Overview

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Title: Phase II Study of Sequential Gemcitabine Followed by Docetaxel for Recurrent Ewing Sarcoma, Osteosarcoma, or Unresectable or Locally Recurrent Chondrosarcoma: Results of Sarcoma Alliance for Research Through Collaboration Study 003

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Sponsor(s): Sarcoma Alliance Through Collaboration

Principal Investigator: Elizabeth Fox

IRB Approved: Yes

Disclosures:
Elizabeth Fox: Alternative Use: Neither gemcitabine or docetaxel are labeled for used in sarcomas. In this study, the dosing and schedule did not differ significantly from FDA approved doses in other cancers
Shreyaskumar Patel: Novartis (H), Johnson and Johnson, PharmaMar (RF)
Scott Schuetze: Alternative Use: The use of gemcitabine and docetaxel in treatment of bone sarcomas is unlabeled use of the chemotherapy; One-time consultant in 2008 for Lilly (maker of gemcitabine) for discussion of an unrelated product (CA)
David Harmon: Alternative Use: These drugs and this combination are not FDA approved for these diseases
Rashmi Chugh: Alternative Use: This is a clinical trial of gemcitabine/docetaxel in bone sarcomas- and that combination is not yet FDA approved for this set of diseases
Jay K Wathen, Sant Chawla, Denise Reinke, Lee Helman, Robert Benjamin: None

Author Summary: Abstract and Brief Discussion

Background
Gemcitabine and docetaxel have a broad spectrum of clinical activity in patients with carcinoma. The Sarcoma Alliance for Research Through Collaboration conducted a phase II trial of gemcitabine in combination with docetaxel in children and adults with recurrent Ewing sarcoma (EWS), osteosarcoma (OS), or unresectable or recurrent chondrosarcoma. The primary objective was to determine the objective response rate using Response Evaluation Criteria in Solid Tumors (RECIST).

Methods
Gemcitabine (675 mg/m^2 i.v. over 90 minutes on days 1 and 8) was administered in combination with docetaxel (75 mg/m^2 i.v. over 1 hour on day 8) every 21 days. All patients received filgrastim or pegfilgrastim. A Bayesian formulation was used to

determine the probability of achieving the target response rate in each subtype— 0.35 for EWS and OS or 0.20 for chondrosarcoma. If the probability of achieving the target response rate was <0.05, the combination was considered inactive. Toxicity was graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

Results

Fifty-three eligible patients were enrolled into three subtype groups—OS ($n=14$), EWS ($n=14$), and chondrosarcoma ($n=25$). Toxicities included neutropenia, thrombocytopenia, fatigue, dyspnea, bronchospasm, edema, neuropathy, and liver function abnormalities. Dose modification for toxicity was required for eight patients during cycle 1 and 16 patients in subsequent cycles. Seven patients withdrew from therapy due to toxicity. No complete responses were observed. Partial responses were observed in OS ($n=1$), EWS ($n=2$), and chondrosarcoma ($n=2$) patients.

Conclusions

Gemcitabine in combination with docetaxel was associated with a probability of reaching the target 35% response rate of $<5\%$ in OS patients and 5.6% in EWS patients; the probability of reaching a 20% response rate in chondrosarcoma patients was 14%.

Trial Information

Disease:	Sarcomas – Adult
Disease:	Pediatric cancer – Osteosarcoma
Disease:	Pediatric cancer – Ewings
Stage of disease / treatment:	Metastatic / Advanced
Prior Therapy:	2 prior regimens
Type of study – 1:	Phase II
Type of study – 2:	Single arm

Additional Details of Endpoints or Study Design:

Tumors were evaluated by RECIST at baseline and prior to cycle 3, 5, 7, 9, 13, 15 then prior to every 4th cycle of therapy.

Statistical Design: A Bayesian formulation was used to estimate the probability of achieving the target objective response rate in each subtype. Under a Bayesian formulation, the prior means reflect the targeted values (threshold interesting response rate) of 0.35 in Ewing and osteosarcoma subtypes and 0.20 in the chondrosarcoma subtype. At each evaluation, the patient's disease was categorized as R= CR/PR (complete or partial response), F = progressive disease or death (failure), or S (stable disease = neither R nor F). A patient with outcome R or F at any stage was scored as having that overall outcome, while a patient with outcome S was re-evaluated after subsequent cycles of therapy. A generalized logistic model assuming $pj,k = \exp(hj,k)/\{1+\exp(hR,k)+\exp(hF,k)\}$ for j=R or F, with $pS,k = 1/\{1+\exp(hR,k)+\exp(hF,k)\}$ was used. The overall probability of outcome j = R or F over 4 evaluations is given explicitly by $xj,4 = pj,1 + pS,1\,pj,2 + pS,1\,pS,2\,pj,3 + pS,1\,pS,2\,pS,3\,pj,4$. We assumed a .50 probability of S in each stage, with the stage effects assuming if a patient responded in 4 evaluations (prior to cycle 9), then the probabilities that it occurs in evaluation 1, 2, 3 or 4 were .70, .10, .05, .05, respectively.

Investigator's Assessment of Activity:	Inactive

Drug Information

Drug 1:

Generic/Working name:	Gemcitabine
Trade name:	N/A
Drug type:	Small molecule
Drug class:	Antimetabolite
Dose:	675 milligrams (mg) per squared meter (m^2)
Route:	IV
Schedule of Administration:	Over 90 minutes on days 1 and day 8 every 21 days

Drug 2:	
Generic/Working name:	Docetaxel
Trade name:	N/A
Drug type:	Small molecule
Drug class:	Microtubule-targeting agent
Dose:	75 milligrams (mg) per squared meter (m^2)
Route:	IV
Schedule of Administration:	Over 1 hour on day 8 every 21 days

Patient Characteristics

Number of patients, male:	33
Number of patients, female:	20
Stage:	Not Collected
Age:	Median (range): 37.7 (12.9–77.6)
Number of prior systemic therapies:	Median (range): 1 (0–3)
Performance Status:	ECOG: Not Collected
Other:	Between May 2005 and September 2009, 54 subjects were enrolled at 11 participating sites. One patient with chondrosarcoma was ineligible due to lack of measurable disease at enrollment. All patients have met criteria for discontinuation of protocol therapy.
Cancer Types or Histologic Subtypes	
Osteosarcoma	14
Ewings Sarcoma	14
Chondrosarcoma	25

Primary Assessment Method

Experimental Arm: Chondrosarcoma

Number of patients screened:	N/A
Number of patients enrolled:	26
Number of patients evaluable for toxicity:	25
Number of patients evaluated for efficacy:	25
Evaluation method:	RECIST 1.0
Response assessment CR:	0%
Response assessment PR:	8%
Response assessment SD:	56%
Response assessment PD:	36%
Response assessment other:	
(Median) duration assessments PFS:	N/A
(Median) duration assessments TTP:	N/A
(Median) duration assessments OS:	N/A
(Median) duration assessments response duration:	N/A
(Median) duration assessments duration of treatment:	12 weeks

Experimental Arm: Ewings Sarcoma

Number of patients screened:	N/A
Number of patients enrolled:	14
Number of patients evaluable for toxicity:	14
Number of patients evaluated for efficacy:	14
Evaluation method:	RECIST 1.0
Response assessment CR:	0%
Response assessment PR:	14%
Response assessment SD:	43%
Response assessment PD:	43%
Response assessment other:	
(Median) duration assessments PFS:	N/A
(Median) duration assessments TTP:	N/A
(Median) duration assessments OS:	N/A
(Median) duration assessments response duration:	N/A
(Median) duration assessments duration of treatment:	6 weeks

Experimental Arm: Osteosarcoma

Number of patients screened:	N/A
Number of patients enrolled:	14
Number of patients evaluable for toxicity:	14
Number of patients evaluated for efficacy:	14
Evaluation method:	RECIST 1.0
Response assessment CR:	0%
Response assessment PR:	7%
Response assessment SD:	21%
Response assessment PD:	72%
Response assessment other:	
(Median) duration assessments PFS:	N/A
(Median) duration assessments TTP:	N/A
(Median) duration assessments OS:	N/A
(Median) duration assessments response duration:	N/A
(Median) duration assessments duration of treatment:	6 weeks

Experimental Arm: Total Patient Population

Number of patients screened:	N/A
Number of patients enrolled:	53
Number of patients evaluable for toxicity:	53
Number of patients evaluated for efficacy:	53
Evaluation method:	RECIST 1.0
Response assessment CR:	0%
Response assessment PR:	9%
Response assessment SD:	49%
Response assessment PD:	42%
Response assessment other:	
(Median) duration assessments PFS:	N/A

(Median) duration assessments TTP:	N/A
(Median) duration assessments OS:	N/A
(Median) duration assessments response duration:	N/A
(Median) duration assessments duration of treatment:	9 weeks

Adverse Events

Name	*NC/NA	1	2	3	4	5	All Grades

*No Change from Baseline/No Adverse Event

Serious Adverse Events

Name	Grade	Attribution
Infection/Cellulitis	3	Unrelated
Infection/Cellulitis	3	Probable
Pneumonitis	3	Possible
Pain/Back	3	Unrelated
Myositis/Radiation recall	3	Probable
Anemia requiring hospitalization	3	Possible
Disease progression/Death	5	Unrelated
Pericardial effusion	3	Probable
Cardiac tamponade	3	Unrelated
Infection/Pneumonia	3	Unrelated
Progressive disease	4	Unrelated
Hemoptysis	3	Unrelated
Pneumonitis/Pneumonia	3	Possible

Pharmacokinetics/Pharmacodynamics

N:	Not Collected
Cmax:	Not Collected
AUC:	Not Collected
Half-life:	Not Collected
Volume of distribution:	Not Collected
Clearance:	Not Collected
Notes:	Not Collected

Assessment, Analysis, and Discussion

Completion:	Study completed
Completed Study Assessment:	Inactive
Pharmacokinetics / Pharmacodynamics:	Correlative Endpoints Not Met
Investigator's analysis:	Inactive because results did not meet primary endpoint

Discussion

The Bayesian formulation permitted estimation of the probability of achieving the target response rate for each subtype after each response evaluation. By allowing multiple looks at the data, this design stopped the trial after considering the probability of achieving the target response rate and accrual rate. Because this design did not specify a rule for declaring the treatment as "active," a direct comparison with a standard two-stage phase II design is not appropriate. The decision to close the EWS and chondrosarcoma subtype arms was based, in part, on slow accrual and was supported by the low probability of achieving the target response rate. The rate of enrollment, rather than the statistical design, had a significant effect on the trial duration.

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Table

Table 1. Subject Characteristics.

	Osteosarcoma	Ewing Sarcoma	Chondro-sarcoma	Total
N	14	14	25	53
Female; Male	8:6	2:12	10:15	20:33
Median Age (years)	36.2	25.9	55.2	37.7
(Range)	(12.9–75.8)	(16.9–42.2)	(25.9–77.6)	(12.9–77.6)
Race/Ethnicity				
White	10	12	20	42
Black	2	0	1	3
Hispanic	1	2	4	1
Other	1	0	0	1
No. Prior chemotherapy regimens				
Median (range)	2 (1–3)	2 (1–3)	0 (0–2)	1 (0–3)
No. cycles gemcitabine + docetaxel				
Median (range)	2 (1–15)	2 (1–12)	4 (1–21)	3 (1–21)
Total cycles delivered	53	43	130	226
Best Response				
CR	0	0	0	
PR	1	2	2	
SD post Cycle 4	3	6	14	
SD post Cycle 8	0	0	2	
PD	13	12	21	