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Full Title: A Phase I and Randomized, Controlled, Phase II trial of the Safety and Efficacy of the Combination of Gemcitabine and Docetaxel with Ontuxizumab (MORAb-004) in Metastatic Soft Tissue Sarcomas

Running Title: Ontuxizumab in Metastatic Soft Tissue Sarcomas

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Condensed Abstract: Endosialin is involved in tumor blood vessel formation and is expressed on sarcoma tumor cells. This Phase I/II randomized, controlled trial showed that ontuxizumab, an endosialin-directed monoclonal antibody, did not enhance efficacy in sarcomas when combined with chemotherapy (gemcitabine/docetaxel), although the combination was generally well tolerated.

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Abstract
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Background: Ontuxizumab, a humanized monoclonal antibody, targets endosialin, (tumor endothelial marker-1 [TEM-1] or CD248) which is expressed on sarcoma cells and is believed to be involved in tumor angiogenesis. This is the first trial to evaluate ontuxizumab in sarcoma patients.

Methods: Part 1 was an open-label, dose-finding, safety lead-in: 4, 6 or 8 mg/kg ontuxizumab (administered on Days 1 and 8 of a 21 day cycle) combined with gemcitabine/docetaxel (G/D, 900 mg/m^2 on Days 1/8 and 75 mg/m^2 Day 8, respectively). In Part 2, patients were randomized in a double-blind 2:1 ratio to ontuxizumab (8 mg/kg) or placebo with G/D. Randomization was stratified by 4 histological cohorts.

Results: In Part 2 with 209 patients, no significant difference in PFS between ontuxizumab + G/D and placebo + G/D was observed (4.3 [95% Confidence Interval (CI): 2.7, 6.3] months and 5.6 [95%CI: 2.6, 8.3] months respectively, *P*=0.67, Hazard Ratio (HR) 1.07 [95%CI: 0.77, 1.49]). Similarly, there was no significant difference in median overall survival (OS) between the 2 groups (18.3 [95%CI: 16.2, 21.1] months in the ontuxizumab + G/D group and 21.1 [95%CI: 14.2, not reached] in the placebo + G/D group, *P*=0.32 and HR 1.23 [95%CI: 0.82, 1.82]). No significant differences between treatment groups occurred for any efficacy parameter by sarcoma cohort. The combination of ontuxizumab + G/D was generally well tolerated.

Conclusion: Ontuxizumab + G/D showed no enhanced activity over chemotherapy alone in soft tissue sarcomas, whereas the safety profile of the combination was consistent with G/D alone.

Key words: sarcomas, endosialin, tumor endothelial marker-1, TEM-1, ontuxizumab, MORAb-004

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Introduction

Soft tissue sarcomas are rare solid tumors of mesenchymal origin, with over 50 different histological subtypes, each with their own underlying biology [1]. Despite optimal surgery, approximately 50% of patients will develop metastatic disease. The outcome of patients with metastatic disease is poor, with median overall survival (OS) of 12-18 months and few systemic therapy options [1]. Consequently, there is an unmet need for more effective systemic therapies for advanced sarcomas.

Endosialin, or tumor endothelial marker-1 (TEM-1), is a cell surface glycoprotein that is expressed in the stromal compartment of nearly all human tumors [2]. Pre-clinical studies showed that endosialin plays a key role in tumor growth and vessel formation in numerous tumor types, including sarcomas [3, 4]. Endosialin expression was noted in all 9 sarcoma subtypes and 83% of all sarcoma specimens [2]. Rouleau et al. [2] demonstrated that endosialin is expressed by malignant, perivascular, and stromal cells in human specimens. Endosialin expression was found in human specimens of high-grade/advanced sarcomas [5]. Consequently, endosialin was considered a potential therapeutic target in sarcomas. Other studies confirmed these findings [6].

Ontuxizumab is a humanized immunoglobulin G-1-kappa antibody directed against endosialin and the first of this class to undergo clinical evaluation. Non-clinical pharmacological studies have shown that ontuxizumab has the ability to interfere with specific endosialin receptor ligand interactions [7]. The combination of gemcitabine and docetaxel (G/D) is well established in the treatment of metastatic sarcomas [8]. The aim

of this trial was to assess the optimal dose of ontuxizumab in combination with G/D and to evaluate the ability of the antibody to enhance the anti-tumor activity of G/D.

Patients and Methods

Patients

Patients over the age of 18 years with histological proven metastatic soft tissue sarcomas and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 were eligible. In addition, patients had to have measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, and have been treated with 0-2 prior lines of systemic therapy and have fully recovered from all toxicity of previous treatments (apart from alopecia). Patients had to have adequate hematologic, renal, and liver parameters; and no brain metastases, primary bone sarcomas, other active malignancy, or an uncontrolled medical condition.

Prior to commencing enrollment, local institutional review board/ethics committee approval was obtained in accordance with the Declaration of Helsinki. Investigators obtained informed consent from each participant.

Study Design and Treatment

This was a multi-center, sequential 2-part trial. Part I was an open-label, dose-escalation design, to establish the safety of ontuxizumab combined with G/D and define the recommended Phase II dose. The dose-escalation phase consisted of ontuxizumab (Days 1 and 8 of a 21 day cycle) in combination with gemcitabine 900 mg/m^2 (Days 1 and 8) and docetaxel 75 mg/m^2 (Day 8).

The recommended Phase II dose was defined as the highest ontuxizumab dose administered in combination with G/D at which 0 of 3 or no more than 1 out of a maximum of 6 patients in a given dose cohort experienced a dose-limiting toxicity (DLT). Patients were treated until disease progression. A DLT was defined as

treatment-related and occurring within the first 28 days of treatment, including 1) nonhematologic toxicity of Grade ≥ 3 (excluding Grade 3 asthenia unless lasting >3 days, nausea/vomiting unless optimally treated, and alopecia); 2) hematologic toxicity of Grade 4 neutropenia lasting >7 days, Grade 4 febrile neutropenia, Grade 3/4 infection with associated Grade 3/4 neutropenia, Grade 4 hematologic toxicity not resolving in <14 days, and Grade 3 thrombocytopenia with clinically significant bleeding; 3) delayed recovery causing delay of the next dose by >28 days; 4) infusion-related toxicity excluding those controlled ≤ Grade 2 by management and anaphylactic reactions.

Part 2 was a randomized, double-blind, placebo-controlled, trial of G/D with either 8 mg/kg ontuxizumab or placebo, using the same doses and schedule used in Part 1. Patients were randomly assigned in a 2:1 ratio to ontuxizumab+G/D or placebo+G/D, respectively, and stratified into 4 sarcoma cohorts.

Study Assessments

Response to treatment was determined by computed tomography or magnetic resonance imaging performed at screening and every 6 weeks for the first 24 ± 1 weeks, then every 12 weeks. Patients who discontinued study drug were followed for documentation of disease progression, any additional anti-cancer therapies and survival.

The primary endpoint for Part 2 was progression-free survival (PFS). Secondary endpoints included OS, overall response rate (ORR) based on RECIST 1.1, safety and tolerability. Exploratory objectives included the evaluation of putative predictive markers of response.

Safety was evaluated by monitoring adverse events (AEs) (graded via Common Toxicity Criteria for Adverse Events [CTCAE] v4.03), serious adverse events (SAEs), laboratory measurements, vital signs, electrocardiograms (ECGs), ECOG assessments, and physical examinations.

Biomarkers, anti-drug antibody (ADA) and pharmacokinetic analysis

Tumor tissue was obtained from all patients from an initial diagnostic tissue sample or an optional biopsy during screening or previous treatment. Formalin-fixed-paraffin-embedded slides underwent immunohistochemistry for endosialin and platelet derived growth factor receptor-ß (PDGFR-β) as previously described [7, 9], using endosialin antibody clone 9G5 (Morphotek; Exton, PA) and PDGFR-β antibody 28E1 (Cell Signaling Technology; Danvers, MA). Immunohistochemistry was validated and performed by PhenoPath Labortories (Seattle, WA). Tumor content of slides was reviewed and tissues controls were incorporated into each run.

Slides were evaluated by a board-certified pathologist as percentages of cells with expression at intensities 0 (negative), 1+ (weak), 2+ (moderate), and 3+ (strong). The level of biomarker expression in each subcompartment was assessed as the M Score, calculated as [(% population scored 1+) + (2x % population scored 2+) + (3x % population scored 3+)]/6.

Baseline serum biomarkers were assayed to quantitate the level of endosialin and PDGFR-β as previously described [10]. Detection of ontuxizumab anti-drug antibody in serum samples was performed as previously described [11]. Serum concentrations of ontuxizumab were measured at each cycle for pharmacokinetic analysis. Ontuxizumab concentrations were measured using an endosialin-antigen based electrochemiluminescent immunoassay to capture and quantify the serum concentration of free/partially complexed ontuxizumab [11].

Statistics

Part 1 and Part 2 of the study were summarized and analyzed separately. The sample size was planned to be a maximum of 19 patients for Part 1 and 225 patients for Part 2 (120 to 200 patients in Part 2, with a particular sarcoma cohort to have no more than

60 patients). An independent unblinded committee monitored the trial. Part 1 data were summarized descriptively by dose level.

In Part 2, the primary analysis of PFS was conducted at the time at which 185 PFS events (progression or death) were observed, using Kaplan-Meier curves, with 95% confidence intervals (CI) for medians calculated according to Brookmeyer and Crowley [12]. PFS in treatment groups was compared in the intent-to-treat population, based on the log-rank test and hazard ratio (HR) was estimated based on Cox's proportional hazards model. These analyses were also conducted separately by sarcoma cohort. Overall survival was summarized in a similar manner.

Overall response rate (complete or partial) was summarized with 95%CIs using the Clopper-Pearson exact binomial CI [13] for each treatment group. In order to identify differences between treatment groups overall and within sarcoma cohort, a Bayesian hierarchical model was used to model PFS across the 4 strata [14]. Safety data were summarized using descriptive statistics.

Cox regression modeling was used to assess the influence of baseline tissue and serum biomarkers as covariates on PFS and OS. If the univariate regression model P-value (using the Wald chi-square test) for the factor was <0.2, then the factor was included as a candidate for inclusion in a step-wise selection process using a multivariate Cox regression model. Interactions between treatment and each factor were explored to assess the factor's ability to predict a clinical response. Exposure-response relationships were evaluated using Kaplan-Meier curves and were characterized in terms of median PFS and OS with 2-sided 95%CI constructed using the methodology of Brookmeyer and Crowley.

Results

Part 1

Sixteen patients enrolled in Part 1. Two dose levels of ontuxizumab (4 and 8 mg/kg) were planned in combination with G/D. No DLTs were observed in the 3 patients treated

within Cohort 1 (ontuxizumab 4 mg/kg). One of the 6 patients in Cohort 2 (ontuxizumab 8 mg/kg) experienced Grade 4 febrile neutropenia. An additional patient in Cohort 2 experienced a non-DLT event of Grade 4 neutropenia. Both patients in Cohort 2 had previously received more than 6 months of combination chemotherapy. Therefore, the G/D reduction criterion was amended to require a decrease of 25% of the starting dose for G/D for those previously been treated with more than 6 months of combination chemotherapy. Using this new criterion, two further de-escalation dose cohorts (Cohorts 3 & 4) were opened. In Cohort 3, the dose was decreased to 6 mg/kg and no DLTs were observed. Therefore, the dose was re-escalated to 8-mg/kg in Cohort 4 and no additional DLTs were observed.

In total, 3 patients received 4 mg/kg ontuxizumab, 4 patients received 6 mg/kg ontuxizumab, and 9 patients received 8 mg/kg ontuxizumab. The recommended Phase II dose of ontuxizumab in combination with G/D was 8 mg/kg. There were no treatment-related deaths or SAEs, and no AEs resulting in discontinuation from the trial in Part 1.

Part 2

A total of 255 patients were screened for entry into Part 2 and 209 were randomized. Of the 46 screen failures, 2 patients (0.8%) did not have measurable disease by RECIST v1.1, 1 patient (0.4%) failed to meet inclusion/exclusion criteria, and 43 patients (16.9%) were excluded for other reasons.

Patients were enrolled at 31 sites in the US, Australia, and Europe and randomized to either ontuxizumab+G/D (139 patients) or placebo+G/D (70 patients) and were included in the intent-to-treat population.

Of the 209 randomized patients, 2 patients in the ontuxizumab+G/D arm discontinued the trial prior to dosing, 1 due to death from progressive disease and 1 due to complications of hypertension. A total of 207 patients received at least 1 dose of ontuxizumab+G/D or placebo+G/D, of which 204 (97.6%) discontinued from the trial.

The baseline disease characteristics are displayed in Table 1. The study population consisted of 114 (55%) males and the median age was 56 (range 21 to 81) years. The proportion of patients with baseline ECOG scores of 1 was higher in the ontuxizumab+G/D group (72/139 patients, 52%) than in the placebo+G/D group (31/70 patients, 44%).

The duration of treatment for the ontuxizumab+G/D group was a mean of 5.1 (range: 0.3 to 21.4) months, with a mean relative dose intensity of 97%. The duration of treatment for the placebo+G/D group was 5.4 (range: 0.3 to 21.2) months, with a mean relative dose intensity of 99.9%. Treatment delays associated with an AE occurred in 42% of patients receiving ontuxizumab+G/D and in 45% of patients receiving placebo+G/D. Dose reductions occurred in 8% of patients in both arms.

There was no significant difference between treatment arms for PFS. The median PFS was 4.3 (95%CI: 2.7–6.3) months in the ontuxizumab+G/D arm compared to 5.6 (95%CI: 2.6–8.3) months in the placebo+G/D arm, *P*=0.67 and HR=1.07 (95%CI: 0.77, 1.49). The Kaplan Meier curve for PFS is displayed in Figure 1. No significant difference between treatment arms was apparent by sarcoma cohort (Table 2).

There was no significant difference in median OS between the two arms; 18.3 (95%CI: 16.2, 21.1) months in the ontuxizumab+G/D arm and 21.1 (95%CI: 14.2, not reached) months in the placebo+G/D arm, *P*=0.32 and HR=1.23 (95%CI: 0.82, 1.83). The Kaplan Meier curve for OS is displayed in Figure 2.

The only sarcoma cohort with a longer median PFS in the ontuxizumab group was the “other” category. The “other” cohort comprised of at least 13 different histological subtypes; consisting of angiosarcoma (n=5), spindle cell sarcoma (n=5), peripheral nerve sheath tumor (n=7), synovial sarcoma (n=20), and miscellaneous (n=20). Patients with spindle cell sarcoma treated with ontuxizumab had a longer median PFS and OS compared to placebo (median PFS: 2.8 months for ontuxizumab and 1.6 months for placebo) and (median OS: 10.7 months for ontuxizumab and 2.0 months for placebo). Patients treated with ontuxizumab in the miscellaneous subcategory also had a longer

median PFS and OS compared to placebo. These were exploratory analyses and no statistical comparisons were made.

There was no significant difference in ORR between the 2 arms (P=1.00) or by sarcoma cohort (P<0.2 for HR<0.75). Three patients achieved a complete response, 1 (1%) treated with ontuxizumab+G/D and 2 (3%) treated with placebo+G/D. Partial response was achieved in 38 patients, 26 (19%) treated with ontuxizumab+G/D and 12 (17%) treated with placebo+G/D. Sixty patients (43%) in the ontuxizumab+G/D arm and 33 (47%) in the placebo+G/D arm had stable disease as best response.

At trial termination, 2 patients with partial responses continued ontuxizumab. Both patients achieved a partial response at Cycle 17 that continued for over 2 years on therapy.

Safety

All patients in both arms had at least one treatment-emergent AE, the most common (in ≥40% of all patients) were fatigue (74% vs 66%), anemia (61% vs 60%), nausea (56% vs 52%), diarrhea (44% vs 36%), peripheral edema (42% vs 45%) and thrombocytopenia (41% vs 43%) in the ontuxizumab+G/D group and placebo+G/D arms, respectively.

A numerically higher proportion of patients in the ontuxizumab+G/D group (86%) than in the placebo+G/D group (76%) had treatment-emergent AEs that were considered related to treatment (Table 3). Treatment-related AEs that occurred in a higher proportion of patients (>10% difference) in the ontuxizumab+G/D than the placebo+G/D arm included fatigue, headache, pyrexia, diarrhea, and vomiting. Rash occurred more frequently in the placebo + G/D (18/67, 27%) than the ontuxizumab + G/D arm (16/140, 11%).

The frequency of patients with at least 1 SAE was similar in both arms, 50% in the ontuxizumab+G/D and 48% in the placebo+G/D arm. The most frequent treatment-related SAEs were pyrexia (3% overall, 4% in ontuxizumab+G/D, 0% in placebo+G/D)

and anemia (2% overall, 1% in ontuxizumab+G/D, 3% in placebo+G/D). There were no differences in laboratory values, vital signs or ECG parameters between the two arms.

One patient in each arm died of a treatment-related AE (cardiac arrest in the ontuxizumab+G/D and respiratory failure in the placebo+G/D arm). Two patients (1%) in the ontuxizumab+G/D arm experienced drug hypersensitivity AEs (infusion-related reaction and pyrexia, flushing); all were non-serious and Grade 1. None of the drug hypersensitivity AEs resulted in an interruption or discontinuation of ontuxizumab. One patient on ontuxizumab+G/D developed a transient treatment-induced ADA response.

Biomarkers and pharmacokinetics

Baseline tumor tissue expression of endosialin and PDGFR-β were measured in the sub-compartments of arterial endothelial, capillary endothelial, cytoplasmic tumor endothelial, lymphatic endothelial, membranous tumor endothelial, nonvascular stromal, perivascular and venous endothelial cells (Table 4). No significant difference in baseline biomarker expression between arms was observed. The highest levels of endosialin were measured in non-vascular stromal, perivascular, and venous endothelial cells. The highest levels of PDGFR-β were measured in capillary endothelial, cytoplasmic tumor, lymphatic endothelial, non-vascular stromal, and perivascular cells.

A prognostic biomarker demonstrates an association with outcome regardless of therapy. Factors considered possibly prognostic of PFS included log serum endosialin concentration (P=0.06), tissue endosialin in venous endothelial cells (P=0.04), and tissue PDGFR-β in capillary endothelial cells (P=0.10). Longer PFS was associated with higher serum endosialin concentration (HR=0.61; 95%CI: 0.36-1.03), lower tissue endosialin in venous endothelial cells (HR=1.01; 95%CI: 1.0=1.02), and lower tissue PDGFR-β in capillary endothelial cells (HR=0.74; 95%CI: 0.51-1.06). Factors considered possibly prognostic of OS were endosialin cytoplasmic tumor endothelial cells (P=0.09) and endosialin membranous tumor endothelial cells (P=0.12). Longer OS was associated with lower tissue endosialin in cytoplasmic tumor endothelial cells (HR=1.01; 95%CI: 1.0=1.02) and higher tissue endosialin in membranous tumor

endothelial cells (HR=1.02; 95%CI: 1.0=1.04).

A predictive biomarker provides information about the effect of a therapeutic intervention on clinical outcome and can potentially be used to select patients for therapy. Tissue PDGFR-β in capillary endothelial cells showed a significant treatment interaction (*P*=0.02), with values below median associated with an improved PFS, (HR=0.55, 95%CI: 0.29, 1.04). No baseline biomarkers were predictive of improved OS with ontuxizumab.

Ontuxizumab had no clear exposure effect on PFS or OS.

Discussion

Ontuxizumab in combination with G/D was well tolerated in patients with soft tissue sarcomas. Despite promising pre-clinical and some durable benefit in sarcoma patients treated within Phase I trials [11], the combination did not show superior activity compared to G/D alone in this randomized trial. This was consistent in all 4 histological cohorts studied in the randomized component of the trial.

The combination of G/D was utilized in this study because it has proven efficacy in advanced sarcomas [8, 15, 16]. A previous trial reporting a median PFS of 7.5 months with G/D and bevacizumab [17], provided support for the combination of G/D with anti-angiogenic agents in sarcomas.

Ontuxiumab was utilized in this trial to evaluate the hypothesis that blocking endosialin-mediated tumor angiogenesis will enhance the efficacy of G/D in sarcomas. However, no improvement in PFS or OS was observed with ontuxizumab. A major difficulty in conducting trials in sarcomas is the profound heterogeneity of these diseases. One of the goals of this trial was to evaluate the benefit of ontuxizumab in all soft tissue

sarcomas, as well as specific cohorts, in order to potentially identify subsets that might benefit from ontuxizumab. Ontuxizumab showed no additional benefit in liposarcoma, leiomysarcoma, and undifferentiated pleomorphic sarcoma. However, in the heterogeneous 'other' cohort, longer median PFS (not statistically significant) was observed with ontuxizumab. In order to evaluate potential benefit in specific subtypes included in the "other" cohort, we performed an exploratory analysis. The spindle cell and miscellaneous sarcoma subcategories showed a non-significant, but numerically longer median PFS with ontuxizumab treatment.

The choice of ontuxizumab dose in this trial was based on the completed, single-agent ontuxizumab Phase I trial with an MTD of 12 mg/kg (11). One potential criticism of our trial is that the dose of ontuxizumab was not high enough. In the Phase I study, pharmacokinetic data suggested accumulation of ontuxizumab at 4 mg/kg, and that exposures were similar between 8 mg/kg and 12 mg/kg with weekly administration. For this reason, the decision was made a priori not go above 8 mg/kg ontuxizumab in combination with G/D for the current trial. Because of the potential accumulation of ontuxizumab at doses above 4 mg/kg, we may not have given a high enough dose of ontuxizumab. However, pharmacokinetic analyses indicated that ontuxizumab exposure had no effect on PFS and OS.

The profile of AEs occurring more frequently in the ontuxizumab arm (fatigue, headache, pyrexia, diarrhea, and vomiting) resembles the profile of most frequent AEs observed in the Phase I trial [11]. These results suggest that ontuxizumab did have a pharmacologic effect in the current trial. Whether this dose was sufficiently high to block the angiogenic effect of endosialin is not certain.

Endosialin is believed to increase proliferation of pericytes resulting in enhanced tumor angiogenesis via a PDGR receptor signaling pathway (3). In the current trial, patients were not selected on the basis of endosialin expression.

A longer PFS was associated with a higher serum endosialin concentration, a lower tissue endosialin in venous endothelial cells, and a lower tissue PDGFR-β in capillary endothelial cells at baseline. Among ontuxizumab-treated patients, a lower tissue

PDGFR-β in capillary endothelial cells was associated with an improved PFS, indicating it was a potential predictive indicator of improved PFS with ontuxizumab.

Although compelling evidence linked the expression of endosialin with tumor growth and progression in pre-clinical studies, the biomarkers measured in this trial showed no predictive association with outcome in the ontuxizumab+G/D arm. One potential reason for the weak association between endosialin-associated biomarkers and outcome is the low efficacy of ontuxizumab in this trial.

Based on these data, further trials of ontuxizumab in soft tissue sarcomas are not warranted. Due to the stratification by subtype, this trial provides a benchmark of the subtype specific efficacy of G/D. In the future, the potential use of antibody-drug conjugates to selectively deliver cytotoxic agents to tumor sites could be evaluated. Since endosialin is highly expressed in sarcomas [2, 5], ontuxizumab could be used to target sarcoma cells and deliver cytotoxic agents linked to it. In a human endosialin positive sarcoma xenograft model, prolonged anti-tumor activity of an anti-endosialin antibody conjugated to cytotoxic agents was observed compared to controls [18].

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Table 1: Baseline Characteristics for Patients Enrolled in Part 2 (Intent-To-Treat Population)

	Ontuxizumab 8 mg/kg+G/D (*N*=139)	Placebo+ G/D(*N*=70)	Total (*N*=209)
Age (years)			
Mean (SD)	55 (13)	54 (14)	55 (14)
Sex, *N* (%)			
Male	76 (55)	38 (54)	114 (55)
Female	63 (45)	32 (46)	95 (46)
Race, *N* (%)			
White	116 (84)	57 (81)	173 (83)
Black or African American	12 (9)	9 (13)	21 (10)
Other	11 (8)	4 (6)	15 (7)
Initial Histologic Diagnosis Grade, *N* (%)			
Grade 1	3 (2)	4 (6)	7 (3)
Grade 2	21 (15)	13 (19)	34 (16)

	Ontuxizumab 8 mg/kg+G/D (*N*=139)	Placebo+ G/D(*N*=70)	Total (*N*=209)
Grade 3	82 (59)	38 (54)	120 (57)
Grade Unknown	22 (16)	9 (13)	31 (15)
Missing	11 (8)	6 (9)	17 (8)
Baseline ECOG Performance Status, *N* (%)			
0	67 (48)	39 (56)	106 (51)
1	72 (52)	31 (44)	103 (49)
Prior Chemotherapy in the Metastatic Setting		40	114 (55)
First line	65 (47)	30 (43)	95 (45)
Second line	53 (38)	29 (41)	82 (39)
Third line	21 (15)	11 (16)	32 (15)
Histologic Subtype, *N* (%)			
Liposarcoma	30 (22)	15 (21)	45 (22)
Leiomyosarcoma	41 (29)	21 (30)	62 (30)
Undifferentiated pleomorphic sarcoma or myxofibrosarcoma	30 (22)	15 (21)	45 (22)
Other	38 (27)	19 (27)	57 (27)
Angiosarcoma	3	2	5
Spindle cell sarcoma	3	2	5
Peripheral nerve sheath tumor	6	1	7
Synovial sarcoma	14	6	20

	Ontuxizumab 8 mg/kg+G/D (*N*=139)	Placebo+ G/D(*N*=70)	Total (*N*=209)
Miscellaneous or unclassified	12	8	20

ECOG = Eastern Cooperative Oncology Group, G/D = gemcitabine/docetaxel, SD=standard deviation. Miscellaneous or unclassified histologic subtypes include patients with histologic diagnosis of rhabdomyosarcoma (3), unclassified sarcoma (3), epitheliod saracoma (3), hemangiopericytoma (2), endometrial sarcoma (2), adenosarcoma (1), clear cell sarcoma (1), fibrosarcoma (1), intimal sarcoma (1), phyllodes (1), other liposarcoma (1), and small blue round cell tumor (1).

Table 2: Progression-Free Survival Using Bayesian Hierarchical Model (Part 2)

Sarcoma Type Parameter	Ontuxizumab 8.0 mg/kg+G/D	Placebo+G/D
Liposarcoma		
N	30	15
PFS observed median (weeks)	14.6	24.1
Hazard ratio (95% CI)	1.12 (0.69 - 1.89)	
OS observed median (weeks)	58.5	54.4
Hazard ratio (95% CI)	1.1 (0.56 - 1.87)	
BOR (% with response)	20/30 (67%)	12/15 (80%)
P-value	0.236	
Leiomyosarcoma		
N	41	21
PFS observed median (weeks)	18.3	24.0
Hazard ratio (95% CI)	1.08 (0.68 - 1.61)	
OS observed median (weeks)	64.6	69.1
Hazard ratio (95% CI)	1.3 (0.74 – 2.28)	
BOR (% with response)	27/41 (66%)	16/21 (76%)
P-value	0.551	
UPS		
N	30	15
PFS observed median (weeks)	10.3	33.6
Hazard ratio (95% CI)	1.23 (0.73 - 2.09)	
OS observed median (weeks)	54.1	55.3
Hazard ratio (95% CI)	1.2 (0.68 – 2.00)	
BOR (% with response)	16/30 (53%)	11/15 (73%)
P-value	0.174	

Other		
N	38	19
PFS observed median (weeks)	10.3	6.7
Hazard ratio (95% CI)	1.01 (0.60 - 1.54)	
OS observed median (weeks)	56.6	57.1
Hazard ratio (95% CI)	1.1 (0.63 - 1.70)	
BOR (% with response)	24/38 (63%)	8/19 (42%)
P-value	0.389	

G/D=gemcitabine/docetaxel; PFS=progression-free survival; CI=Confidence Interval; OS=overall survival; BOR=percentage of patients with stable disease, partial response, or complete response as best overall response; UPS= undifferentiated pleomorphic sarcoma

Table 3: Treatment-Emergent Adverse Events Considered Related to Treatment by the Investigator in ≥15% of Patients in Either Treatment Group, Part 2 (Safety Population)

Preferred Term[a]	Ontuxizumab 8 mg/kg+G/D (*N*=140) n (%)	Placebo+G/D (*N*=67) n (%)	Total (*N*=207) n (%)
Fatigue	66 (47)	23 (34)	89 (43)
Nausea	44 (31)	15 (22)	59 (29)
Headache	42 (30)	9 (13)	51 (25)
Anemia	39 (28)	18 (27)	57 (28)

Pyrexia	35 (25)	8 (12)	43 (21)
Diarrhea	31 (22)	6 (9)	37 (18)
Thrombocytopenia	29 (21)	11 (16)	40 (19)
Edema peripheral	28 (20)	13 (19)	41 (20)
Decreased appetite	28 (20)	10 (15)	38 (18)
Myalgia	25 (18)	5 (8)	30 (15)
Vomiting	24 (17)	3 (5)	27 (13)
Chills	21 (15)	3 (5)	24 (12)
Rash	16 (11)	18 (27)	34 (16)

G/D= gemcitabine/docetaxel

a: Adverse events were coded using Medical Dictionary for Drug Regulatory Activities (MedDRA) version 14.1.

Table 4: Mean Baseline Biomarker Values for Patients Enrolled in Part 2 (Intent-To-Treat Population)

Biomarker	Ontuxizumab 8 mg/kg+G/D (*N*=139)	Placebo+ G/D(*N*=70)
Endosialin lymphatic endothelial cell M-score	12.8	13.3
Endosialin membranous tumor cell M-score	4.2	4.3
Endosialin non-vascular stromal cell M-score	18.3	18.7
Endosialin perivascular cell M-score	24.1	22.9
Endosialin venous endothelial cell M-score	19.1	16.8
Log plasma endosialin (ng/mL)	11.463	11.486

Biomarker	Ontuxizumab 8 mg/kg+G/D (*N*=139)	Placebo+ G/D(*N*=70)
PDGFR-β arterial endothelial cell M-score	3.4	3.2
PDGFR-β capillary endothelial cell M-score	30.0	29.0
PDGFR-β cytoplasmic tumor cell M-score	22.7	21.5
PDGFR-β lymphatic endothelial cell M-score	22.0	21.7
PDGFR-β membranous tumor cell M-score	8.3	4.7
PDGFR-β non-vascular stromal cell M-score	21.4	23.4
PDGFR-β perivascular cell M-score	31.8	29.8
PDGFR-β venous endothelial cell M-score	3.6	3.5
Log plasma PDGFR-β (ng/mL)	7.830	7.872

G/D = gemcitabine/docetaxel; PDGFR-β = platelet derived growth factor receptor-ß.

Figure Legends

Figure 1: Kaplan Meier Curve of Progression-Free Survival for All Sarcoma Subtypes, Part 2 (Intent-to-Treat Population)

Figure 2: Kaplan Meier Curve of Overall Survival for All Sarcoma Subtypes, Part 2 (Intent-to-Treat Population)

Table 1: Baseline Characteristics for Patients Enrolled in Part 2

	Ontuxizumab 8 mg/kg+G/D (*N*=139)	Placebo+G/D (*N*=70)	Total (*N*=209)
Age (years)			
Mean (SD)	55 (13)	54 (14)	55 (14)
Sex, *N* (%)			
Male	76 (55)	38 (54)	114 (55)
Female	63 (45)	32 (46)	95 (46)
Race, *N* (%)			
White	116 (84)	57 (81)	173 (83)
Black or African American	12 (9)	9 (13)	21 (10)
Other	11 (8)	4 (6)	15 (7)
Disease Stage at Initial Diagnosis, *N* (%)			
Stage IA	8 (6)	1 (1)	9 (4)
Stage IB	4 (3)	4 (6)	8 (4)
Stage IIA	10 (7)	5 (7)	15 (7)
Stage IIB	17 (12)	10 (14)	27 (13)
Stage III	39 (28)	24 (34)	63 (30)
Stage IV	47 (34)	19 (27)	66 (32)
Missing	14 (10)	7 (10)	21 (10)
Initial Histologic Diagnosis Grade, *N* (%)			
Grade 1	3 (2)	4 (6)	7 (3)
Grade 2	21 (15)	13 (19)	34 (16)
Grade 3	82 (59)	38 (54)	120 (57)
Grade X	22 (16)	9 (13)	31 (15)
Missing	11 (8)	6 (9)	17 (8)

	Ontuxizumab 8 mg/kg+G/D (*N*=139)	Placebo+G/D (*N*=70)	Total (*N*=209)
Baseline ECOG Performance Status, *N* (%)			
0	67 (48)	39 (56)	106 (51)
1	72 (52)	31 (44)	103 (49)

ECOG = Eastern Cooperative Oncology Group, G/D = gemcitabine/docetaxel, SD=standard deviation.

Table 2: Progression-Free Survival Using Bayesian Hierarchical Model (Part 2)

Sarcoma Type Parameter	Placebo+G/D	Ontuxizumab 8.0 mg/kg+G/D
Liposarcoma		
N	15	30
Observed median (weeks)	24.1	14.6
Hazard ratio (95% CI)	1.12 (0.69 - 1.89)	
Leiomyosarcoma		
N	21	41
Observed median (weeks)	24.0	18.3
Hazard ratio (95% CI)	1.08 (0.68 - 1.61)	
UPS		
N	15	30
Observed median (weeks)	33.6	10.3
Hazard ratio (95% CI)	1.23 (0.73 - 2.09)	
Other		
N	19	38
Observed median (weeks)	6.7	10.3
Hazard ratio (95% CI)	1.01 (0.60 - 1.54)	

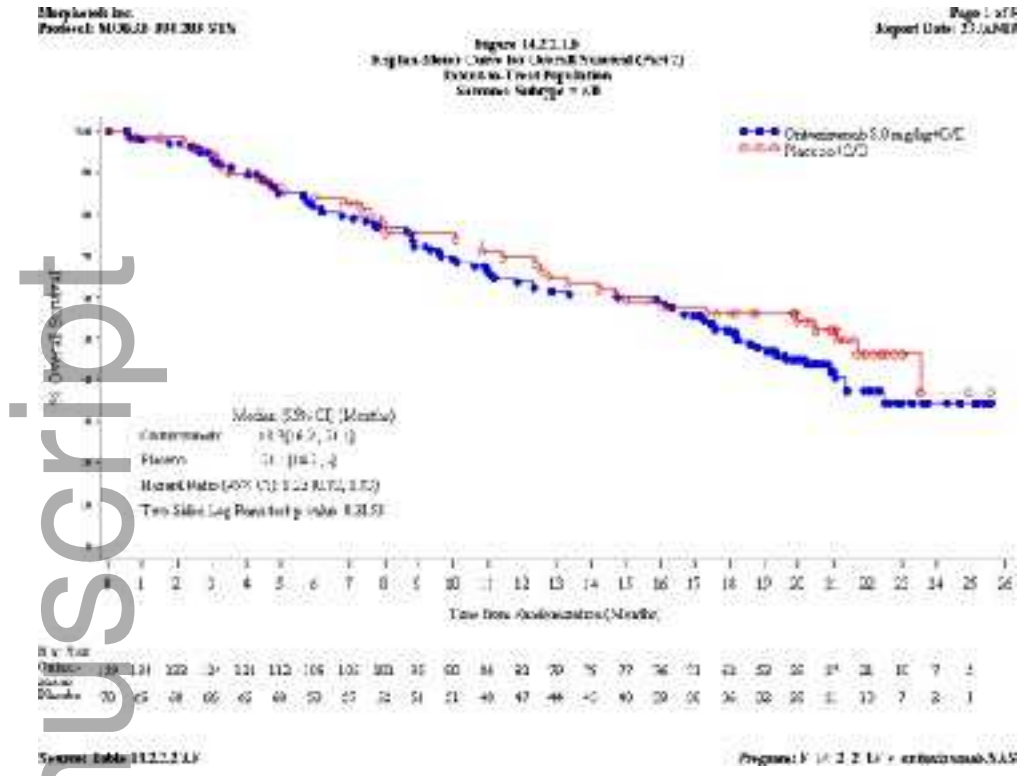
G/D=gemcitabine/docetaxel; CI=Confidence Interval; UPS= undifferentiated pleomorphic sarcoma

Table 3: Treatment-Emergent Adverse Events Considered Related to Treatment by the Investigator in ≥15% of Patients in Either Treatment Group, Part 2

Preferred Term[a]	Ontuxizumab 8 mg/kg+G/D (*N*=140) n (%)	Placebo+G/D (*N*=67) n (%)	Total (*N*=207) n (%)
Fatigue	66 (47)	23 (343)	89 (43)
Nausea	44 (31)	15 (22)	59 (29)
Headache	42 (30)	9 (13)	51 (25)
Anemia	39 (28)	18 (27)	57 (28)
Pyrexia	35 (25)	8 (12)	43 (21)
Diarrhea	31 (22)	6 (9)	37 (18)
Thrombocytopenia	29 (21)	11 (16)	40 (19)
Edema peripheral	28 (20)	13 (19)	41 (20)
Decreased appetite	28 (20)	10 (15)	38 (18)
Myalgia	25 (18)	5 (8)	30 (15)
Vomiting	24 (17)	3 (5)	27 (13)
Chills	21 (15)	3 (5)	24 (12)
Rash	16 (11)	18 (27)	34 (16)

G/D= gemcitabine/docetaxel

a: Adverse events were coded using Medical Dictionary for Drug Regulatory Activities (MedDRA) version 14.1.



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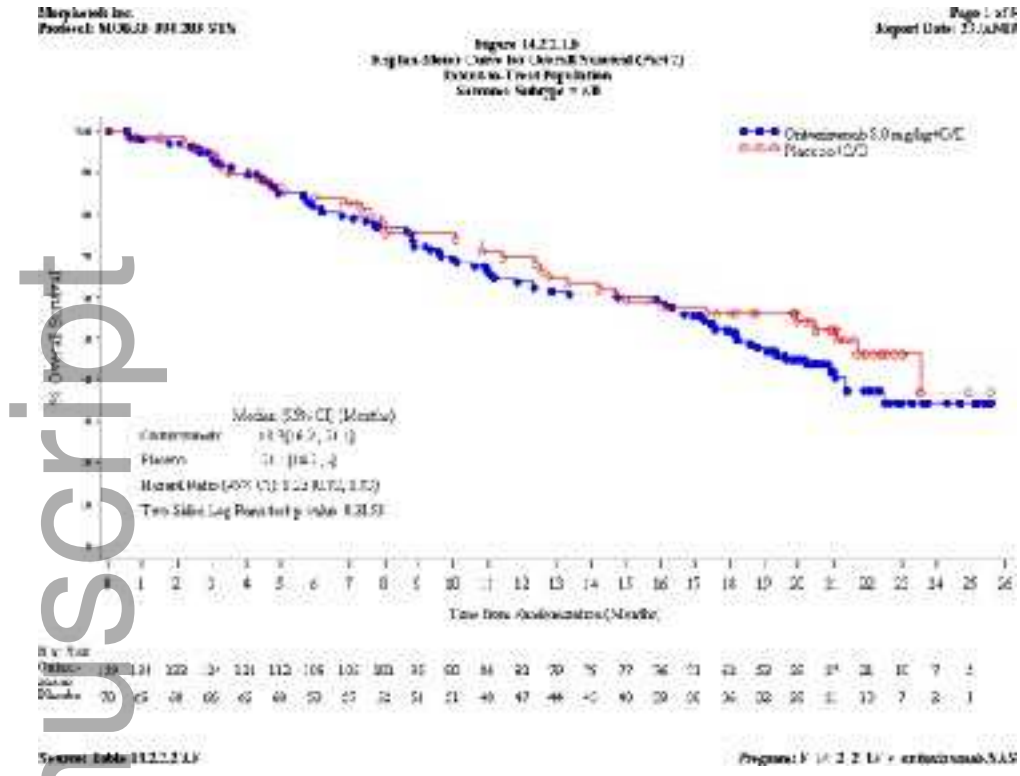

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