ≥20% of Patients

<table>
<thead>
<tr>
<th></th>
<th>All (N=31)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
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<tbody>
<tr>
<td>Diarrhea</td>
<td>25 (81%)</td>
<td>21 (68%)</td>
<td>3 (10%)</td>
<td>1 (3%)</td>
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<tr>
<td>Fatigue</td>
<td>24 (77%)</td>
<td>13 (42%)</td>
<td>9 (29%)</td>
<td>2 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (52%)</td>
<td>12 (39%)</td>
<td>3 (10%)</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (52%)</td>
<td>13 (42%)</td>
<td>3 (10%)</td>
<td>2 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>15 (48%)</td>
<td>14 (45%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>↑AST/ALT</td>
<td>11 (35%)</td>
<td>3 (10%)</td>
<td>5 (16%)</td>
<td>3 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10 (32%)</td>
<td>10 (32%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (29%)</td>
<td>6 (19%)</td>
<td>2 (7%)</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>8 (26%)</td>
<td>8 (26%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8 (26%)</td>
<td>5 (16%)</td>
<td>3 (10%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>7 (23%)</td>
<td>6 (19%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (23%)</td>
<td>4 (13%)</td>
<td>3 (10%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>7 (23%)</td>
<td>5 (16%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>0</td>
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Figure 1a. Progression-Free Survival with Pointwise 95% CI Intervals (dotted lines)

N=31
Median PFS = 6 months, 95% CI (4 – 9)
Figure 1b. Overall Survival with Pointwise 95% CI Intervals (dotted lines)

N=31

Median OS = 17 months, 95% CI (16–28)
Figure 2. Best response in target lesions ** (%)

**not available for 5 patients (4 inevaluable; 1 with clinical POD)

- pr = partial response
- sd = stable disease
- pd = progressive disease
HSP90 Inhibition is Effective in Breast Cancer: A Phase 2 Trial of Tanespimycin (17AAG) plus Trastuzumab in Patients with HER2-Positive Metastatic Breast Cancer Progressing on Trastuzumab

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