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## Phase II Trial of Gemcitabine and Tanespimycin (17AAG) in Metastatic Pancreatic Cancer: A Mayo Clinic Phase II Consortium Study

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### Abstract

**Objectives**—Heat Shock Protein 90 (HSP90) is a molecular chaperone that stabilizes many oncogenic proteins. HSP90 inhibitors may sensitize tumors to cytotoxic agents by causing client protein degradation. Gemcitabine, which has modest activity in pancreas cancer, activates Chk1, a client protein of HSP90. This phase II trial was designed to determine whether 17AAG could enhance the clinical activity of gemcitabine through degradation of Chk1 in patients with stage IV pancreatic cancer.

**Methods**—A multicenter, prospective study combining gemcitabine and 17AAG enrolled patients with stage IV pancreatic adenocarcinoma, adequate liver and kidney function, ECOG performance status 0-2, and no prior chemotherapy for metastatic disease. The primary goal was to achieve a 60% overall survival at six months. Sixty-six patients were planned for accrual, with an interim analysis after 25 patients enrolled. Results: After a futility analysis to achieve the endpoint, accrual was halted with 21 patients enrolled. No complete or partial responses were seen. 40% of patients were alive at 6 months. Median overall survival was 5.4 months. Tolerability was moderate, with 65% of patients having grade 3 adverse events (AE), and 15% having grade 4 events.

**Conclusions**—The lack of clinical activity suggests that targeting Chk1 by inhibiting HSP90 is not important in pancreatic cancer sensitivity to gemcitabine alone. Further studies of HSP90 targeted agents with gemcitabine alone are not warranted.

## Keywords

HSP90 inhibitor; 17AAG; gemcitabine; Chk1; pancreatic cancer; phase II

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## Introduction

Pancreas cancer remains a highly lethal malignancy with little improvement in survival gained from various therapies over the past half-century [1]. For instance, gemcitabine, a pyrimidine nucleoside analog that induces G1/S cell cycle arrest via increased Chk1 expression, as monotherapy for pancreatic cancer has modest activity [2]. As evidenced by its successful combination with nab-paclitaxel [3], gemcitabine could be a more effective drug if further synergistic combinations were found.

Heat shock protein 90 (HSP90) is a key chaperone protein responsible for stabilizing and maintaining the activity of multiple client proteins, such as Chk1, akt, mutant p53, Cdk4, and erbB2, that are potentially involved in the cell cycle dysregulation and results in pancreatic carcinogenesis, [4-10]. 17-N-Allylamino-17-demethoxygeldanamycin (Tanespimycin/17AAG) is a geldanamycin-analog HSP90 inhibitor that leads to increased ubiquitin-mediated degradation of its client proteins. Gemcitabine inhibits DNA synthesis leading to premature chain termination during replication. This leads to activation of Chk1 and subsequent cell-cycle arrest, which can prevent cell death and increase survival [11]. Chk1 is a serine-threonine kinase that functions to induce cell cycle arrest at S-phase in response to DNA damage [12]. Arlander et al. [12] demonstrated that 17AAG targeting of HSP90 led to Chk1 degradation, thus enhancing the cytotoxicity of gemcitabine. In view of the 17AAG and gemcitabine synergy demonstrated in vitro [12], the clinical activity of the combination in patients with metastatic pancreatic cancer was evaluated. Previously we found that the maximally tolerated doses of gemcitabine and tanespimycin on a 21 day cycle were 750 mg/m<sup>2</sup> on days 1 and 8 and 154 mg/m<sup>2</sup> on days 2 and 9 respectively [13]. We report the results of a phase II multicenter trial of 17AAG and gemcitabine using these doses and schedule of administration.

## Methods

### Patient Selection and Characteristics

Patients were required to have histologically or cytologically confirmed metastatic pancreatic adenocarcinoma, were ≥ 18 years old, had a life expectancy of ≥ 12 weeks, ECOG performance score of 0, 1, or 2, absolute neutrophil count > 1500, platelet count > 100,000, total bilirubin within institutional upper limit of normal (ULN), AST ≤ 2.5× ULN, alkaline phosphatase ≤ 2× ULN (unless liver metastases present when up to 5× ULN), and creatinine within normal range. Patients had to be able and willing to sign and understand written consent, and to use adequate birth control methods if of reproductive age.

Patients using concurrent chemotherapy, having a history of allergic reactions to gemcitabine or 17AAG, having uncontrolled intercurrent illness, having prior radiation to the heart, being predisposed to cardiac arrhythmias or heart failure were excluded. No prior therapy for metastatic disease was allowed. Adjuvant therapy or therapy for locally advanced disease was allowed if greater than three months prior to enrollment. Prior radiation must have been completed three weeks prior to registration.

## Trial Design

Eligible patients were given combination 17AAG (154 mg/m<sup>2</sup>, National Cancer Institute Investigational Drug Branch, Bethesda, MD) and gemcitabine (750 mg/m<sup>2</sup>) over 21 day cycles. All patients received gemcitabine on days 1 and 8 with 17AAG on days 2 and 9. Treatment was continued until evidence of disease progression, unacceptable adverse events, development of a significant comorbid condition, or patient withdrawal occurred.

The primary outcome was survival at six months, with secondary endpoints of overall survival, progression free survival, response rate, and toxicity. When noting no responses, a futility analysis was performed after accrual of 20 patients.

## Statistical Methods

Historically, the 6-month survival for patients treated with gemcitabine alone is approximately 46% [2]; therefore, improving the survival rate to 60% or more was deemed to be of clinical interest and considered sufficiently promising to explore further.

All patients who met the eligibility criteria, signed a consent form, and began treatment were considered evaluable for the primary endpoint. This study design had a 90% probability of concluding that the regimen was promising if the true success rate was 60%, at a 5% level of significance. Per study design, an interim analysis was to be performed after the first 25 evaluable patients entered the trial. If at least 12 patients lived for 6 months or longer, the study would then proceed to the full accrual of 66 evaluable patients. At the final analysis, if 33 or more patients (50%) lived at least 6 months, this would be considered adequate evidence of promising activity, and would warrant further testing of this regimen in subsequent studies. A confidence interval for the 6-month survival rate was calculated using the exact binomial method. After only 21 patients were enrolled, a futility analysis was undertaken and, as the endpoint could not be reached, the trial was summarily closed.

Secondary endpoints included adverse events, the confirmed response rate, progression-free survival, and overall survival. Adverse events were summarized in a tabular manner as the maximum grade for a given type of event for each patient. The commonly occurring grade 3+ adverse events are also reported. Kaplan-Meier methodology [14] was used to describe the distributions of progression-free and overall survival.

## Results

### Baseline Characteristics

Between May of 2008 and September of 2010, 21 patients were enrolled from the Mayo Clinic and Washington University in St. Louis and the characteristics are summarized in

Table 1. Of these 21 patients, 20 were evaluable for analysis (one patient withdrew prior to receiving any treatment). The median age was 61.5 years (range: 51-81), the majority of patients were men (55%), nearly all had an ECOG PS of 0 or 1 (95%), and most did not have any prior adjuvant therapy.

### Outcome measures

Of the 20 patients evaluable for the outcome measures of survival, progression-free survival, and response (Table 2), all have died and 16 (80%) had a documented disease progression prior to expiration. Eight of the 20 patients (40%) survived at least six months (95% CI: 19% to 64%). After 21 accruals, there was a <10% probability that the goal of improved six-month survival rate could be achieved with only five patients left to accrue. Given the 40% six-month survival rate in the first 20 patients, the trial was concluded early.

The median survival (Table 2; Figure 1A) was 5.4 months (95% CI: 3.1 to 7.7 months) and the median progression-free survival (Table 2; Figure 1B) was 2.6 months (95% CI: 1.4 to 4.0 months). There were no confirmed responses to 17AAG/gemcitabine therapy, although ten patients had a best clinical response of stable disease.

### Adverse Events

Twenty patients were evaluable for adverse events (AE). Across all patients with adverse events at least “possibly” related to therapy, 13 (65%) experienced at least one grade 3 or worse AE, and two patients had a grade 4 AE (Table 3): one with grade 4 neutropenia and one with grade 4 lymphopenia (possibly related to treatment). No patients experienced a grade 5 AE. Commonly occurring Grade 3 adverse events included: nausea (15%), vomiting (15%), dehydration (10%), constipation (10%), anorexia (10%), lymphopenia (10%), and leukopenia (10%).

Of the 20 patients receiving treatment, 15 (75%) discontinued early due to disease progression, and five (25%) refused further treatment. A median of two cycles of therapy were given (range: 1- 8). All patients received the full dose of gemcitabine and 17AAG during cycle 1. From cycles 2-6, the percentage of patients receiving the full dose varied from 33% to 68% for gemcitabine and 25% to 60% for 17AAG.

### Discussion

This phase II multicenter study of gemcitabine chemotherapy in combination with 17AAG, an HSP90 inhibitor, unfortunately did not result in significantly increased six-month, overall, or progression-free survival over expected in an interim analysis of 20 patients with metastatic pancreas adenocarcinoma. This result is consistent with studies of 17AAG in other malignancies, including acute leukemia and ovarian cancer [15,16].

Preclinical studies showed that, while 17AAG appears to decrease levels of Chk1 leading to an absence of S-phase checkpoint inhibition and synergistic cytotoxicity with gemcitabine in a dose-dependent manner, clinical trials have not borne out similar results for 17AAG combinations [15,16]. This could indicate that Chk1 is a clinically relevant marker, but when proteins such as akt, Chk1, and Raf have been isolated from patients' mononuclear cells and

densitometrically assessed, there has often been only modest decreases in expression and this effect is transient, suggesting that targets are not affected long enough to see clinical benefit. Additionally, Chk1 may not be the most important mechanism of resistance. If degradation, nuclear transport, or other activation processes play a larger role in limiting gemcitabine activity, then HSP90 inhibition would play a lesser role in improving treatment efficacy. Another potential explanation for the lack of clinical response in this combination therapy is the activity of heat shock factor 1 (HSF1), a transcription factor activated during the heat shock response and when HSP90 interacts with the parent drug of 17AAG, geldanamycin [17-21]. HSF<sup>-/-</sup> knockout mice show increased 17AAG inhibition of HSP90 activity compared to normal mice [22]. As the gemcitabine/17AAG combination does not block HSF activity, there may be attenuation of its clinical benefit via the HSF1-induced protective mechanism.

Additional limitations in the efficacy of 17AAG in the clinic are secondary to the drug's toxicity in this combination. In our study, the majority of patients experienced grade 3 or higher adverse events. While phase I data suggest that the drug is well tolerated in monotherapy, even at higher dose levels than used in this trial [23,13,16], only one was carried out in combination with gemcitabine which showed similar tolerance to this regimen. As a result, the doses of both gemcitabine and 17AAG had to be dose reduced compared to the maximally tolerated doses in monotherapy. This could have conceivably led to the lower than expected response to the combination. While the goal of combined therapy was synergistic cytotoxicity, this was not achieved in this trial. There is certainly still the opportunity; however, that newer, less toxic HSP90 inhibitors [24] may be more effective if toxicity can be limited and doses or target effects maximized [25-27].

In conclusion, this phase II clinical trial supports the hypothesis that 17AAG can be administered in combination with gemcitabine in patients with pancreatic adenocarcinoma; however, there is a steep increase in toxicity over what would be expected for gemcitabine alone without any evident benefit in outcomes. Whether the failure is a result of this particular HSP90 inhibitor's limitations or of the approach as a whole has yet to be determined. With our finding, other HSP90 inhibitory agents in treatment of pancreatic cancer should be pursued with caution.

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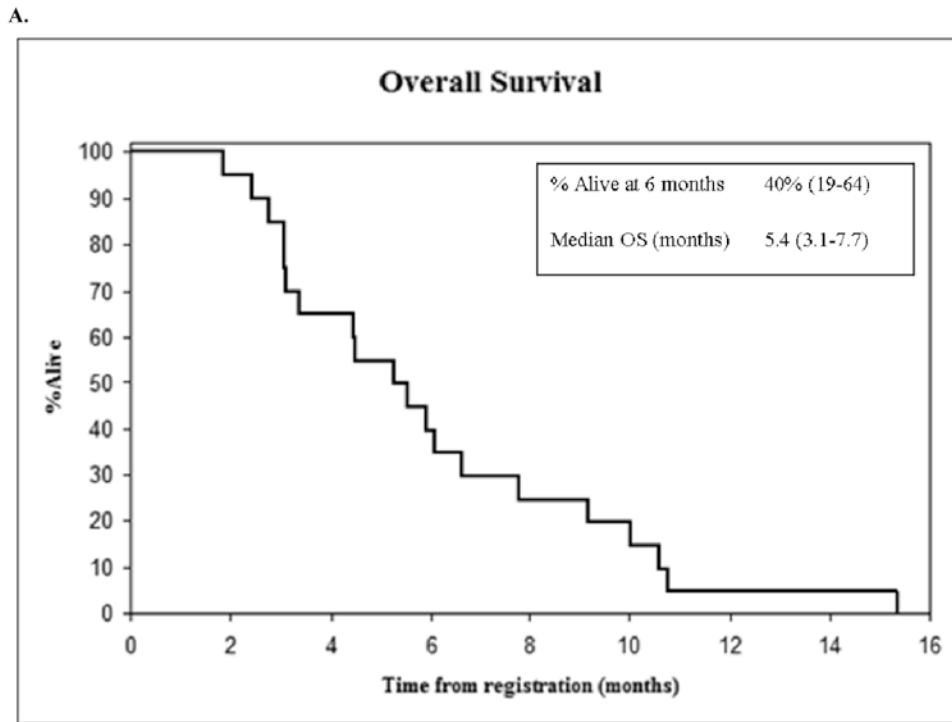
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B.

Figure 1a

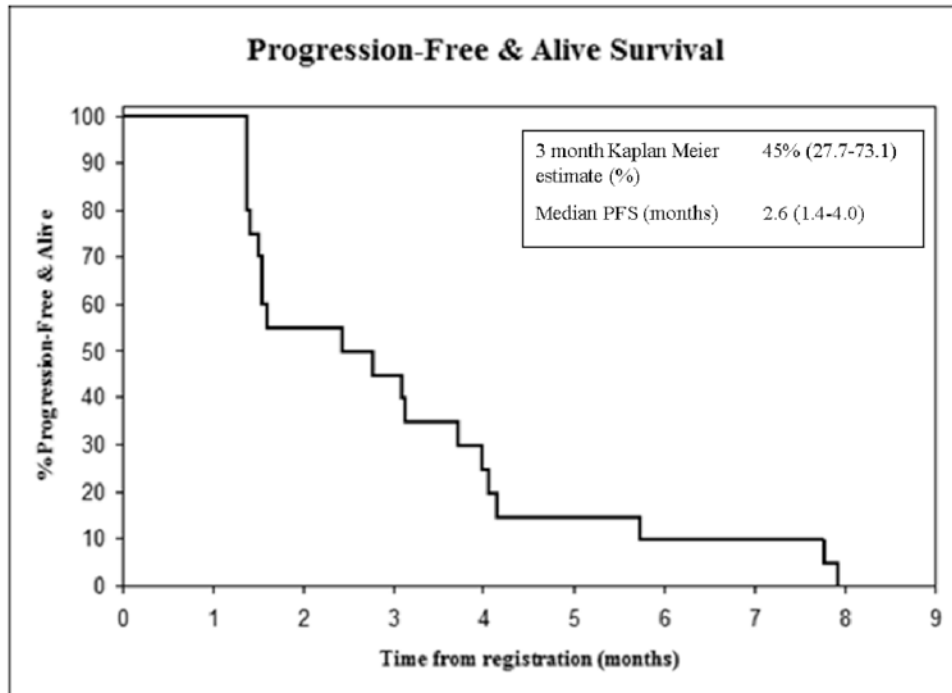


Figure 1b

Figure 1.



(A) Overall survival and (B) progression free survival of 20 evaluable patients by Kaplan-Meier estimation.

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**Table 1**

Patient baseline demographics.

	<b>Total (N=20)</b>
<b>Age</b>	
Median	61.5
Range	(51.0-81.0)
<b>Gender</b>	
Female	9 (45.0%)
Male	11 (55.0%)
<b>Ascites Present</b>	
Yes	2 (10.0%)
No	18 (90.0%)
<b>Performance Score</b>	
0	10 (50.0%)
1	9 (45.0%)
2	1 (5.0%)
<b>Race</b>	
White	19 (95.0%)
Black or African American	1 (5.0%)
<b>Prior Surgery</b>	
Yes	8 (40.0%)
No	12 (60.0%)
<b>Previous Radiation Therapy</b>	
Yes	2 (10.0%)
No	18 (90.0%)
<b>Prior Therapy</b>	
Yes	2 (10.0%)
No	18 (90.0%)

**Table 2**

Patient disease responses with 17AAG and gemcitabine therapy. Objective responses by RECIST criteria are reported.

Clinical Outcome	Total (%) <sup>*</sup>
<b>Objective Response</b>	
Complete Response	0 (0)
Partial Response	0 (0)
Stable Disease	10 (53)
Progression	9 (47)

\* One patient did not have a post-baseline tumor assessment and was excluded.

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**Table 3**

Commonly Occurring Maximum Severity (Grade 3/4) Adverse Events across all cycles of treatment (at least “possibly” attributed to therapy). There were no treatment related deaths.

NCI CTC CATEGORY *	Frequency (%) (N=20)	
	Grade 3	Grade 4
<b>Hematologic</b>		
Lymphopenia	2 (10)	1 (5)
Leukopenia	2 (10)	0 (0)
Neutropenia	1 (5)	1 (5)
<b>GI</b>		
Nausea	3 (15)	0 (0)
Vomiting	3 (15)	0 (0)
Anorexia	2 (10)	0 (0)
Constipation	2 (10)	0 (0)
Dehydration	2 (10)	0 (0)
Dyspepsia	1 (5)	0 (0)
Increased alanine aminotransferase	1 (5)	0 (0)
Increased alkaline phosphatase	1 (5)	0 (0)
<b>Miscellaneous</b>		
Thrombosis	1 (5)	0 (0)
Peripheral edema	1 (5)	0 (0)
Asthenia	1 (5)	0 (0)
Abdominal pain	1 (5)	0 (0)
Fatigue	1 (5)	0 (0)
Rash	1 (5)	0 (0)
Syncope	1 (5)	0 (0)

\* NCI CTC Version 3.0