European Journal of Cancer (2012) 48, 547–563

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejconline.com

First-line treatment of metastatic or locally advanced unresectable soft tissue sarcomas with conatumumab in combination with doxorubicin or doxorubicin alone: A Phase I/II open-label and double-blind study

George D. Demetri [a,*], Axel Le Cesne [b], Sant P. Chawla [c], Thomas Brodowicz [d], Robert G. Maki [e], Bruce A. Bach [f], Dominic P. Smethurst [g], Sarah Bray [g], Yong-jiang Hei [f], Jean-Yves Blay [h]

[a] *Ludwig Center at Dana-Farber/Harvard Cancer Center, Boston, MA, USA*
[b] *Institut Gustave Roussy, Villejuif, France*
[c] *Sarcoma Oncology Center, Santa Monica, CA, USA*
[d] *Medical University Vienna—General Hospital, Vienna, Austria*
[e] *Mount Sinai School of Medicine, New York, NY, USA*
[f] *Amgen Inc., Thousand Oaks, CA, USA*
[g] *Amgen Ltd., Uxbridge, UK*
[h] *Centre Léon Bérard, Lyon, France*

Available online 11 January 2012

KEYWORDS
Conatumumab
Doxorubicin
Soft tissue sarcomas
Death receptor 5
TRAIL

Abstract *Background:* Conatumumab is a fully human monoclonal agonist antibody that binds to death receptor 5 and induces apoptosis in sensitive cells. This study evaluated the safety and efficacy of doxorubicin ± conatumumab as first-line systemic therapy for metastatic or locally advanced/unresectable soft-tissue sarcoma.
Methods: In Phase I, six patients received doxorubicin (75 mg/m^2) with conatumumab (15 mg/kg) every 3 weeks. In Phase II, patients were randomised (2:1) to receive doxorubicin with either double-blind conatumumab 15 mg/kg (conatumumab–doxorubicin; $n = 86$) or placebo (placebo–doxorubicin; $n = 42$). Patients who progressed on placebo–doxorubicin could receive open-label conatumumab monotherapy post-chemotherapy ($n = 21$).
Findings: The expected histopathologic subtypes (e.g. leiomyosarcoma, liposarcoma, others) were represented in this trial. No unexpected adverse events were noted in either Phase I or II. Median progression-free survival in Phase II was 5.6 and 6.4 months in the conatumumab–doxorubicin and placebo–doxorubicin arms, respectively (stratified HR: 1.00; $p = 0.973$), with more early progressions noted in the first 3.5 months in the conatumumab–doxorubicin arm. Median overall survival was not reached after 8.6 months

* *Corresponding author:* Address: Dana-Farber Cancer Institute, 450 Brookline Avenue, Dana 1212, Boston, MA 02215, USA. Tel.: +1 617 632 6563; fax: +1 617 632 3408.
E-mail address: gdemetri@partners.org (G.D. Demetri).

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2011.12.008

median follow-up in either arm. Common adverse events were nausea (conatumumab–doxorubicin: 66%; placebo–doxorubicin: 80%), alopecia (55%; 63%), fatigue (60%; 38%) and neutropenia (32%; 50%). Post-chemotherapy results were not notably improved by conatumumab dosing.

Interpretation: Addition of conatumumab to doxorubicin appeared to be safe but did not improve disease control in a heterogeneous unselected group of patients with soft tissue sarcomas. The results of this trial are very useful for estimating the outcomes of first-line therapy of sarcoma patients treated with standard doxorubicin.

Funding: This study was supported by Amgen Inc.

1. Introduction

Soft tissue sarcomas are a heterogeneous group of mesenchymal tumours, associated in 2010 with approximately 10,520 new cases and 3920 deaths in the United States.[1] Doxorubicin monotherapy is a standard treatment for metastatic or unresectable soft tissue sarcomas,[2] but is historically associated with median overall survival (OS) of only 1 year.[3–6] Adding other chemotherapeutic agents to doxorubicin has not demonstrated a clear advantage over doxorubicin monotherapy for OS,[5–7] but may improve treatment response and progression-free survival (PFS), particularly in selected, sensitive histologic subtypes of soft tissue sarcoma.[2]

Tumour necrosis factor-related apoptosis inducing ligand (TRAIL) is expressed by a variety of normal human tissues and transformed cells.[8,9] Binding to death receptor 4 (DR4) or death receptor 5 (DR5) can transduce an apoptotic signal to trigger cell death, particularly in transformed cells.[10,11]

Conatumumab is a fully human monoclonal agonist antibody that binds to DR5 and mimics the effect of endogenous TRAIL.[12] Conatumumab has antitumour activity in solid tumours and enhances activity of several cytotoxic chemotherapy agents.[13] In Phase I studies of patients with advanced solid tumours, conatumumab was well tolerated at doses up to 20 mg/kg every 2 weeks.[14,15] Objectives of this study were to identify, in Phase I, a dose of conatumumab that is safe and well tolerated when administered in combination with doxorubicin, and to look for a preliminary signal in Phase II whether the combination improves PFS in advanced soft tissue sarcomas compared with doxorubicin alone.

2. Methods

2.1. Study design

This study was conducted at 19 centres in the United States, Belgium, France, Austria and Netherlands (Appendix A). The first patient was dosed on 12th November 2007, the last patient was randomised on 12th November 2008, and the cutoff date for the efficacy and safety analyses was 8th May 2009. The data cutoff for the Phase II rollover was 3rd March 2010. Analyses of PFS and OS were repeated with follow-up data through 10th January 2011.

Limited run-in Phase I testing was performed to assess tolerability of the conatumumab–doxorubicin combination. Patients enroled in Phase I received doxorubicin 75 mg/m^2 and open-label conatumumab 15 mg/kg every 3 weeks.

This study also included a randomised, double-blind, placebo-controlled Phase II portion as well as an open-label post-chemotherapy 'rollover.' Patients in Phase II received doxorubicin 75 mg/m^2 in double-blind combination with either conatumumab 15 mg/kg (conatumumab–doxorubicin arm) or matching placebo (placebo–doxorubicin arm). Centralised randomisation (in a 2:1 ratio) was stratified by sarcoma histopathology (liposarcoma or leiomyosarcoma or other) and Eastern Cooperative Oncology Group (ECOG) Performance Status (0 or 1). Treatment was administered every 3 weeks for up to six cycles. Thereafter, patients received double-blind conatumumab 15 mg/kg or placebo monotherapy for up to 30 months until disease progression. Patients in the placebo–doxorubicin arm who had documented disease progression could enrol in the rollover portion to receive open-label conatumumab 15 mg/kg monotherapy every 3 weeks for up to 30 months.

2.2. Eligibility criteria

Key inclusion criteria were age $\geqslant$ 18 years, ECOG Performance Status of 0 or 1, and pathologically confirmed metastatic, locally advanced/unresectable or recurrent Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) Grade 2 or 3 soft tissue sarcoma with at least one measureable lesion per Response Evaluation Criteria in Solid Tumours (RECIST).[16]

Key exclusion criteria were any prior chemotherapy, radiotherapy to target lesion, uncontrolled CNS disease, concurrent other malignancy, infection requiring systemic anti-infective treatment within the prior 14 days, uncontrolled cardiovascular disease within the prior 12 months, left ventricular ejection fraction below the lower limit of normal, hepatitis or HIV, major surgery

within the prior 28 days, minor surgery within the prior 7 days, pregnancy and breast feeding. Patients with alveolar soft part sarcoma, clear cell sarcoma, chondrosarcoma, desmoid tumour, desmoplastic small round cell tumour, embryonal rhabdomyosarcoma, Ewing sarcoma/primitive neuroectodermal tumour, gastrointestinal stroma tumour, Kaposi sarcoma, mesothelioma, mixed mesodermal tumour, neuroblastoma or osteosarcoma were excluded. The protocol was approved by an institutional review board or independent ethics committee for each site. Written informed consent was obtained for each patient.

2.3. Statistical methods

The primary efficacy end-point in Phase II was PFS. Secondary efficacy end-points were objective response (complete or partial), time to response, duration of response, disease control rate (complete response, partial response or stable disease) and OS. Safety end-points were adverse events (AE), clinical laboratory parameters, antibodies to conatumumab and doxorubicin pharmacokinetics (at cycles 1 and 3). Patient-reported outcome measures included European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30 (functional states and symptom scales) and EuroQoL 5-Dimensions health utility questionnaire (EQ-5D) on day 1 of cycles 1, 2, 3 and 5 and every four cycles thereafter.

Assuming a median PFS of 3.34 months in the placebo–doxorubicin arm and a hazard ratio (HR) of 0.5, a total of 90 patients with a PFS event was required to achieve 90% power at a two-sided 5% significance level. A sample size of 120 patients was projected to result in 90 PFS events in approximately 19 months.

PFS was defined as time from randomisation to first observation of disease progression (by investigator report), death or censoring. If a patient's disease had not progressed and the patient was alive at time of analysis, PFS was censored at the last tumour evaluation date. PFS, OS and duration of response were evaluated with the Kaplan–Meier method and compared between treatment arms with log-rank test methods. The estimated HR for conatumumab treatment effect was calculated with a Cox model stratified by histologic type (leiomyosarcoma or liposarcoma/other). Kaplan–Meier analyses of PFS were repeated within histopathologic subgroups (leiomyosarcoma, liposarcoma, 'fibrohistiocytic' and malignant peripheral nerve sheath tumour [MPNST]). Objective response rates and PFS were also analysed within common genetic variations of FCGR3A that might influence FCGR3A affinity for immunoglobulin G (IgG)1 antibodies and clinical outcomes with conatumumab.

Data from the open-label Phase I and rollover portions were summarised descriptively.

2.4. Role of the funding source

The academic investigators and study sponsor collaborated independently in the study design, the collection, analysis and interpretation of data, the writing of the report and the decision to submit the paper for publication.

3. Results

3.1. Patient disposition

Of the six patients enroled in Phase I, three (50%) discontinued (two died from disease and one withdrew consent) early. In Phase II (Fig. 1), 150 patients were screened and 128 were randomised to the conatumumab–doxorubicin arm ($n = 86$) or placebo–doxorubicin arm ($n = 42$). Twenty-one patients in the placebo–doxorubicin arm rolled over to open-label conatumumab monotherapy upon disease progression. At the time of data cut-off, eight had died and 13 remained on study.

3.2. Patient characteristics

Patient characteristics for Phase I are summarised in Appendix B. Three (50%) patients had liposarcoma and one (17%) patient each had leiomyosarcoma, 'fibrohistiocytic' sarcoma and fibrosarcoma. In Phase II (Table 1), baseline characteristics generally were similar between treatment groups, but in the conatumumab–doxorubicin arm there was a lower incidence of MPNST (5%, 17%), a higher incidence of 'other sarcomas' (17%, 7%) and a lower incidence of only one target lesion site (35%, 52%). In the rollover (Appendix C), primary histologic types were leiomyosarcoma (38%), liposarcoma (19%), 'fibrohistiocytic' (10%) and other sarcoma (33%).

3.3. Efficacy

3.3.1. Primary efficacy variable (Phase II)

Median follow-up (i.e. censoring time) for PFS was 6.2 months. No significant difference ($p = 0.973$) in PFS time was observed between the conatumumab–doxorubicin arm (median: 5.6 months; 95% CI: 5.1, 6.9) and placebo–doxorubicin arm (median: 6.4 months; 95% CI: 5.3, 7.1) (Table 2). Stratified HR for the conatumumab treatment effect (95% CI) was 1.00 (0.64, 1.57).

A sensitivity analysis in which PFS was based on radiographic progression and death only (not clinical progression) showed no significant treatment effect (stratified HR: 1.05; 95% CI: 0.66, 1.67).

Kaplan–Meier analysis of PFS (Fig. 2A) revealed a higher percentage of early progressions in the first 3.5 months in the conatumumab–doxorubicin arm versus the placebo–doxorubicin arm (29%, 19%). In a

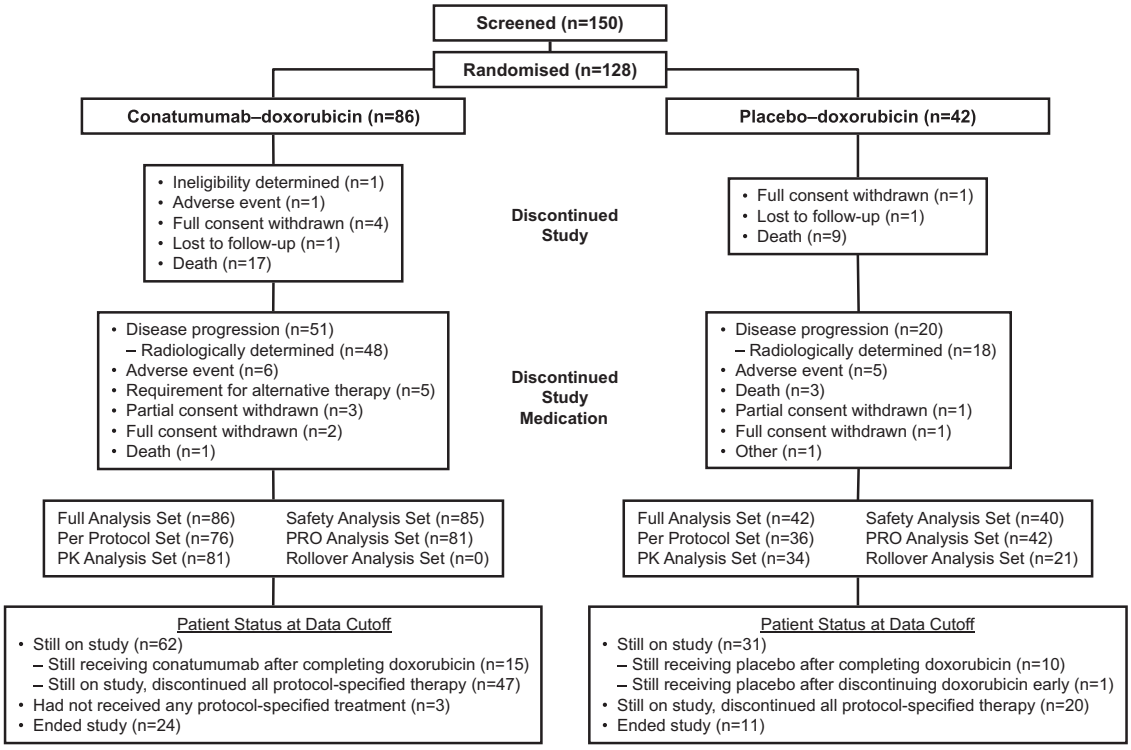

Fig. 1. Patient disposition (Phase II).

piecewise Cox analysis, unstratified HR (95% CI) was 1.73 (0.78, 3.84) up to 3.5 months and 0.73 (0.42, 1.26) after 3.5 months.

In univariate analyses (Appendix D), PFS was influenced significantly by histological FNCLCC grade, with an HR (95% CI) of 1.89 (1.19, 2.99) for Grade 3 versus Grade 2 ($p = 0.007$), but there was no evidence of a treatment-by-FNCLCC grade interaction ($p = 0.861$). PFS was also significantly different amongst patients with liposarcoma, leiomyosarcoma or other sarcoma ($p = 0.016$). Relative to patients with leiomyosarcoma, patients with liposarcoma had a longer PFS (HR: 0.62; 95% CI: 0.33, 1.18) and those with 'other sarcoma' diagnoses had a shorter PFS (HR: 1.55; 95% CI: 0.97, 2.48). However, based on the planned pooling strategy of leiomyosarcoma or liposarcoma/other, significance of histological subtype was no longer observed ($p = 0.580$) and there was no evidence of a treatment-by-histology interaction ($p = 0.853$). No other covariate was a significant prognostic factor for PFS and there were no significant treatment-by-covariate interactions.

Median PFS by histologic subtype was as follows (conatumumab–doxorubicin versus placebo–doxorubicin): leiomyosarcoma, 5.5 versus 7.0 months; liposarcoma, 6.6 versus 9.9 months; 'fibrohistiocytic,' 5.6 versus 6.3 months; MPNST, 3.9 versus 6.8 months. Plots for PFS by histologic subgroup are provided in Appendix E.

Re-analysis of PFS with additional follow-up data (Table 2) also found no significant difference ($p = 0.477$) between the conatumumab–doxorubicin arm (median: 5.6 months; 95% CI: 5.1, 6.7) and placebo–doxorubicin arm (median: 6.8 months; 95% CI: 5.3, 8.0). Stratified HR (95% CI) was 1.15 (0.78, 1.69) for the conatumumab treatment effect, including additional follow-up data.

3.3.2. Secondary efficacy variables (Phase II)

Median follow-up for OS in the original analysis was 8.6 months (Fig. 2B). There were 17 (20%) and nine (21%) deaths in the conatumumab–doxorubicin and placebo–doxorubicin arms, respectively—including death due to disease in 20% and 12% of patients, respectively—so median OS was not evaluable in either treatment arm. Conatumumab was not associated with improvement in other secondary efficacy analyses, including objective response, disease control rate, change in target lesion dimension, time to response or duration of response (Table 3). With additional follow-up, there were 56 (65%) and 26 (62%) deaths in the conatumumab–doxorubicin and placebo–doxorubicin arms, respectively, and median OS (95% CI) was 18.2 (14.7, 22.6) months and 21.6 (14.9, 27.5) months, respectively (Table 3 and Appendix F).

No notable difference between treatment arms was observed in analyses of objective response rate and PFS by FCGR3A genotype (Appendix G).

For measures of patient-reported outcomes, baseline EORTC QLQ C30 and EQ-5D scores were closely aligned between treatment groups for all assessments

Table 1
Baseline demographics and disease characteristics (Phase II).

	Conatumumab–doxorubicin ($n = 86$)		Placebo–doxorubicin ($n = 42$)	
	No.	%	No.	%
Sex, female	44	51	25	60
Race/ethnicity				
White or Caucasian	75	87	34	81
Black or African American	4	5	2	5
Hispanic or Latino	3	3	1	2
Asian	3	3	3	7
Native Hawaiian/Pacific Islander	1	1	0	0
Other	0	0	2	5
Age, years, median (range)	57.5 (23–88)		56.5 (32–82)	
Target lesion sites[a]				
Lung parenchyma	46	53	16	38
Other	23	27	15	36
Pelvis	23	27	9	21
Liver	21	24	8	19
Retroperitoneum	15	17	5	12
Peritoneum	8	9	6	14
Primary histologic type				
Leiomyosarcoma	30	35	15	36
Liposarcoma	15	17	7	17
Well-differentiated liposarcoma	3	3	2	5
Dedifferentiated liposarcoma	7	8	2	5
Myxoid liposarcoma	4	5	2	5
Pleomorphic liposarcoma	1	1	1	2
Malignant peripheral nerve sheath tumour	4	5	7	17
'Fibrohistiocytic'[b]	6	7	4	10
Fibroblastic/myofibroblastic	7	8	1	2
Tumours of uncertain differentiation	5	6	3	7
Vascular	2	2	2	5
Skeletal muscle	2	2	0	0
Other	15	17	3	7
Months since primary diagnosis, mean ± SD	31.7 ± 67.1		25.4 ± 32.0	
Months since unresectable disease, mean ± SD	4.03 ± 14.9		3.82 ± 15.3	
FNCLCC grade				
Grade 2	29	34	19	45
Grade 3	55	64	21	50
Unknown	2	2	2	5
Disease stage				
Stage III	12	14	2	5
Stage IV	74	86	40	95
ECOG performance status[c]				
0	58	67	28	67
1	28	33	14	33
No. of sites of target lesions				
1	30	35	22	52
2	35	41	9	21
3	11	13	7	17
4	6	7	3	7
⩾5	4	5	1	2
No. of sites of non-target lesions				
0	31	36	14	33
1	32	37	16	38
2	14	16	10	24
3	5	6	1	2
4	2	2	1	2
⩾5	2	2	0	0
Prior surgery or procedure	84	98	40	95
Prior radiotherapy	41	48	16	38

[a] Other sites reported in <10% of patients each were extremities, lymph node, pleura or pleural wall, kidney, chest wall, adrenal gland, pancreas, thyroid, oesophagus, stomach, bone, colon, spleen and skin. Individual lesions were counted separately and there could be more than one lesion per site.
[b] Includes fibrohistiocytic sarcoma and plexiform fibrohistiocytic tumour.
[c] Per interactive voice response system data at randomisation.

Table 2
Progression-free survival time per investigator review (Phase II).

	Conatumumab–doxorubicin ($n = 86$)		Placebo–Doxorubicin ($n = 42$)	
	No.	%	No.	%
Primary analysis (May 8, 2009)				
Progression-free survival				
Events[a]	60	70	30	71
Censored	26	30	12	29
PFS time, months, median (95% CI)	5.6 (5.1, 6.9)		6.4 (5.3, 7.1)	
Stratified[b] hazard ratio (95% CI)	1.00 (0.64–1.57)			
Stratified p-value	0.973			
Unstratified hazard ratio (95% CI)	0.99 (0.64–1.55)			
Unstratified p-value	0.984			
Follow-up analysis (January 10, 2011)				
Progression-free survival				
Events[a]	75	87	40	95
Censored	11	13	2	5
PFS time, months, median (95% CI)	5.6 (5.1, 6.7)		6.8 (5.3, 8.0)	
Stratified[b] hazard ratio (95% CI)	1.15 (0.78, 1.69)			
Stratified p-value	0.477			
Unstratified hazard ratio (95% CI)	1.15 (0.78, 1.69)			
Unstratified p-value	0.470			

[a] Events were clinical progressions, radiologic progressions, or deaths.
[b] Stratified by histologic type (leiomyosarcoma or liposarcoma/other).

and no notable differences were seen between groups or within a group over time (data not shown).

3.3.3. Open-label efficacy of conatumumab–doxorubicin (Phase I)

Of six patients enroled in Phase I, one withdrew consent shortly after the second infusion and was censored for PFS and OS. Three patients had disease progression on study (1.6, 5.7 and 14.0 months) and two patients were progression-free approximately 16 months after enrolment. Two patients died on study (4.1 and 16.7 months) due to disease progression, and three patients were still being followed for survival at the time of analysis.

3.3.4. Open-label efficacy of conatumumab monotherapy after doxorubicin (rollover)

Of 21 patients who rolled over after disease progression with doxorubicin to receive open-label conatumumab monotherapy, 18 (86%) had a PFS event. Median PFS was 1.3 months (95% CI: 1.2, 1.6). Of 16 patients with measurable disease in the rollover, none had an objective response, five (31%) had stable disease, 10 (63%) had progressive disease and one (6%) had an unknown overall best response. Plots of PFS and OS in the rollover are provided in Appendix H.

3.4. Safety

3.4.1. Phase I (open-label conatumumab–doxorubicin)

Six patients in Phase I received a mean of 13.8 infusions of conatumumab. Three patients (50%) experienced Grade 4 treatment-related haematologic AEs (neutropenia, thrombocytopenia) and one (17%) patient experienced Grade 3 treatment-related haematologic AEs (anaemia, leukopenia). There were no Grade $\geqslant 3$ treatment-related non-haematologic toxicities, no treatment-related serious AEs, no fatal AEs and no dose-limiting toxicities.

3.4.2. Phase II (double-blind conatumumab–doxorubicin or placebo–doxorubicin)

Patients received a mean of 7.4 infusions of conatumumab and 8.1 infusions of placebo. The average dose of doxorubicin delivered in the conatumumab–doxorubicin and placebo–doxorubicin arms was 72.4 and 73.1 mg/m^2/infusion, respectively. Patients received a lower cumulative dose of doxorubicin in the conatumumab–doxorubicin arm compared with the placebo–doxorubicin arm (mean, 330.1 versus 403.2 mg/m^2); however, they also received fewer doxorubicin infusions (mean, 4.6 versus 5.5), resulting in similar average doxorubicin doses delivered (mean, 72.4 versus 73.1 mg/m^2/infusion).

Nearly every patient (98% in each arm) experienced at least one AE. AEs that occurred in more than half of patients in either treatment group were nausea (conatumumab–doxorubicin: 66%, placebo–doxorubicin: 80%), alopecia (55%, 63%), fatigue (60%, 38%) and neutropenia (32%, 50%) (Table 4). The incidence of Grade 3 events was higher for the conatumumab–doxorubicin arm than for the placebo–doxorubicin arm (41%, 25%), but the incidence of Grade 4 events was higher for the placebo–doxorubicin arm (29%, 43%). There were two fatal AEs (gastrointestinal haemorrhage and septic shock), both of which occurred in the placebo–doxorubicin arm.

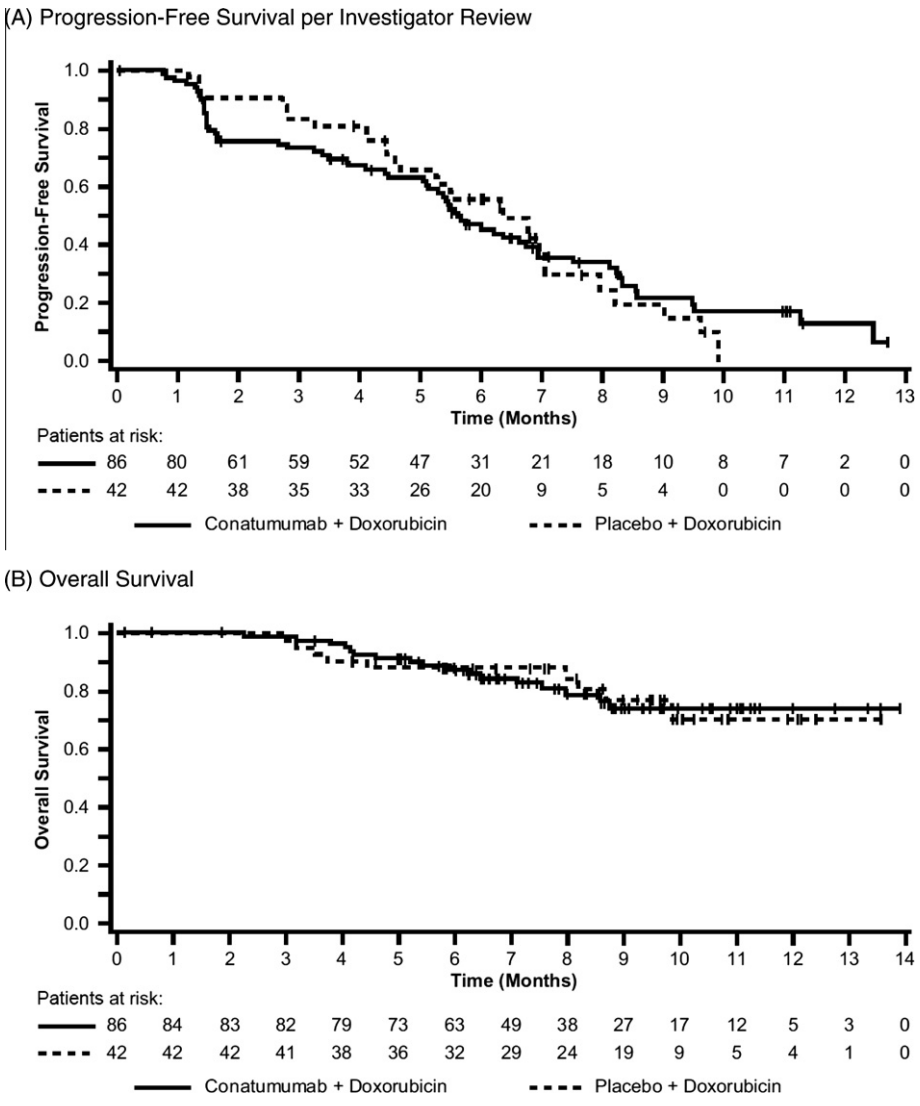

Fig. 2. Kaplan–Meier plots (Phase II). (A) Progression-free survival per investigator review. (B) Overall survival.

The incidence of treatment-related AEs was balanced between treatment groups (95% conatumumab–doxorubicin, 93% placebo–doxorubicin). The incidence of serious treatment-related AEs was lower for conatumumab–doxorubicin than for placebo–doxorubicin (25%, 35%). AEs resulted in treatment discontinuation for two patients in the conatumumab–doxorubicin arm (mucosal inflammation, increased blood creatine kinase) and one patient in the placebo–doxorubicin arm (delusions and confusional state).

More infusion reactions occured in the conatumumab–doxorubicin arm than in the placebo–doxorubicin arm (8% versus 3%). No conatumumab-related effects were evident in clinical laboratory values. No patient developed anti-conatumumab antibodies after treatment, but one tested positive for anti-conatumumab antibodies prior to administration of study treatment. Doxorubicin exposure was similar between treatment arms (Appendix I).

3.4.3. Rollover (open-label conatumumab monotherapy)

Twenty-one patients entered the rollover and received a mean of 3.0 conatumumab infusions. The overall incidence of AEs was 71% (Grade 3, 10%; Grade 4, 5%) and 14% of patients experienced a treatment-related AE. There were no treatment-related serious AEs or fatal AEs.

4. Discussion

Preclinical studies indicated that combining conatumumab and doxorubicin might be more effective at inducing cancer cell death than chemotherapy alone. In this Phase I/II trial, combining conatumumab 15 mg/kg and doxorubicin 75 mg/m^2 every 3 weeks was generally safe and tolerable for first-line treatment of metastatic or unresectable soft-tissue sarcoma with no unexpected toxicities. Combination therapy was tolerated as well as—or better than—doxorubicin monotherapy, possibly because patients in the

Table 3
Secondary efficacy outcomes (Phase II).

	Conatumumab–doxorubicin ($n = 86$)		Placebo–doxorubicin ($n = 42$)	
	No.	%	No.	%
Overall survival (primary analysis)				
Events	17	20	9	21
Censored	69	80	33	79
Months, median (range)		NE (0.2, 13.9)		NE (2.9, 13.5)
Best overall response				
Objective response	17	20	10	24
Complete response	1	1	0	0
Partial response	16	19	10	24
Stable disease	45	52	29	69
Unconfirmed partial response	3	3	2	5
Progressive disease	19	22	3	7
Unknown[a]	5	6	0	0
Disease control[b]				
At week 6	62	72	38	90
At week 12	53	62	35	83
At week 18	42	49	27	64
Percentage change in size[c], mean ± SD				
At week 6		−2.6% ± 25.9%		−3.6% ± 13.9%
At week 12		−15.0% ± 25.8%		−11.2% ± 21.1%
At week 18		−22.2% ± 22.2%		−10.7% ± 25.9%
Time to response, months, median (range)		3.0 (1.3, 8.3)		2.8 (1.2, 4.3)
Duration of response, months, median (range)		4.2 (1.6, 8.3)		4.2 (2.4, 5.7)
Overall survival (follow-up analysis)				
Events	56	65	26	62
Censored	30	35	16	38
Months, median (range)		18.2 (14.7, 22.6)		21.6 (14.9, 27.5)

Abbreviation: NE, not evaluable.
[a] No post-baseline assessment or unevaluable.
[b] Complete response, partial response, or stable disease.
[c] Sum of longest diameter.

conatumumab–doxorubicin arm received fewer doxorubicin infusions and lower cumulative doses of doxorubicin. However, the conatumumab–doxorubicin combination did not improve the primary efficacy endpoint of PFS compared with placebo–doxorubicin. Other measures of benefit, such as objective response rate and patient-reported outcomes, also did not indicate any improvement with conatumumab treatment.

A higher incidence of early disease progression was seen in the conatumumab–doxorubicin arm during the first 3.5 months of treatment, which is not fully understood. In a meta-analysis of older studies that included a total of 660 patients who received doxorubicin monotherapy, median PFS was approximately 3–4 months.[4,6,17–20] Whilst the study design assumed that doxorubicin monotherapy would be associated with median PFS of 3.34 months, the actual median PFS of 6.4 months observed was nearly twice as long as expected. Additionally, ORR of 24% in the doxorubicin monotherapy arm of this study was greater than expected based on previous randomised studies.[4,6,17–20]

Current outcomes in patients with soft tissue sarcoma may be better than historical controls due to improvements in diagnosis and classification of soft tissue sarcoma. For example, patients with aggressive neoplasms such as poorly differentiated carcinoma are no longer diagnosed as having soft tissue sarcoma. Incorrect assessment of disease progression was possible in this study, but secondary analyses of PFS that censored patients with no radiographic evidence of progression had similar results to investigator ratings of progression. Additionally, as observed in several EORTC trials of soft tissue sarcoma, results in Phase II trials tend to be better than those achieved in subsequent Phase III trials presumably because of selection biases and small numbers of patients.[3,21,22] This trial used only a single cytotoxic agent, and physicians may have been biased in patient accrual for more indolent subtypes, perhaps to treat more aggressive tumours with combination chemotherapy. Differences in baseline disease severity also may have influenced efficacy results. The results from this trial will be very important to take into account when designing other therapeutic trials to study the outcomes of unselected patients with a variety of soft tissue sarcomas treated in first line.

The lack of significant improvement with the addition of a new agent to doxorubicin was not unusual. Although numerous previous studies have evaluated

Table 4
Adverse events in ⩾20% of patients total (Phase II).

Toxicity	Grade 1				Grade 2				Grade 3				Grade 4			
	CMAB[a]		Placebo[b]		CMAB[a]		Placebo[b]		CMAB[a]		Placebo[b]		CMAB[a]		Placebo[b]	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Nausea	36	42	21	53	19	22	11	28	1	1	0	0	0	0	0	0
Alopecia	15	18	8	20	30	35	16	40	2	2	1	3	0	0	0	0
Fatigue	25	29	7	18	19	22	7	18	7	8	1	3	0	0	0	0
Neutropenia	0	0	2	5	3	4	1	3	11	13	3	8	13	15	14	35
Anaemia	3	4	2	5	8	9	5	13	13	15	4	10	2	2	2	5
Vomiting	11	13	13	33	11	13	2	5	1	1	0	0	0	0	0	0
Pyrexia	21	25	5	13	9	11	2	5	0	0	0	0	0	0	0	0
Diarrhoea	15	18	8	20	10	12	3	8	0	0	0	0	0	0	0	0
Stomatitis	10	12	10	25	7	8	4	10	4	5	0	0	0	0	0	0
Constipation	14	16	7	18	7	8	3	8	0	0	0	0	0	0	0	0
Asthenia	2	2	5	13	13	15	7	18	0	0	2	5	0	0	0	0
Anorexia	15	18	4	10	6	7	3	8	0	0	0	0	0	0	0	0

[a] Conatumumab–doxorubicin arm ($n = 85$).
[b] Placebo–doxorubicin arm ($n = 42$).

combination chemotherapy in first-line treatment of advanced soft tissue sarcoma, they have not provided compelling evidence that they improve outcomes compared with doxorubicin monotherapy.[2]

Soft tissue sarcoma includes more than 50 subtypes that may vary in aggressiveness and treatment response.[23] For example, leiomyosarcoma is sensitive to the combination of gemcitabine and docetaxel or gemcitabine monotherapy,[24] whereas doxorubicin/ifosfamide may be more active in synovial sarcoma than in leiomyosarcoma.[25–27] Newer agents such as tyrosine kinase inhibitors and mTOR inhibitors may also be more active in selected histologic subtypes of soft tissue sarcoma.[28] In this study, patients with liposarcoma tended to have longer PFS than patients with leiomyosarcoma, whereas patients in the broad category of 'other' soft tissue sarcoma tended to have shorter PFS. Larger, adequately powered studies would be required to evaluate the activity of conatumumab–doxorubicin within specific subtypes of soft tissue sarcoma.

Conversely, subtypes of soft tissue sarcoma that differ in histology may have very similar molecular aberrations.[29] Future studies of biologic therapies may benefit from a focus on pathway-specific activity rather than histology-specific activity. For example, soft tissue sarcomas that preferentially express DR5 may be more likely to respond to conatumumab treatment. Conatumumab activity was similar by FCGR3A genotype, but the small number of patients with each genotype limited conclusions that could be made from these analyses.

In conclusion, the addition of conatumumab to doxorubicin was generally safe and tolerable, but did not prolong PFS or survival, or improve response rates, in patients with soft tissue sarcoma. Because soft tissue sarcoma may include more than 50 tumour types, it may be necessary to enrol patients with specific histological subtypes and/or tumours that arise from known pathogenetic molecular aberrations in future studies of combination therapy for soft tissue sarcoma.

Conflict of interest statement

George Demetri has served as a paid consultant to Amgen, Genentech, Novartis, Pfizer, Ariad, Johnson & Johnson, PharmaMar, Infinity Pharmaceuticals, EMD-Serono, GlaxoSmithKline, Daiichi-Sankyo, ArQule, Millennium/Takeda and Plexxikon; and has received research funding from Amgen, Novartis, Pfizer, Ariad, Johnson & Johnson, PharmaMar, Infinity Pharmaceuticals and Daiichi-Sankyo. Axel Le Cesne has received honoraria from Novartis, Pfizer and PharmaMar. Sant Chawla has received research funding from Amgen, Threshold, GlaxoSmithKline, Johnson & Johnson and Cytotech. Thomas Brodowicz has served as a paid consultant to Amgen. Bruce Bach, Dominic Smethurst, Sarah Bray and Yong-jiang Hei are employed by and hold stock in Amgen Inc. Jean-Yves Blay has served as a paid consultant to, and received research funding from Novartis, Pfizer, GlaxoSmithKline, PharmaMar and Roche.

Author contributions

All authors contributed to the drafting and editing of this article for intellectual content, and all authors approved the manuscript for submission. George Demetri, Axel Le Cesne, Sant Chawla, Thomas Brodowicz, Bruce Bach, Dominic Smethurst, Sarah Bray, Yong-jiang Hei and Jean-Yves Blay contributed to the study conception and design, the collection and assembly of data and the interpretation of results. Robert Maki contributed to the study conception and design.

Acknowledgements

Amgen Inc. supported this study. Jonathan Latham and Kathryn Boorer provided writing and editorial assistance on behalf of Amgen Inc. The authors thank Yang Pan et al. for the biomarker analyses (Appendix G) and the Study 20060324 investigators (Appendix A) for their contributions.

Appendix A

The Study 20060324 investigators were as follows (listed alphabetically by country): Austria: Thomas Brodowicz, Wien; Belgium: Thierry Gil, Brussels; Patrick Schöffski, Leuven; France: Jean Yves Blay, Lyon; Axel Le Cesne, Villejuif; Netherlands: Hans Gelderblom, Leiden; United States: Bruce Brockstein, Evanston, IL; Sant Chawla, Santa Monica, CA; Warren Chow, Duarte, CA; Lee Cranmer, Tucson, AZ; George Demetri, Boston, MA; Kenneth Hande, Nashville, TN; Robert Maki, New York, NY; Christopher Ryan, Portland, OR; Arthur Staddon, Philadelphia, PA; William D. Tap, Los Angeles, CA; Katherine Thornton, Baltimore, MD; Samir Undevia, Chicago, IL; Margaret von Mehren, Philadelphia, PA.

Appendix B. Baseline characteristics (Phase I)

	Conatumumab–doxorubicin	
	No.	%
No. of patients enroled	6	100
Sex, female	4	67
Race/ethnicity		
White or Caucasian	4	67
Hispanic or Latino	1	17
Asian	1	17
Age, years, median (range)	68.5 (46–86)	
Target lesion sites[a]		
Liver	2	33
Peritoneum	2	33
Lung parenchyma	2	33
Pleura or pleural wall	1	17
Chest wall	1	17
Kidney	1	17
Lymph node	1	17
Primary histologic type, *n* (%)		
Leiomyosarcoma	1	17
Liposarcoma	3	50
'Fibrohistiocytic'	1	17
Fibrosarcoma	1	17
Months since primary diagnosis, mean ± SD	25.5 ± 38.2	
FNCLCC grade		
Grade 2	4	67
Grade 3	2	33
Disease stage at enrolment		
Stage IV	6	100
ECOG performance status		
0	4	67
1	2	33
No. of sites of target lesions		
1	3	50
2	2	33
3	1	17
Prior surgery or procedure	6	100
Prior radiotherapy	3	50

[a] Individual lesions were counted separately and there could be more than one lesion per site.

Appendix C. Baseline characteristics (rollover)

	Rolled over from placebo–doxorubicin to conatumumab alone	
	No.	%
No. of patients enroled	21	100
Sex, female	12	57
Race/ethnicity		
White or Caucasian	17	81
Black or African American	2	10
Asian	1	5
Other	1	5
Age, years, median (range)	54.0 (39–82)	
Target lesion sites[b]		
Pelvis	4	19
Peritoneum	4	19
Lung parenchyma	4	19
Pleura or pleural wall	3	14
Retroperitoneum	2	10
Bone	2	10
Primary histologic type, *n* (%)		
Leiomyosarcoma	8	38
Liposarcoma	4	19
Well-differentiated liposarcoma	1	5
Dedifferentiated liposarcoma	1	5
Myxoid liposarcoma	1	5
Pleomorphic liposarcoma	1	5
'Fibrohistiocytic'	2	10
Other	7	33
FNCLCC grade		
Grade 2	9	43
Grade 3	10	48
Unknown	2	10
Disease stage		
Stage IV	21	100
ECOG performance status[a]		
0	13	62
1	8	38
No. of sites of target lesions[a]		
0	5	24
1	7	33
2	6	29
3	2	10
4	1	5
⩾5	0	0

[a] At the time of enrolment in the rollover.

[b] Other sites reported by one patient each were kidney, lymph node, thyroid, extremities and liver; five patients had 'other' sites. Individual lesions were counted separately and there could be more than one lesion per site.

Appendix D. Univariate analysis of progression-free survival (Phase II)

	Events/ patients	Median PFS	Hazard ratio (95% CI)	Wald X^2 (p-value)
Histological cell type				8.28 (0.016)
Leiomyosarcoma	34/45	6.37	Reference	
Liposarcoma	13/22	6.74	0.62 (0.33, 1.18)	
Other	43/61	5.52	1.55 (0.97, 2.48)	
Histological cell type				0.31 (0.580)
Leiomyosarcoma	34/45	6.37	Reference	
Liposarcoma and other	56/83	5.68	1.13 (0.74, 1.73)	
Age				2.69 (0.261)
40 to <60	49/65	5.49	Reference	
<40	8/10	6.21	0.87 (0.41, 1.84)	
⩾60	33/53	6.93	0.69 (0.44, 1.07)	
Age				2.54 (0.111)
<60	57/75	5.52	Reference	
⩾60	33/53	6.93	0.71 (0.46, 1.08)	
Time since initial diagnosis				4.63 (0.099)
<6 months	40/48	5.06	Reference	
6–12 months	14/22	5.39	0.93 (0.50, 1.72)	
>12 months	36/58	6.77	0.62 (0.39, 0.97)	
Time since initial diagnosis				3.23 (0.072)
<6 months	40/48	5.06	Reference	
⩾6 months	50/80	6.74	0.68 (0.45, 1.04)	
Disease extension				ND (ND)
Locally recurrent, unresectable	53/77	6.64	Reference	
Locally advanced, unresectable	3/4	2.32	ND (ND, ND)	
Metastatic	33/46	5.52	1.10 (0.71, 1.70)	
Disease extension				0.08 (0.773)
Locally recurrent or advanced, unresectable	56/81	6.37	Reference	
Metastatic	33/46	5.52	1.07 (0.69, 1.64)	
ECOG				0.19 (0.666)
0	57/78	6.21	Reference	
1	32/49	5.68	1.10 (0.71, 1.70)	
Histological grade				7.33 (0.007)
Grade 2	31/48	6.93	Reference	
Grade 3	55/76	5.42	1.89 (1.19, 2.99)	
Liver metastases				0.01 (0.937)
No	65/94	5.55	Reference	
Yes	25/34	6.37	1.02 (0.64, 1.62)	
Lung metastases				0.23 (0.629)
No	35/53	6.74	Reference	
Yes	55/75	5.52	1.11 (0.73, 1.70)	
Prior adjuvant chemotherapy				2.41 (0.121)
No	83/120	6.21	Reference	
Yes	7/8	4.11	1.85 (0.85, 4.02)	
Prior pelvic radiation				0.15 (0.699)
No	85/119	6.01	Reference	
Yes	5/9	4.11	0.84 (0.34, 2.07)	
Gender				0.10 (0.753)
Male	42/59	5.68	Reference	
Female	48/69	6.64	1.07 (0.70, 1.64)	
Geographical location				0.32 (0.570)
North America	47/69	6.01	Reference	
Europe	43/59	5.52	0.89 (0.58, 1.35)	
Treatment				0.00 (0.979)
Placebo	30/42	6.37	Reference	
Conatumumab	60/86	5.62	0.99 (0.64, 1.55)	

Appendix E. Kaplan–Meier plots of progression-free survival by histologic type (Phase II)

See Fig. E1.

Appendix F. Kaplan–Meier plot of overall survival (Phase II follow-up analysis as of 10th January 2011)

See Fig. F1.

Appendix G. Biomarker analysis [Conducted by Yang Pan, Sue Cottrell, Chang-pin Huang, Ren Xu, Matt Peach, Liming Sui, and Dan Branstetter]

PFS and objective response rates were analysed within common genetic variations of FCGR3A. The FF, VF and VV genotypes and combinations of these genotypes were analysed to investigate whether specific FCGR3A polymorphisms affected the treatment outcomes for patients with locally advanced or metastatic, unresectable STS. Preclinical data generated at Amgen suggest an FCGR-dependent apoptosis by conatumumab in *ex vivo* experiments. For this study, it was hypothesised that patients with the VV or VF genotype may demonstrate an improved PFS time and objective response rate with conatumumab treatment

compared with patients with the FF genotype and patients of the respective genotype from the placebo treatment arm. Patients included in these analyses were those with blood samples collected and pharmacogenomics consent form signed for biomarker analyses. All analyses were performed on the subset of patients with a given genotype in the full analysis set. These analyses were limited to the small number of patients with each respective FCGR3A polymorphism.

G.1. FDGR3A polymorphism FF patients

Twenty-three patients in the conatumumab treatment arm and 15 patients in the placebo treatment arm were characterised as having the FF genotype. For an analysis of PFS, there were a total of 15 (65%) events in the conatumumab treatment arm and 11 (73%) events in the placebo treatment arm. Kaplan–Meier estimate (95% CI) of median PFS was 7.5 months (5.1, 11.3) in the conatumumab treatment arm and 7.0 months (6.3, 8.0) in the placebo treatment arm. The unstratified HR (95% CI) was 0.68 (0.29, 1.57); the *p*-value from the unstratified log rank used to compare treatments was 0.372.

There were seven patients in the conatumumab treatment arm and six patients in the placebo treatment arm with an objective response. The objective response rate (95% CI) was 30.4% (13.2, 52.9) in the conatumumab arm as compared with 40.0% (16.3, 67.7) in the placebo treatment arm.

The proportion of FF genotype patients with a best overall response of stable disease was higher in the placebo treatment arm (60%) compared with (43%) in the conatumumab treatment arm. There was one confirmed complete response for an FF genotype patient receiving conatumumab. Six patients in each treatment arm had confirmed partial response.

G.2. FDGR3A polymorphism VV patients

Data were available for 11 patients in the conatumumab treatment arm and three patients in the placebo arm with the VV genotype. There were few events for the PFS analyses in this genotype subset with seven (64%) and three (100%) in the conatumumab and placebo treatment arms. The Kaplan–Meier estimate (95% CI) of median PFS was 6.9 months (5.4, 8.3) and 4.6 months (2.8, 6.8) in the conatumumab and placebo treatment arms, respectively. For these unstratified analyses the HR (95% CI) was 0.27 (0.06, 1.23) with a *p*-value from the unstratified log-rank test of 0.070.

Four VV genotype patients (all in the conatumumab treatment arm) were identified as having an objective response. The objective response rate (95% CI) was 36.4% (10.9, 69.2).

The proportion of VV genotype patients with a best response of stable disease was higher in the placebo treatment arm (100%) compared with the conatumumab treatment arm (64%). There were no patients with a confirmed complete response. Four (36%) patients with the VV genotype who received conatumumab treatment had a confirmed partial response.

G.3. FDGR3A polymorphism FV patients

Thirty-four patients in the conatumumab treatment arm and 19 patients in the placebo treatment arm were characterised as having the FV genotype. There were a total of 26 (76%) events in the conatumumab treatment arm and 14 (74%) events in the placebo treatment arm for the PFS analysis. Kaplan–Meier estimate (95% CI) of median PFS was 5.1 months (1.6, 6.6) in the conatumumab treatment arm and 4.7 months (4.1, 6.8) in the placebo treatment arm. The unstratified HR (95% CI) was 1.09 (0.57, 2.11) and the *p*-value from the unstratified log-rank test was 0.785.

Three FV genotype patients in the conatumumab arm and four FV genotype patients in the placebo treatment arm had an objective response. The objective response rate (95% CI) was 8.8% (1.9, 23.7) in the conatumumab treatment arm compared with 21.1% (6.1, 45.6) in the placebo treatment arm.

The proportion of patients with a best response of stable disease was higher in the placebo treatment arm (63%) compared with (50%) in the conatumumab treatment arm. No patients with the FV genotype had confirmed complete response.

G.4. FDGR3A polymorphism VV and FV patients combined

PFS was also evaluated by combining the patients with VV and FV genotypes. There were a total of 33 (73%) events in the conatumumab treatment arm and 17 (77%) events in the placebo treatment arm for the PFS analysis. The Kaplan–Meier estimate (95% CI) of median PFS was 5.4 months (3.8, 6.9) in the conatumumab treatment arm and 4.6 months (4.1, 6.8) in the placebo treatment arm. No significant treatment differences were observed (unstratified HR = 0.86, 95% CI = 0.48–1.56; unstratified log-rank test *p*-value = 0.646).

Eleven patients (seven in the conatumumab treatment arm and four in the placebo treatment arm) were identified as having an objective response. The objective response rate (95% CI) was 15.6% (6.5, 29.5) in the conatumumab treatment arm and 18.2% (5.2, 40.3) in the placebo treatment arm.

The proportion of patients with a best response of stable disease was 53% in the conatumumab treatment arm and 68% in the placebo treatment arm. For the VV and FV genotype patients with an objective response, a confirmed partial response was reported as the best overall response and there were no confirmed complete responses in either treatment arm.

G.5. FDGR3A polymorphism FF and FV patients combined

An analysis of PFS was also performed upon combining patients with the FF and FV genotype. There were a total of 41 (72%) events in the conatumumab treatment arm and 25 (74%) events in the placebo treatment arm for the PFS analysis. The Kaplan–Meier estimate (95% CI) of PFS was 5.5 months (4.1, 7.5) in the conatumumab treatment arm and 6.3 months (4.7, 7.1)

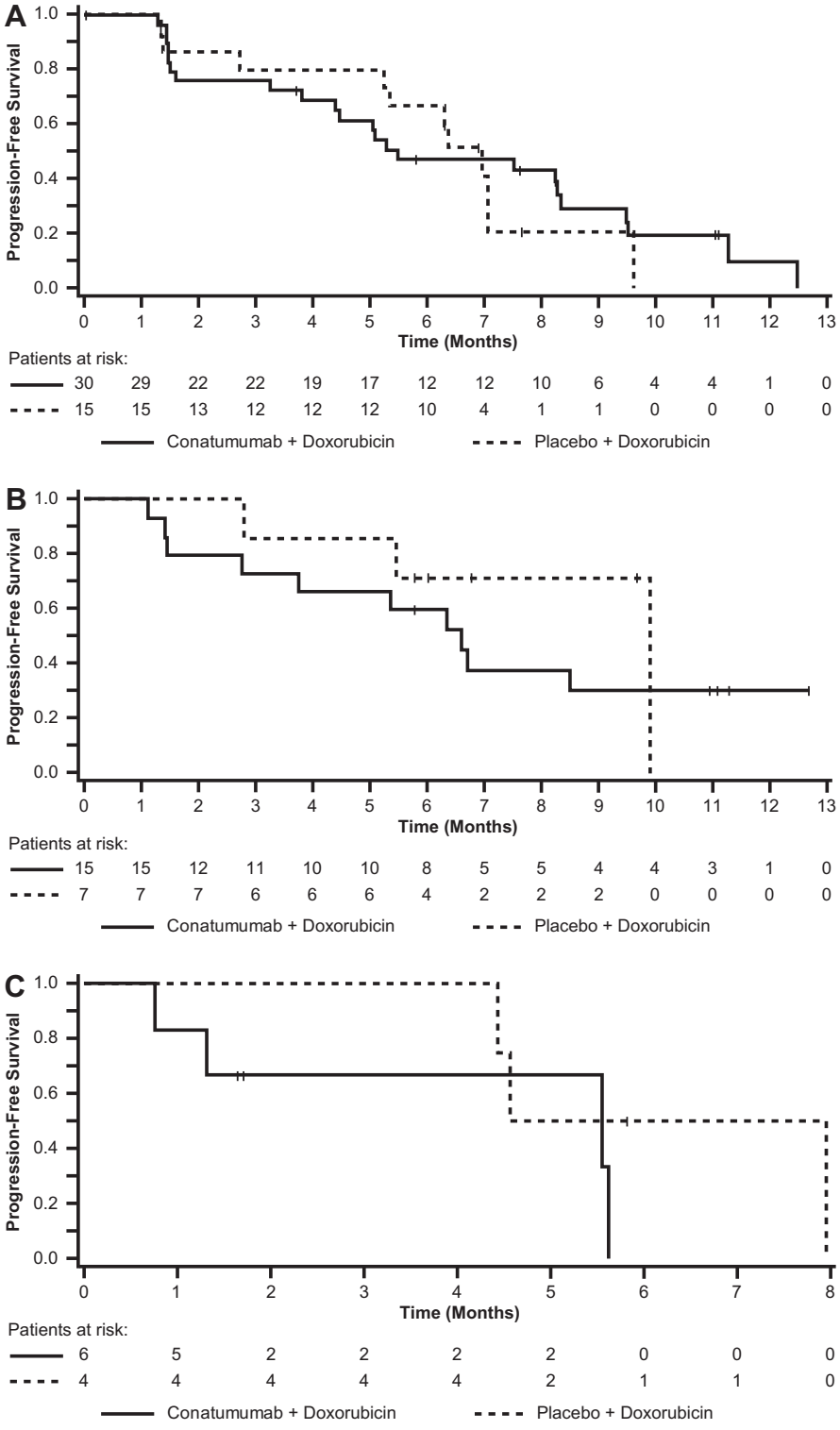

Fig. E1. Kaplan-Meier plots of progression-free survival by histologic type (Phase II). (A) Leiomyosarcoma. (B) Liposarcoma. (C) 'Fibrohistiocytic' (including undifferentiated pleomorphic sarcoma/MFH). (D) MPNST. (E) All subgroups combined.

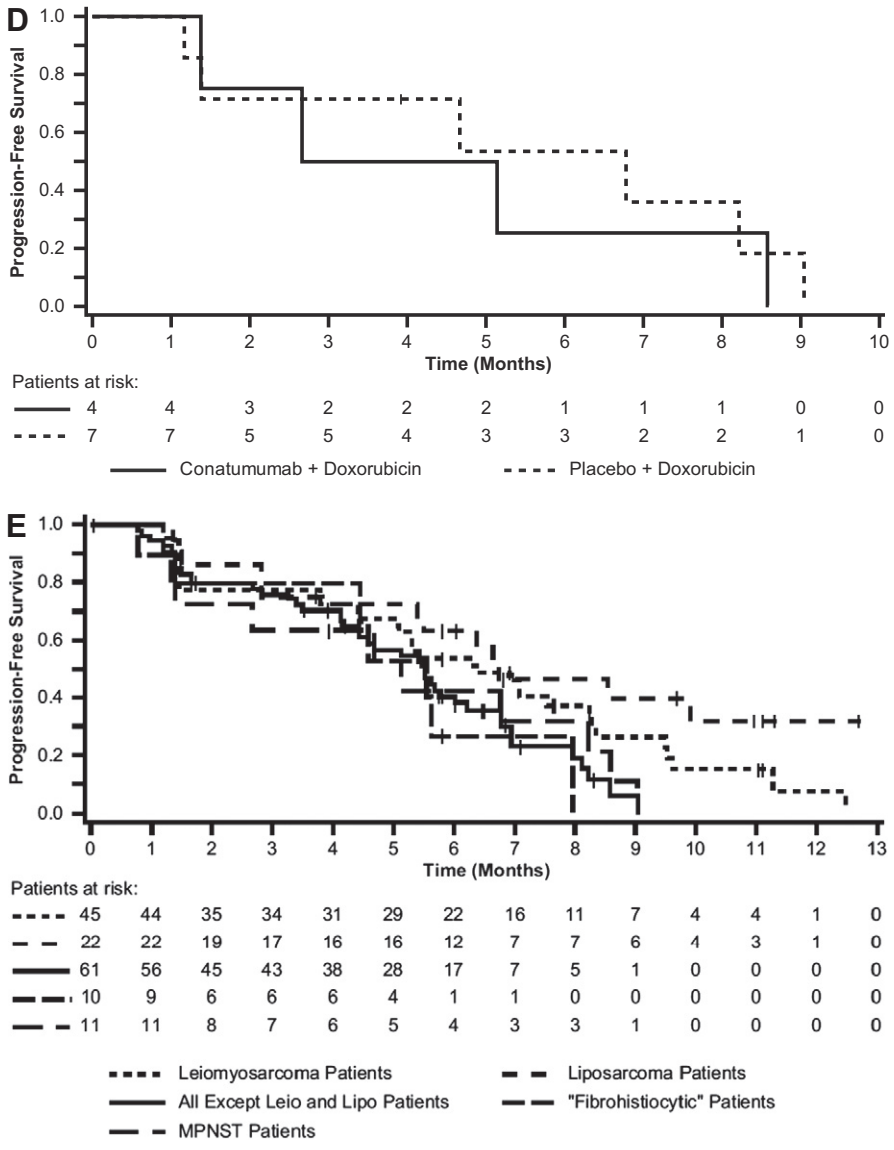

Fig E1. *(continued)*

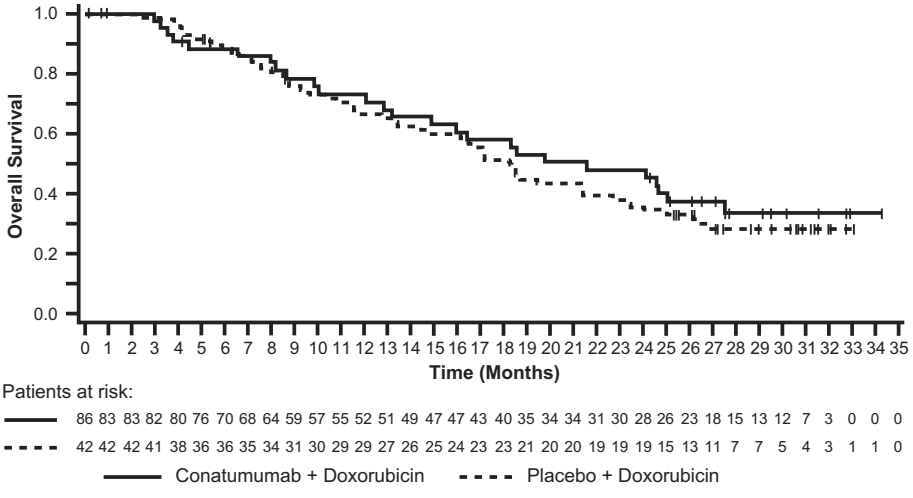

Fig. F1. Kaplan-Meier plot of overall survival (Phase II follow-up analysis as of January 10, 2011).

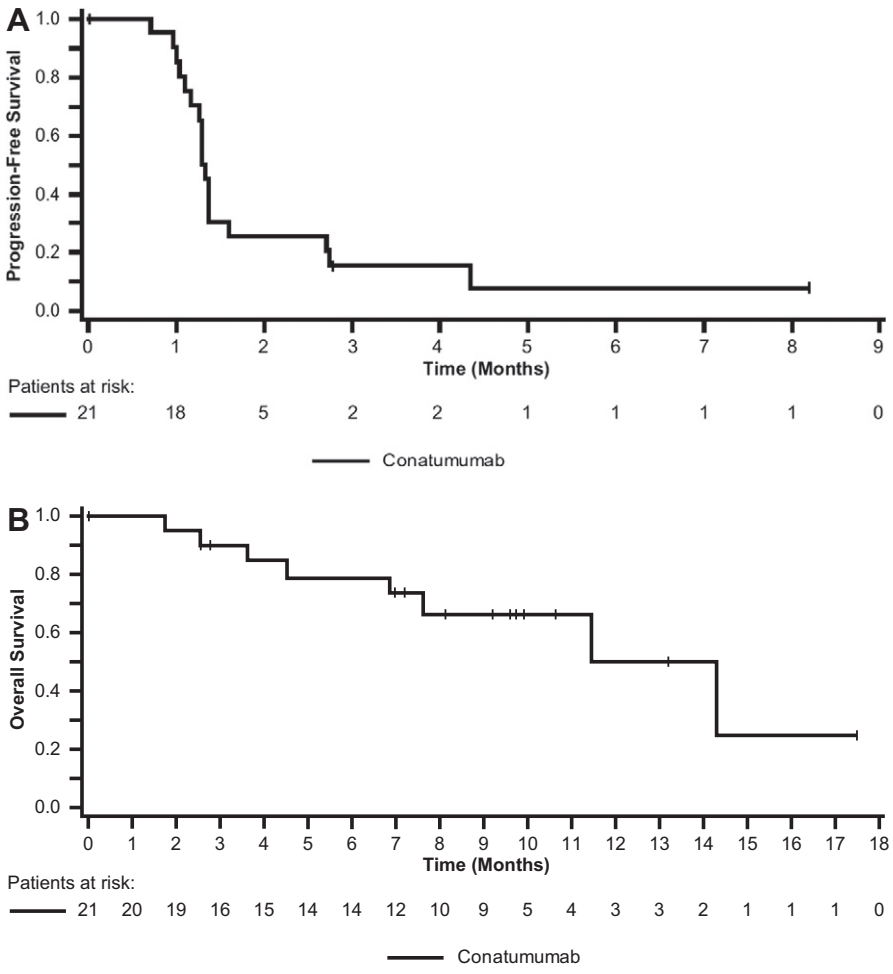

Fig. H1. Kaplan-Meier plots (after rollover from doxorubicin to conatumumab monotherapy). (A) Progression-free survival. (B) Overall survival.

in the placebo treatment arm. No significant treatment differences were observed (unstratified HR = 0.91, 95% CI = 0.54–1.51; unstratified log-rank test *p*-value = 0.705).

Twenty patients in the combined FF and FV genotype subset (10 in each treatment arm) were identified as having an objective response. The objective response rate (95% CI) was 17.5% (8.8, 29.9) in the conatumumab treatment arm compared with 29.4% (15.1, 47.5) in the placebo treatment arm.

The proportion of patients with a best response of stable disease was higher in the placebo treatment arm (62%) compared with (47%) in the conatumumab treatment arm. There was one confirmed complete response in the conatumumab treatment arm when combining the FF and FV genotypes into a single subset.

In summary, the conclusions from these analyses are limited by the small number of patients with each respective FCGR3A genotype. No notable difference between treatment arms in PFS time or objective response rate was observed in the analyses by genotype.

Appendix H. Kaplan–Meier plots (after rollover from doxorubicin to conatumumab monotherapy)

See Fig. H1.

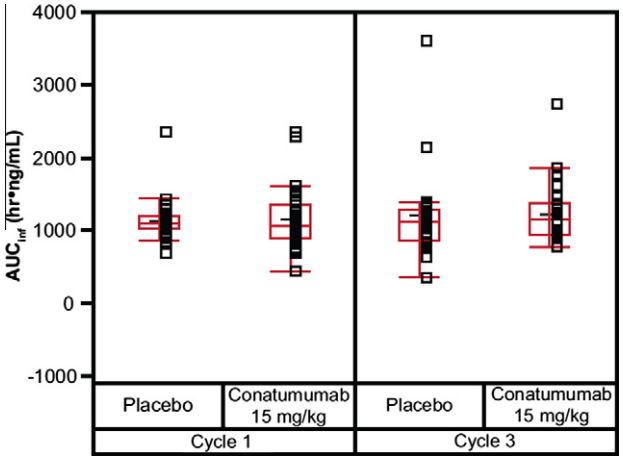

Fig. I1. Doxorubicin pharmacokinetics (Phase II).

Table I1
Doxorubicin pharmacokinetics.

Cycle	Summary statistics	Doxorubicin CL (L/h)		Doxorubicin AUC_{inf} (h ∗ ng/mL)	
		Conatumumab	Placebo	Conatumumab	Placebo
Cycle 1	N	40	26	40	26
	Mean	134	123	1160	1150
	SD	47.0	22.0	376	293
Cycle 3	N	27	24	27	24
	Mean	126	131	1230	1200
	SD	38.4	58.4	415	611

AUC_{inf} = area under the serum concentration–time curve from time zero to infinity.
CL = apparent clearance.

Appendix I. Doxorubicin pharmacokinetics (Phase II)

See Fig. I1 and Table I1.

References

1. American Cancer Society. *Cancer facts & figures*. Atlanta, GA: American Cancer Society; 2010.
2. Casali PG, Blay JY. Soft tissue sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;**21**(Suppl. 5):v198–203.
3. Edmonson JH, Ryan LM, Blum RH, et al. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. *J Clin Oncol* 1993;**11**(7):1269–75.
4. van Glabbeke M, van Oosterom AT, Oosterhuis JW, et al. Prognostic factors for the outcome of chemotherapy in advanced soft tissue sarcoma: an analysis of 2185 patients treated with anthracycline-containing first-line regimens—a European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. *J Clin Oncol* 1999;**17**(1):150–7.
5. Maurel J, López-Pousa A, de Las Peñas R, et al. Efficacy of sequential high-dose doxorubicin and ifosfamide compared with standard-dose doxorubicin in patients with advanced soft tissue sarcoma: an open-label randomized phase II study of the Spanish group for research on sarcomas. *J Clin Oncol* 2009;**27**(11):1893–8.
6. Sleijfer S, Ouali M, van Glabbeke M, et al. Prognostic and predictive factors for outcome to first-line ifosfamide-containing chemotherapy for adult patients with advanced soft tissue sarcomas: an exploratory, retrospective analysis on large series from the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG). *Eur J Cancer* 2010;**46**(1):72–83.
7. Verma S, Younus J, Stys-Norman D, Haynes AE, Blackstein M. Meta-analysis of ifosfamide-based combination chemotherapy in advanced soft tissue sarcoma. *Cancer Treat Rev* 2008;**34**(4):339–47.
8. Pitti RM, Marsters SA, Ruppert S, et al. Induction of apoptosis by Apo-2 ligand, a new member of the tumor necrosis factor cytokine family. *J Biol Chem* 1996;**271**(22):12687–90.
9. Wiley SR, Schooley K, Smolak PJ, et al. Identification and characterization of a new member of the TNF family that induces apoptosis. *Immunity* 1995;**3**(6):673–82.
10. Rowinsky EK. Targeted induction of apoptosis in cancer management: the emerging role of tumor necrosis factor-related apoptosis-inducing ligand receptor activating agents. *J Clin Oncol* 2005;**23**(36):9394–407.
11. Ashkenazi A, Holland P, Eckhardt SG. Ligand-based targeting of apoptosis in cancer: the potential of recombinant human apoptosis ligand 2/Tumor necrosis factor-related apoptosis-inducing ligand (rhApo2L/TRAIL). *J Clin Oncol* 2008;**26**(21):3621–30.
12. Rosevear HM, Lightfoot AJ, Griffith TS. Conatumumab, a fully human mAb against death receptor 5 for the treatment of cancer. *Curr Opin Investig Drugs* 2010;**11**(6):688–98.
13. Kaplan-Lefko PJ, Graves JD, Zoog SJ, et al. Conatumumab, a fully human agonist antibody to death receptor 5, induces apoptosis via caspase activation in multiple tumor types. *Cancer Biol Ther* 2010;**9**(8):618–31.
14. Doi T, Murakami H, Ohtsu A, et al. Phase 1 study of conatumumab, a pro-apoptotic death receptor 5 agonist antibody, in Japanese patients with advanced solid tumors. *Cancer Chemother Pharmacol* 2011;**68**(3):733–41.
15. Herbst RS, Kurzrock R, Hong DS, et al. A first-in-human study of conatumumab in adult patients with advanced solid tumors. *Clin Cancer Res* 2010;**16**(23):5883–91.
16. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;**92**(3):205–16.
17. Judson I, Radford JA, Harris M, et al. Randomised phase II trial of pegylated liposomal doxorubicin (DOXIL/CAELYX) versus doxorubicin in the treatment of advanced or metastatic soft tissue sarcoma: a study by the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 2001;**37**(7):870–7.
18. Nielsen OS, Dombernowsky P, Mouridsen H, et al. High-dose epirubicin is not an alternative to standard-dose doxorubicin in the treatment of advanced soft tissue sarcomas. A study of the EORTC soft tissue and bone sarcoma group. *Br J Cancer* 1998;**78**(12):1634–9.
19. Borden EC, Amato DA, Edmonson JH, Ritch PS, Shiraki M. Randomized comparison of doxorubicin and vindesine to doxorubicin for patients with metastatic soft-tissue sarcomas. *Cancer* 1990;**66**(5):862–7.
20. Mouridsen HT, Bastholt L, Somers R, et al. Adriamycin versus epirubicin in advanced soft tissue sarcomas. A randomized phase II/phase III study of the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer Clin Oncol* 1987;**23**(10):1477–83.
21. Schütte J, Mouridsen HT, Stewart W, et al. Ifosfamide plus doxorubicin in previously untreated patients with advanced soft tissue sarcoma. The EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 1990;**26**(5):558–61.
22. Le Cesne A, Judson I, Crowther D, et al. Randomized phase III study comparing conventional-dose doxorubicin plus ifosfamide versus high-dose doxorubicin plus ifosfamide plus recombinant human granulocyte–macrophage colony-stimulating factor in advanced soft tissue sarcomas: a trial of the European Organization for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group. *J Clin Oncol* 2000;**18**(14):2676–84.

23. Eriksson M. Histology-driven chemotherapy of soft-tissue sarcoma. *Ann Oncol* 2010;**21**(Suppl. 7):vii270–6.
24. Hensley ML, Maki R, Venkatraman E, et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. *J Clin Oncol* 2002;**20**(12):2824–31.
25. Antman KH, Ryan L, Elias A, Sherman D, Grier HE. Response to ifosfamide and mesna: 124 previously treated patients with metastatic or unresectable sarcoma. *J Clin Oncol* 1989;**7**(1):126–31.
26. Benjamin RS, Legha SS, Patel SR, Nicaise C. Single-agent ifosfamide studies in sarcomas of soft tissue and bone: the M.D. Anderson experience. *Cancer Chemother Pharmacol* 1993;**31**(Suppl. 2):S174–9.
27. Le Cesne A, Antoine E, Spielmann M, et al. High-dose ifosfamide: circumvention of resistance to standard-dose ifosfamide in advanced soft tissue sarcomas. *J Clin Oncol* 1995;**13**(7):1600–8.
28. Chao J, Chow WA, Somlo G. Novel targeted therapies in the treatment of soft-tissue sarcomas. *Expert Rev Anticancer Ther* 2010;**10**(8):1303–11.
29. Verweij J, Baker LH. Future treatment of soft tissue sarcomas will be driven by histological subtype and molecular aberrations. *Eur J Cancer* 2010;**46**(5):863–8.