Circulating Tumor Cells and Biomarker Modulation with Olaratumab Monotherapy Followed by Olaratumab plus Doxorubicin: Phase Ib Study in Patients with Soft-Tissue Sarcoma

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ABSTRACT

This phase Ib study enumerated whole blood circulating tumor cells (CTC) and evaluated biomarkers in patients with potentially resectable soft-tissue sarcoma (STS) treated with olaratumab monotherapy (20 mg/kg) for one cycle followed by up to six cycles of olaratumab (20 mg/kg, cycles 1–2; 15 mg/kg, cycles 3–7) plus doxorubicin (75 mg/m^2 on day 1). CTCs, platelet-derived growth factor receptors (PDGFR), and PDGF ligand expression in tumor tissue pre- and post-olaratumab monotherapy were evaluated. Antitumor activity, safety, pharmacokinetics, and PET/biomarker association with clinical outcome were assessed. Of 51 treated patients, 35, 43, and 37 were evaluable for CTC enumeration, PDGFRs, and PDGF ligand expression, respectively. An increase in CTCs at cycle 1 day 8 was observed, followed by a significant reduction by cycle 3 day 1 or 30-day follow-up. Decrease in CTC counts after olaratumab monotherapy was higher in patients with disease control than without disease control (57.9% vs. 31.2%). Baseline IHC expression was positive in most patients for PDGFRα [n = 31 (72.1%)] and PDGFRβ [n = 36 (83.7%)]. Similar rates were observed post-olaratumab monotherapy [PDGFRα, n = 30 (69.8%); PDGFRβ, n = 33 (76.7%)]. Eleven patients (29.7%) showed a 30% reduction by RT-PCR in PDGFRα at cycle 2. PDGFR expression and PET response showed no correlation with clinical outcome. Safety and pharmacokinetic profiles were consistent with previous reports. This study, the first to use a validated method for CTC detection, confirms that CTC enumeration in STS is feasible. However, no correlation was observed between PDGFRα expression and clinical outcome.

Introduction

Soft-tissue sarcomas (STS) are a group of rare and heterogeneous mesenchymal tumors, comprising approximately 1% of adult cancers (1). The management of STS remains challenging, partly due to a lack of effective systemic therapies. Despite optimal management, localized disease develops into incurable, metastatic disease in approximately 50% of patients (2, 3). Single-agent doxorubicin, introduced in the early 1970s, remains the standard treatment option for many patients with metastatic STS (4, 5). Several randomized trials have failed to show any survival benefit for combination therapies of doxorubicin and novel agents compared with single-agent doxorubicin (6–11).

Olaratumab is a recombinant human IgG, subclass 1 (IgG1) antagonist of the platelet-derived growth factor receptor alpha (PDGFRα), a receptor which plays an important role in mesenchymal biology and in modulating the tumor and stromal microenvironment (12). Olaratumab is a first-in-class IgG1 mAb that binds to PDGFRα, blocking PDGF-AA, PDGF-BB, and PDGF-CC receptor binding and activation (13).

In a phase Ib/II trial, patients treated with olaratumab and doxorubicin (phase II portion) achieved a higher median progression-free survival (PFS), median overall survival (OS), and objective response rate (ORR), with an acceptable safety profile compared with those treated with doxorubicin alone (12). On the basis of these results, olaratumab was granted accelerated approval by the FDA in October 2016, and subsequently conditional marketing authorization by the European Medicines Agency (14). Continued approval was contingent upon verification of clinical benefit in a confirmatory trial; however, the results of the phase III trial, ANNOUNCE, did not confirm a clinical benefit for olaratumab combined with doxorubicin compared with doxorubicin monotherapy in patients with advanced or metastatic STS. Hence, olaratumab was no longer recommended for treatment of advanced STS as of January 2019 (15, 16).

Because atypical expression and/or activation of PDGFRα is implicated in several subtypes of STS, there is great interest in exploring anti-PDGFRα therapies (17). Preliminary analysis of tumor specimens from the phase Ib/II trial of olaratumab and doxorubicin indicated that tumor expression of PDGFRα by IHC was not a predictor of OS (12).

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Possible explanations for this finding include the highly variable and often lengthy time periods between tumor sampling and trial entry, and the analysis of primary versus metastatic lesions. This is further coupled with an incomplete understanding of the possible relationship between efficacy, the level of PDGFRα, and ligands expression in tumor and stroma, and the compensation mechanism as heterodimerization with PDGFRß.

The phase Ib JGDM trial (NCT02783599) was therefore conducted to assess the modulation of biological markers and the mechanism of action of olaratumab in patients with potentially resectable STS prior to the known results from the ANNOUCE trial. This allowed pre- and post-olaratumab dosing tumor sampling of the same tumor lesion, while also providing the potential to examine a resected tumor specimen after combination treatment with olaratumab and doxorubicin. The tissue biopsies were preferably taken from the same primary tumor lesion (if clinically feasible). The current trial also offered the opportunity to evaluate the feasibility of assaying liquid biomarkers, such as circulating tumor cell (CTC) enumeration. Although data regarding the prognostic significance of CTC isolation in sarcomas are limited, a correlation between CTC presence and disease progression has been observed (18). The detection of CTCs in sarcomas could greatly improve the ability to provide prognostic/predictive information and lead to better understanding of drug resistance (19).

The objectives of this phase Ib study were to enumerate whole blood CTCs and to characterize PDGFRα, PDGFRβ, and canonical ligand (PDGF-A, -B, -C, and -D) expression changes pre- and post-olaratumab monotherapy in tumor tissue in patients with potentially resectable STS. Antitumor activity, safety, and pharmacokinetics of olaratumab in combination with doxorubicin were also assessed. An exploratory PET scan analysis was also performed to evaluate associations between PET scan, tissue biomarkers, and CTCs.

Materials and Methods

Study design and participants

This was an open-label, single-arm, multicenter, phase Ib study. The study design is presented in Supplementary Fig. S1. Patients were enrolled at 10 sites in 5 countries: United States, Spain, France, United Kingdom, and Italy. Study participants were required to have a histologically confirmed diagnosis of STS for which olaratumab and doxorubicin would be appropriate therapy, and had potentially resectable disease with primary tumor lesions amenable to serial biopsy. Patients were ages 18 years or older, and had an Eastern Cooperative Oncology Group performance status of 0 to 1. Patients were excluded if they had a diagnosis of gastrointestinal stromal tumors or Kaposi sarcoma; active central nervous system or leptomeningeal metastasis at the time of enrollment; or received prior treatment with an anthracycline, anthracenedione, or olaratumab.

The trial was conducted in accordance with the Declaration of Helsinki, and the International Conference on Harmonisation Guidelines for Good Clinical Practice. All patients provided written informed consent to participate in the study. The study protocol was approved by each institution's review board or ethics committee, or both, and was registered with ClinicalTrials.gov (NCT02783599).

Treatment and assessments

Patients received olaratumab monotherapy in cycle 1, followed by up to six cycles of olaratumab plus doxorubicin (Supplementary Fig. S1). Each cycle of treatment was 21 days. Olaratumab dosage was 20 mg/kg (cycles 1 and 2) or 15 mg/kg (cycles 3–7) on days 1 and 8; doxorubicin was dosed at 75 mg/m^2 on day 1. At the start of cycle 2, dexrazoxane was allowed to reduce the potential of doxorubicin-associated cardiotoxicity.

Tumor response was assessed every 6 weeks according to the RECIST (version 1.1). Tumors were assessed with CT scan or magnetic resonance imaging. Tissue biopsies were required pretreatment and posttreatment with olaratumab monotherapy and whole blood samples were collected at different time points for CTC, pharmacokinetic, and immunogenic analyses. Safety and tolerability of the study drug was determined by reported adverse events (AE), physical examination, laboratory tests, electrocardiograms, dose adjustments, and results from echocardiogram/multigated acquisition scans. AEs and clinical laboratory toxicities were graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE, version 4.0).

In addition, the presence of lung metastasis (yes vs. no) at baseline was also recorded using CT. An exploratory analysis was performed to evaluate efficacy in the two subgroups.

Biomarker analyses

CTC enumeration

The CTC enumeration was performed by Epic Sciences, San Diego, CA following validation of a customization of their antibody expression and image analysis algorithm to detect known sarcoma CTCs. In brief, dilutions of three sarcoma cell lines U2-OS (osteosarcoma), SW872 (undifferentiated liposarcoma), and SKLMS1 (leiomyosarcoma) were spiked into whole normal donor blood at concentrations ranging up to 1,315.6 CTC cells/mL. Approximately 3 million nucleated cells were plated on up to 10 microscope slides per sample. Slides per sample were stained and analyzed with a cocktail of antibodies, including multiple cytokeratins and intermediate filaments, to perform CTC enumeration. Stained slides were scanned by a rapid fluorescence scanning method and examined using Epic Sciences' proprietary algorithm that analyzes approximately 90 cellular parameters, including marker expression [DAPI, cytokeratin (CK), CD45] and cell morphology, to differentiate candidate CTCs from surrounding white blood cells (20). Detection of sarcoma CTCs via low level expression of intermediate filaments, as detected by Epic Sciences' antibody cocktail was confirmed. The assay was analytically validated with multiple runs by multiple operators for a detection range from 27.9 CTC cells/mL to 1,315.6 CTC cells/mL, and mean CK expression from 34.7 to 350.9. A threshold of 2.8 CK signal-to-noise ratio was established as an appropriate cutoff for assessing CK positivity in sarcoma cell lines, and by extension, JGDM patient samples.

Whole blood samples for determination of CTC counts for the study were collected predose (on days 1 and 8 of cycles 1 and 2, on day 1 of cycle 3) and at the end of study treatment or at the time of surgical resection, whichever came first. Two replicate slides per sample were processed and evaluated for CTC enumeration as described above. Traditional CTCs were defined as cytokeratin/intermediate filament cocktail-positive cells and CK-positive clusters. All population CTCs comprised all traditional CTCs plus CK-negative cells, CK-negative clusters, and apoptotic cells.

PDGFRα/β and ligand expression

The PDGFRα and PDGFRβ protein expression in tumor cells was assessed by IHC at Clinical Diagnostics Laboratory, Eli Lilly and Company, Indianapolis, IN. Tumor tissue samples sufficient to establish PDGFRα and PDGFRβ expression were required to be collected pre- and post-olaratumab monotherapy for all evaluable patients. The PDGFRα status was determined using the Cell Signaling Technology rabbit mAb (clone D13C6) proven to be specific for PDGFRα, with no cross-reactivity for PDGFRβ. The PDGFRβ status was determined

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using the Cell Signaling Technology mouse mAb (clone 2B3) proven to be specific for PDGFRβ, with no cross-reactivity for PDGFRα. The status was provided as a dichotomous variable with "positive" and "negative" expression. A "positive" result showed at least 10% of the tumor (rounded to the nearest decile) demonstrating at least weak, but specific, membranous staining (1+ on a 0, 1+, 2+, 3+ scale of staining intensity); "negative" corresponded to an expression that did not meet these criteria.

The PDGFRα, PDGFRβ, and canonical ligand (PDGF-A, -B, -C, and -D) expression was assessed by RT-PCR at Clinical Diagnostics Laboratory, Eli Lilly and Company, Indianapolis, IN. The RT-PCR with relative quantification was performed on pre- and post-olaratumab monotherapy samples targeting PDGF-A, PDGF-B, PDGF-C, PDGF-D, PDGFRα, and PDGFRβ. In brief, ribonucleic acid was extracted from formalin-fixed paraffin-embedded pre- and post-olaratumab monotherapy on-study biopsies submitted for each patient. Samples were assayed in a validated multiplex PCR assay with primers specific for PDGF-A, PDGF-B, PDGF-C, PDGF-D, PDGFRα, and PDGFRβ, with appropriate controls, alongside reference gene MS2. Relative quantification of expression was calculated between each of the ligand and receptor genes using a delta–delta C_t method with reference gene MS2.

Pharmacokinetic analysis

Human serum derived from patient blood samples was analyzed for olaratumab using a validated enzyme-linked immunosorbent assay method. Pharmacokinetic parameters for olaratumab were determined by noncompartmental analysis using Phoenix WinNonlin 8.0 (Pharsight, a Certara Company).

Immunogenicity analysis

Immunogenicity samples obtained during this study were analyzed for anti-olaratumab antibodies using a validated immunoassay at Pharmaceutical Product Development (PPD), LLC. Samples were assessed using a 4-tiered approach for the detection, confirmation, titer determination, and characterization of neutralizing activity of anti-olaratumab antibodies in human serum. The anti-olaratumab antibody assay (ADA) has a minimal required dilution of 1:10, a validated sensitivity of 13.7 ng/mL, and a drug tolerance of >500 μg/mL olaratumab in the presence of 500 ng/mL affinity purified hyper-immunized monkey anti-olaratumab antibody. The immunogenicity analyses were conducted on all immunogenicity-evaluable patients within the defined safety population. The frequency and percentage (incidence) of evaluable patients with positive, negative, or missing ADA to olaratumab at baseline, and with positive, negative, or inconclusive ADA postbaseline were summarized. Patients who were treatment-emergent (TE)-ADA positive (persistent positive or transient positive), TE-ADA persistent positive, and TE-ADA transient positive were also summarized. Positive neutralizing ADA, negative neutralizing ADA, and inconclusive neutralizing ADA were also reported for patients who were TE-ADA positive.

Efficacy and safety analyses

The secondary objectives assessed antitumor activity, and safety and tolerability. Best overall response was summarized. Objective response rate (ORR), defined as clinical response (CR) + partial response (PR), and disease control rate (DCR), defined as CR + PR + stable disease (SD), were also tabulated along with the 95% exact confidence interval (CI). In patients with CR/PR, the median duration of response, with a 95% CI, was estimated using the Kaplan–Meier method. The median PFS was estimated along with 95% CI using the Kaplan–Meier method. The safety analysis was based on summaries of AEs reported in the CTCAE version 4.0.

Exploratory analyses

Pre- and post-olaratumab monotherapy PET scans were collected (within 28 days before study enrollment and up to 3 days before the first dose of cycle 2, day 1). PET scans were read locally by the investigator and the images were stored at PAREXEL International. Associations between PET scan findings, tissue biomarkers, and CTCs were investigated using standardized uptake values (SUV). Kaplan–Meier curves for PFS by optimal treatment subgroups of PET biomarker (SUV) at baseline were plotted. HRs were calculated for marker high and low subgroups of PET biomarker in treatment arm with marker high as reference. Optimal subgroups were defined as marker high, SUV >7.9 and marker low, SUV ≤7.9. Optimal cut points were determined using maximally selected rank statistics.

Statistical analyses

The planned sample size was 35 patients evaluable for the primary analyses. To be considered evaluable, patients had to complete the pretreatment tissue biopsy; the predose cycle 1 day 1 whole blood draw; one cycle of olaratumab monotherapy; the post-olaratumab monotherapy biopsy; and the predose cycle 2 day 1 whole blood draw. Patients who were not evaluable were replaced. PDGFRα reduction was defined as a decrease of at least 30% from baseline to cycle 2. The sample size for the primary analyses was calculated on the basis of the hypothesis that 49% (17 of 35) or more of patients could have a reduction of at least 30% in PDGFRα level change from baseline to post-olaratumab monotherapy.

The efficacy and safety analyses were performed on the intent-to-treat (ITT) population, which included all enrolled patients who received any quantity of study drug, regardless of their eligibility for the study.

Results

Patients and treatment

From October 11, 2016 to November 23, 2017, 65 patients were enrolled in the trial (data cut-off date was July 4, 2018). Of these, 51 received at least one dose of study drug (Supplementary Fig. S2). Patient demographics and other characteristics at baseline are summarized in **Table 1**. The median age of patients was 55 years, with the majority of patients (72.5%) younger than 65 years of age. No lung metastasis was observed in 58.8% ($n = 30$) of patients.

Eleven patients completed all seven treatment cycles (one cycle of monotherapy and six cycles of combination therapy). Forty patients did not complete the study. The most common reasons for discontinuation were progressive disease (PD) in 23 patients (45.1%) and surgical resection in 10 patients (19.6%). Four patients (7.8%) discontinued study treatment due to AEs. Twenty-four patients (47.1%) had at least 1 olaratumab dose adjustment. Most patients had dose delays ($n = 12$, 23.5%) or dose omissions ($n = 13$, 25.5%) whereas fewer patients had olaratumab dose reductions ($n = 9$, 17.6%). The most common AEs (in >5% of patients; regardless of relationship to study therapy) leading to modification of olaratumab were neutropenia ($n = 7$, 13.7%) and febrile neutropenia ($n = 4$, 7.8%). Fifteen patients (29.4%) had at least 1 doxorubicin dose modification. Some patients had dose delays ($n = 9$, 17.6%) and dose reductions ($n = 7$, 13.7%) while fewer patients had doxorubicin dose omissions ($n = 2$, 3.9%).

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Table 1. Patient baseline demographics and disease characteristics.

		ITT Population ($N = 51$) *n* (%)
Age, years	Median (range)	55 (26–77)
Pooled age group	≥65	14 (27.5)
Sex	Male	27 (52.9)
ECOG PS	0	31 (60.8)
	1	20 (39.2)
Geographical region	Europe	34 (66.7)
	USA	17 (33.3)
Race	Asian	2 (3.9)
	African American	2 (3.9)
	American white	47 (92.2)
Duration of disease	Median (months)	2.8
Initial pathologic diagnosis basis[a]	Cytological	2 (3.9)
	Histopathological	49 (96.1)
Initial pathologic diagnosis	Liposarcoma	18 (35.3)
	Smooth-muscle tumors	14 (27.5)
	Undifferentiated/unclassified sarcoma[b]	9 (17.6)
	Nerve sheath tumors and tumors of uncertain differentiation	4 (7.8)
	Other	6 (11.8)
Lung metastasis	Yes	21 (41.2)
	No	30 (58.8)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intent-to-treat; *n*, number of patients in the category; *N*, total number of patients; NOS, not otherwise specified.
[a]Information derived from local pathologists.
[b]The terms fibrohistiocytic tumor NOS and fibrohistiocytic tumor were included in the undifferentiated/unclassified sarcoma category.

CTC enumeration and disease control

Overall, 35 of the 51 treated patients (68.6%) had blood samples for CTCs at baseline and post-olaratumab monotherapy and qualified for CTC evaluation. The median number of CTCs detected before and after olaratumab monotherapy were 1.0 CTC/mL (range: 0.1–9.2) and 0.1 CTC/mL (range: 0.1–18.7), respectively, in the analysis population (**Fig. 1**). Mean CTC counts decreased by 0.37 CTC/mL for traditional CTCs, and 0.54 CTC/mL for all population CTCs post-olaratumab monotherapy at cycle 2 day 1. The proportion of patients with a decrease in CTC counts after olaratumab monotherapy was 11 of 19 patients with disease control and 5 of 16 patients without disease control. This difference in proportions was not significant ($P = 0.22$, Pearson χ^2 test), however, there is insufficient statistical power to draw definitive conclusions (**Fig. 2**). CTC enumeration patterns were similar between all population CTCs and traditional CTCs.

An increase in CTC/mL at cycle 1 day 8 was observed in several patients [CTC medians by best overall response (*n*): SD, 1.8 (17); PR, 0.5 (2); PD, 0.5 (14)], followed by a significant reduction by cycle 3 day 1 or 30-day follow-up. The CTC enumeration in all population CTCs by best overall response rate along with CTC medians at each time point is presented in Supplementary Fig. S3. No association was observed between the CTC enumeration and clinical outcome.

PDGFRα/β and PDGF ligand expression and clinical outcomes

In the 43 patients evaluable for tumor tissue PDGFR analysis, IHC expression at baseline was positive in 31 (72.1%) patients for PDGFRα and 36 (83.7%) patients for PDGFRβ. Post-olaratumab monotherapy samples showed similar rates of qualitative IHC expression for PDGFRα ($n = 30$, 69.8%) and PDGFRβ ($n = 33$, 76.7%). PDGFRα and β marker shifts in both positive to negative, and negative to positive directions were observed post-olaratumab monotherapy. Change in PDGFRα expression only was observed in 4 patients (negative to positive IHC for PDGFRα, $n = 2$ and positive IHC to negative, $n = 2$), while 4 patients showed a change in PDGFRβ expression only. Three patients went from PDGFRβ IHC positive to negative, while 1 patient went from PDGFRβ negative to positive. Only 1 patient showed a change in expression of PDGFRα and PDGFRβ. This patient went from PDGFRα and PDGFRβ positive by IHC at baseline to negative for both markers post-olaratumab monotherapy. Representative pre- and post-olaratumab monotherapy biopsies, stained with IHC for PDGFRα and PDGFRβ, are presented in Supplementary Fig. S4. As was observed in many patients in this study, there was no significant difference in the staining intensity or percent of tumor cells staining for either marker around olaratumab monotherapy (Supplementary Table S1).

Qualitative IHC expression for either marker did not appear to correlate with clinical outcome in the analysis population. Thirty-seven patients had sufficient tissue to be tested by RT-PCR pre- and post-olaratumab monotherapy. Eleven patients (29.7%) showed a 30% reduction in PDGFRα expression at the post-olaratumab monotherapy measure of PDGFRα by RT-PCR. No association was observed between the PDGFRα expression by RT-PCR and clinical outcome.

Pharmacokinetics and immunogenicity

Phamacokinetic data were evaluated from 51 patients who received at least 1 dose of olaratumab. On both cycle 2 day 1 and day 8, following completion of intravenous infusion, olaratumab serum concentrations decreased steadily. The mean concentration-time profiles on cycle 2 day 1 and day 8 are presented in **Fig. 3**. Peak serum concentration (C_{max}) on cycle 2 day 1 and day 8 were: geometric mean, 624 μg/mL; coefficient of variation (CV), 26% and geometric mean, 711 μg/mL; CV, 28%, respectively. Because of differences in dosing interval on

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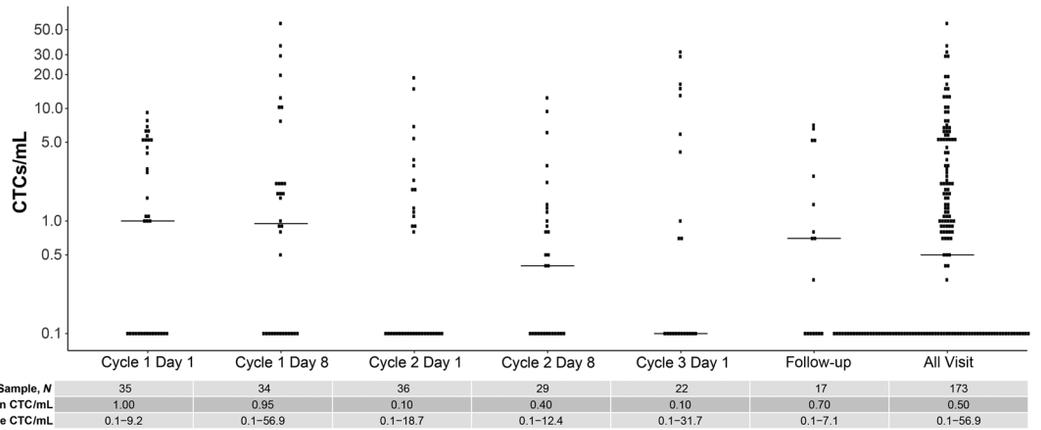

	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 2 Day 1	Cycle 2 Day 8	Cycle 3 Day 1	Follow-up	All Visit
Sample, *N*	35	34	36	29	22	17	173
Median CTC/mL	1.00	0.95	0.10	0.40	0.10	0.70	0.50
Range CTC/mL	0.1–9.2	0.1–56.9	0.1–18.7	0.1–12.4	0.1–31.7	0.1–7.1	0.1–56.9

Figure 1.
CTC enumeration per visit of all population CTCs. CTC enumeration in patient samples per visit. Overall, 35 of the 51 treated patients (68.6%) had blood samples for CTCs at baseline and post-olaratumab monotherapy (C2D1) and qualified for CTC evaluation. The median number of CTCs detected before and after olaratumab monotherapy were 1.0 CTC/mL (range, 0.1–9.2) and 0.1 CTC/mL (range, 0.1–18.7), respectively, in the analysis population. Each dot represents the calculated CTC/mL per sample. Horizontal lines represent median CTC/mL. C2D1, cycle 2 day 1; CTC, circulating tumor cells.

cycle 2 day 1 and day 8, the comparable AUC is limited to the 0- to 168-hour time interval. Cycle 2 day 1 and day 8 AUC 0–168 were: geometric mean, 61,500 μg hours/mL; CV, 32% and geometric mean, 70,700 μg hours/mL; CV, 38%. Serum concentrations of olaratumab and pharmacokinetic parameters estimated by noncompartmental analysis are summarized in **Table 2**.

For immunogenicity, 50 of 51 total patients in the safety population had negative ADAs and 1 ADA result was missing at baseline. One patient had at least one positive TE-ADA result, with a titer value of 1:10 on day 8 and of 1:20 on day 21.

Efficacy

The PFS analysis was based on investigator assessment. Of the 51 patients enrolled, a total of 30 PFS events were observed (58.8%), the median PFS was 2.86 months (95% CI, 1.41–9.72), and the investigator-assessed 3-month PFS rate was 48.8% (95% CI, 34.1–62.0; **Fig. 4A**). PD occurred in 29 patients (56.9%), with most of the patients (n = 24, 82.7%) experiencing progression due to an increase of a pre-existing lesion, rather than due to a new lesion. A total of 22 patients (43%) had progression after the first tumor assessment. In patients with no lung metastasis at baseline,

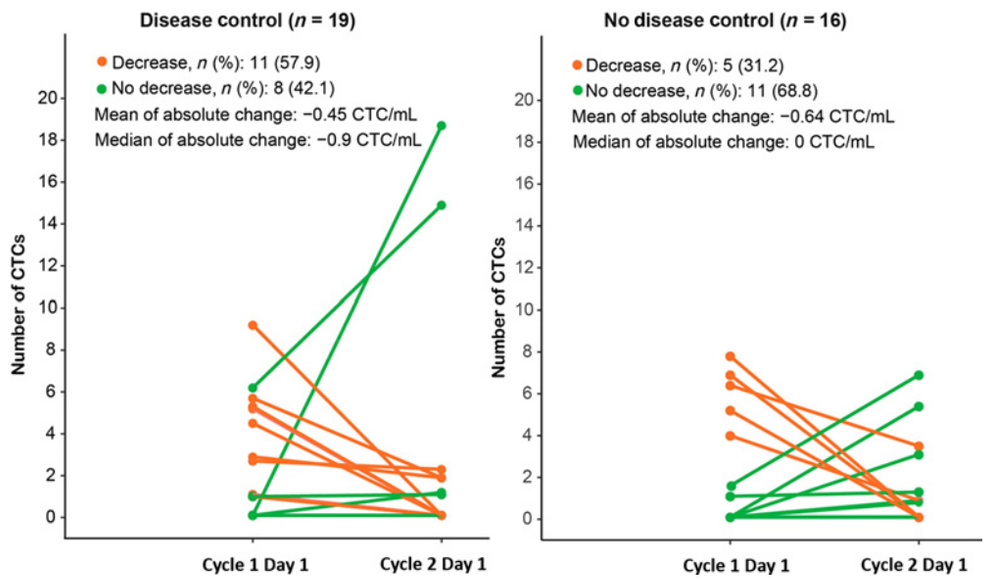

Figure 2.
Enumeration of CTC changes in all population CTCs. Enumeration of CTC changes in patients by disease control. Mean CTC counts decreased by 0.45 CTC/mL for patients with disease control (n = 19) and 0.64 CTC/mL for patients with no disease control. The proportion of patients with a decrease in CTC counts after olaratumab monotherapy was numerically higher in patients with disease control (57.9%; 11 of 19 patients) compared with patients without disease control (31.2%; 5 of 16 patients; P = 0.22). CTC, circulating tumor cell; n, number of patients.

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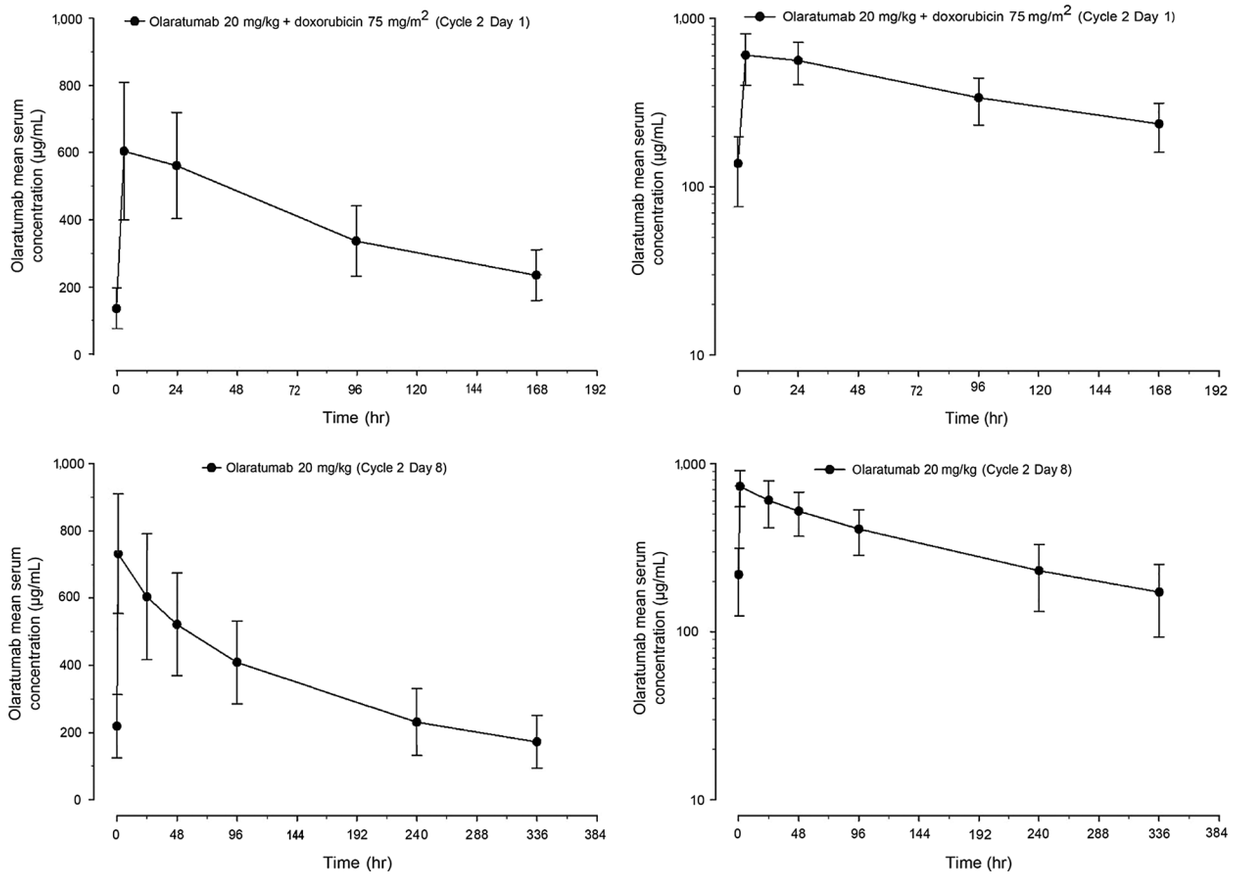

Figure 3.

Olaratumab pharmacokinetics: right, linear scale; left, semilogarithmic scale. Mean serum concentration versus time profiles following administration of olaratumab 20 mg/kg on days 1 ($N = 45$) and 8 ($N = 41$) in cycle 2, combined with or without doxorubicin administered intravenously as 75 mg/m^2 on day 1.

the median PFS was longer (median, 4.21 months) compared with patients with lung metastasis (median, 2.86 months). No relevant differences for PFS were observed among patients with liposarcoma and leiomyosarcoma or other baseline parameters (tumor–node–metastasis, age, other histologies, performance status).

A high censoring rate, mainly due to surgery, was recorded before the median PFS point. Of the 21 patients (41.2%) censored, 15 patients (29.4%) had no radiologic evidence of disease progression by RECIST 1.1 at the time of the cut-off date.

A total of 35.3% of patients ($n = 18$) underwent tumor resection following systemic treatment, and of these, 44.4% ($n = 8$) had surgery postprogression. None of the 11 patients who completed seven cycles of therapy had surgery.

The ORR (PR+CR) was 11.8%, comprised of 6 patients with PR as the best overall response (confirmed PR, $n = 2$, 3.9%). A total of 21 patients (41.2%) had a best overall response of SD; therefore, the DCR (CR+PR+SD) was 52.9% ($n = 27$). Fourteen patients (27.5%) had a decrease in the size of target lesions. DCR was better among patients with liposarcoma ($n = 11$, 61.1%).

The median duration of olaratumab treatment was 12.4 weeks (approximately four cycles; range: 1–7 cycles), with a median cumulative dose of olaratumab of 8,625 mg (range: 100.00–31,740.00 mg). The median duration of doxorubicin treatment was 9 weeks (approximately three cycles; range: 3–21 weeks) with median cumulative dose of doxorubicin of 433 mg (range: 115.00–1128.00 mg).

Safety

TEAEs related to the study drug were reported in 94.1% ($n = 48$) of patients, with Grade ≥3 in 56.9% ($n = 29$) of patients. This toxicity was mainly related to the combination drug cycles. The most common any-grade TEAEs observed were fatigue (68.6%), nausea (52.9%), mucositis (45.1%), neutropenia (39.2%), constipation (39.2%), decreased appetite (33.3%), and alopecia (31.4%). Most TEAEs were grade 1 or 2. TEAEs are summarized in Supplementary Table S2. Grade ≥3 TEAEs were reported in 78.4% of patients. Grade ≥3 TEAEs occurring in at least 10% of patients included neutropenia (37.3%), febrile neutropenia (19.6%), and leukopenia (13.7%).

Immediate infusion related reactions (IRR) were identified in 7 (13.7%) patients and delayed hypersensitivity reactions in 4 (7.8%) patients, all grade 1 or 2 events, except 1 patient with grade 4 anaphylactic reaction. The event occurred during the first infusion and resolved on the same day after appropriate support. As per the protocol, study treatment was discontinued. Of the 51 patients treated, only 1 patient had at least 1 positive TE-ADA result; the patient did not develop any IRR.

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Table 2. Summary of olaratumab pharmacokinetic parameters.

Parameters	Geometric mean (CV%)	
	Cycle 2, day 1 Olaratumab 20 mg/kg + doxorubicin 75 mg/m^2	Cycle 2, day 8 Olaratumab 20 mg/kg
N	46	42
t_{max} (hr)[a]	3.09 (1.97–25.78)	1.17 (0.75–23.83)
C_{max} (μg/mL)	624 (26)	711 (28)
$C_{av,\ tau}$	364 (32)[b]	313 (43)
AUC(0–168; μg hr/mL)	61,500 (32)[c]	70,500 (38)[d]
AUC(0–336; μg hr/mL)	NC	1,05,000 (43)[e]
CL_{ss} (mL/hr)	NC	14.4 (35)[e]
V_{ss} (L)	NC	3.56 (31)[f]
$t_{1/2}$ (days; range)	NC	7.59 (31)[f] (3.61–12.8)

Abbreviations: AUC(0–*t*), area under the serum concentration versus time curve from time zero to *t* hours; $C_{av,tau}$, average drug concentration during dosing interval; CL_{ss}, total body clearance at steady state; C_{max}, observed maximum serum concentration; CV%, percent coefficient of variation; *N*, number of patients; NC, not calculable; $t_{1/2}$, elimination half-life; t_{max}, time of observed maximum serum concentration; V_{ss}, volume of distribution at steady state.
[a]Median (range), referenced to the start of infusion.
[b]$N = 42$.
[c]$N = 41$.
[d]$N = 35$.
[e]$N = 34$.
[f]$N = 33$.

Five patients (9.8%) discontinued study treatment due to TEAEs of anaphylactic reaction, cardiopulmonary failure, intestinal perforation, neutropenia, and pneumonitis (1 patient each).

At the time of data cutoff, there were three deaths reported. One patient died during study therapy due to cardiopulmonary failure. The patient had a significant cardiac history (not considered exclusionary for study entry) and disease progression was reported as an additional cause of death. One death occurred within 30 days after the last dose of study therapy, and 1 after 30 days of treatment discontinuation. None of these deaths were considered to be related to study treatment and were reported by the investigator to be due to study disease and disease progression.

Exploratory PET/biomarker analysis

Patients with lower values of SUV at baseline had improved PFS, with a significant statistical correlation (**Fig. 4B**); however, no correlation was observed between PET response and clinical outcome. The majority of patients with a peak in CTC at cycle 1 day 8, also had an increase of baseline SUV ≥10%. No correlation was observed between PET response, and PDGFRα and β expression.

Discussion

PDGFRs are involved in oncogenesis and drug resistance, and are consequently attractive oncologic targets (21). In addition, they are frequently overexpressed in various tumors, and their expression levels correlate with tumor growth, invasiveness, drug resistance, and poor clinical outcomes, making them potential prognostic markers in some cancers (22). In recent years, many preclinical and clinical studies have evaluated molecules targeting PDGFRα in a variety of malignancies (17, 23, 24).

The potential importance of targeting PDGFR signaling in cancer led to the development of olaratumab, a first-in-class IgG1 mAb blocking PDGF-AA, PDGF-BB, and PDGF-CC receptor binding and activation (12, 25). In the phase Ib/II olaratumab trial, positive expression in tumor samples did not show any predictive value of effectiveness in STS. Furthermore, the negative expression of this marker was associated with a favorable outcome, suggesting that PDGFRα inhibition in the tumor cells may not be the main mechanism of action of olaratumab in STS. It is noteworthy that the IHC assay used to assess PDGFRα expression was not specific to the receptor targeted by olaratumab and could have confounded the findings (12), warranting further investigation.

This study was conducted to enumerate whole blood CTCs and to characterize PDGFRα, PDGFRβ, and canonical ligand (PDGF-A, -B, -C, and -D) expression changes pre- and post-olaratumab monotherapy in tumor tissue in patients with potentially resectable STS. Little or no difference was observed in prebiopsy and postbiopsy measurements using IHC and RT-PCR, and the minor differences were more likely due to tumor heterogeneity. Furthermore, when looking at the tumors, no correlation to response was observed by either the IHC or RT-PCR method. These findings are consistent with those from the phase II trial where no relationship was identified between PDGFRα expression and clinical or radiological outcomes of patients with sarcoma treated with doxorubicin with or without olaratumab (12).

It is difficult to interpret canonical ligands, because data are only available as mRNA expression detected by RT-PCR. There is no clear association between mRNA expression and response in this study. It is noteworthy that both tumor and stromal expression are measured simultaneously. Hence relative overexpression or underexpression of a particular ligand by either tumor or stroma may drown all but the largest of signals. In addition, mRNA expression may not correlate 1:1 with protein expression, release, and signaling via the pathway. Even with improved localization and measurement of protein in addition to mRNA, PDGFR signaling is complex, with homodimers and heterodimers of receptors interacting with corresponding ligands in various combinations. Detection of the presence of a particular ligand does not easily reveal if it is present in homodimeric or heterodimeric form. The dimeric configuration of a ligand signal and/or the dimeric configuration of the PDGFR it interacts with may ultimately be more biologically relevant than simple quantification of presence. This hypothesis would benefit from further exploration in a future study.

To our knowledge, this is the first description of enumeration of sarcoma CTCs in a clinical study. In partnership with Epic Sciences, we first validated their whole-slide imaging method for CTCs. This was done by confirming multiple sarcoma cell lines spiked into normal donor whole blood were detectable in ranges for 27.9 CTC cells/mL to 1315.6 CTC cells/mL via low positive but consistent expression of intermediate filaments detectable with Epic's cytokeratin/intermediate filament cocktail. Sarcoma CTCs were CD45 negative, and positive (with slight cut-off adjustment for the low expression of intermediate filaments) for the cocktail, and the spike in quantity of sarcoma CTCs was routinely detected. Following analytical validation, this method was applied to whole blood collected at several time points from patients in the study at baseline and while on olaratumab monotherapy and combination with doxorubicin.

CTC enumeration demonstrated interesting trends, although the small size of the study meant none reached statistical significance. Most notably, an increase in CTCs from pretreatment baseline at cycle 1 day 8 during the peak olaratumab monotherapy pharmacokinetic/

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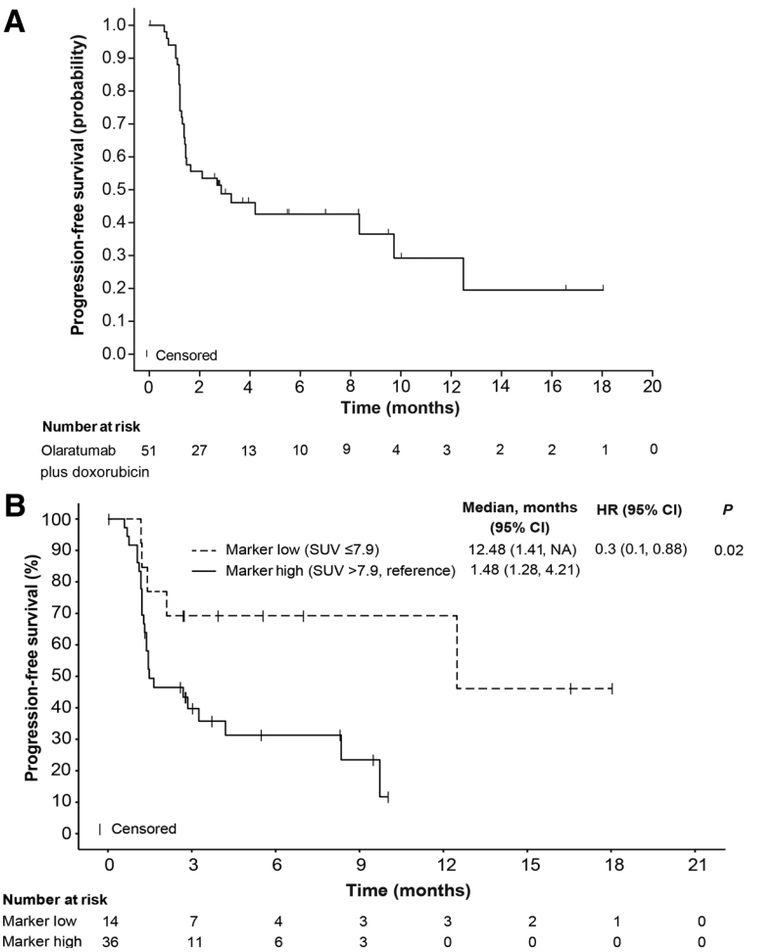

Figure 4.

A, Kaplan–Meier curve for PFS in overall safety population. **B,** Kaplan–Meier curve for PFS for optimal treatment subgroups of PET biomarker at baseline. CI, confidence interval; HR, hazard ratio; NA, not available; SUV, standardized uptake value.

pharmacodynamic collection was observed in several patients. This was followed by a decrease in CTCs by cycle 2 day 1, just prior to beginning combination therapy. In a few patients, the dynamic repeated itself in combination treatment, with a spike of CTCs at cycle 2 day 8 decreasing by cycle 3 day 1. This second spike was of lower amplitude than the olaratumab monotherapy pattern.

The majority of patients with this trend had an associated increase in SUV of >10% by PET analysis compared with baseline. This was observed in patients receiving olaratumab monotherapy and olaratumab plus doxorubicin combination therapy. Despite this radiologic change, patients with this kinetic profile responded better clinically. This finding may be due to the effects of olaratumab on the CTCs or its detection, promotion, or stabilization of circulating cells, or effects on the distant microenvironment ("trapping" cells in circulation when olaratumab concentrations are high). Additional investigation of this observation is warranted as this relationship could be an artifact of olaratumab effects on CTC kinetics or a true tumor-related effect. Given the consistent lack of correlation for PDGFRα, PDGFRβ and, in this study, ligand expression with clinical response to olaratumab (including PET measurements) when measured on the primary tumor, it appears that the clinical effect of olaratumab, if any, is not on the primary tumor itself.

Although there are several sarcoma subtypes, cell lines are only available for a few. The CTC detection technology used in this study (high-definition CTCs) utilizes a combination of morphology and immunofluorescent markers to detect circulating cells. So, it reliably identifies cells in the peripheral blood that are not blood cells. This enabled us to look at markers that may not be present on all CTCs. There is a possibility, however, that some subsets of CTCs might not have been detected, and this is a potential limitation of the study. The assay validation was conducted with spiked sarcoma cell lines representing the range of CTC enumeration consistent with Epic Sciences' experience with typical CTC counts for carcinomas. The assay was thus validated to the lower limit of detection typical for carcinomas, with the known risk that this range might not apply directly to sarcoma CTCs. Indeed, the median number of sarcoma CTCs detected in this study was 1 CTC/mL, substantially lower than ranges typical of carcinoma CTCs. As this was outside the range of linearity established in the validation, the numerical accuracy of these values may be suspect, even if some qualitatively positive sarcoma CTCs are seen. Future studies examining sarcoma CTCs with this method are advised that a lower limit of detection in the validation of the method may need to extend to as few as 1 CTC/mL, if possible, for accurate quantitation of sarcoma CTCs. Furthermore, validation was limited to those subtypes of sarcoma with readily available cell lines for spike in studies. Different subtypes of sarcoma may have different relative abundances of CTCs, as one can hypothesize sarcoma subtypes prone to hematogenous metastatic spread are more likely to have

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detectable CTCs, possibly in higher quantities, than sarcoma subtypes less likely to metastasize.

Other clinically available technologies to detect CTCs are primarily flow cytometry based and do not incorporate the morphologic appearance of the cell as the Epic Sciences' (and RareCyte) methods do. Visual confirmation of cell morphology can help exclude staining artefacts from being identified as CTCs. Flow cytometric–based methods do not have this additional check. The main limitation for CTC evaluation in sarcomas is the multitude of potential cells of differentiation within the classifications of sarcomas, making it difficult to identify a single staining cocktail that can detect all sarcoma subtypes simultaneously and robustly. Traditional CTC platforms have been developed toward carcinomas using EPCAM or cytokeratin cocktails, markers that are not commonly expressed in sarcomas. The study shows that detection of sarcoma CTCs in a clinical setting is possible, and will hopefully spur development toward improved markers and limits of detection for robust qualitative and quantitative assessment.

Microenvironment effects, particularly on fibroblasts active near and far from the tumor, may be the mechanism of action of olaratumab. Alternatively, effects on CTCs directly or indirectly may be a source of olaratumab activity. Action away from the primary tumor would be consistent with the phase Ib/II study of olaratumab and doxorubicin with its "paradoxical" OS benefit in excess of its PFS benefit (12). However, lack of biomarker correlation or changes, particularly with PET measurement, are also consistent with the phase III olaratumab plus doxorubicin trial that did not show a benefit for the combination (15). Even if olaratumab is acting away from the primary tumor, results from the phase III study suggest that this is not sufficient for consistent clinical benefit. Evaluation of CTCs was not included in the phase III study, however, and our limited observations from this study are tantalizing enough that additional investigation of the precise mechanism behind the CTC changes may be warranted, as anti PDGF therapy may be effective in a subgroup of patients. Furthermore, the trends observed in clinical response in this study suggest that sarcoma patients may receive benefit particularly if an alternative mechanism of action of olaratumab is identified.

The pharmacokinetic profiles of olaratumab in this study are consistent with other similar studies and align with the model simulation used to determine dosing strategy (26, 27). Higher serum concentrations of olaratumab on day 8 compared with day 1 were expected because of the slow elimination rate of olaratumab in relation to the dosing interval, leading to drug accumulation. The observed C_{max} were within the previously reported ranges in other clinical studies in patients with STS treated with the same dose levels of olaratumab. Similarly, noncompartmental method of analysis-estimated pharmacokinetic parameters (CL_{ss}, V_{ss} and $t_{1/2}$) were also comparable with those estimated in previous studies. There were insufficient data to assess the effects of immunogenicity on the pharmacokinetic of olaratumab as only 1 patient developed TE-ADA postbaseline. On the basis of previous clinical experience, there has been no indication that immunogenicity has any impact on olaratumab pharmacokinetic or efficacy (26).

The tumor response for olaratumab plus doxorubicin was consistent with that of single-agent doxorubicin (12). Disease progression occurred in many patients at first restaging (6 weeks), and most patients experienced progression due to an increase of a preexisting lesion, rather than a new lesion.

Although OS and distant recurrence (disease-free survival) were not evaluated, and the study population was ultimately small, there are still indications for correlation between CTC enumeration and stable disease as a response to treatment.

The safety and tolerability findings from this study are consistent with those from previous studies of olaratumab plus doxorubicin (1, 12). Grade 4 IRR was observed in 1 patient. In this patient, baseline IgE anti–galactose-a-1,3-galactose (alpha-Gal) antibodies were 1.04 kU/L (upper limit normal is <0.10 kU/L), supporting the observation that severe hypersensitivity reactions occurring during the initial infusion of olaratumab can be mediated by preexisting IgE antibodies for alpha-Gal, that are likely recognizing alpha-Gal containing glycosylation sites of the Fab region of olaratumab (28).

In conclusion, this study confirms the feasibility of CTC enumeration in STS patients treated with olaratumab. To our knowledge, this is the first study to use a validated method to detect circulating sarcoma cells. Furthermore, qualitative detection of PDGFRα in tumor samples showed no association with clinical outcome. Although the study is limited by the small sample size, heterogeneity of disease, and the lack of clinical outcome assessment of OS, the biomarker findings could provide a foundation for future studies targeting PDGFR. The quantitative exploration of tissue biopsy and its correlations with CTCs warrants further investigation. Taken together, the novel biomarker modulation may extend our understanding of the underlying biology in patients treated with olaratumab and doxorubicin compared with doxorubicin monotherapy.

Authors' Disclosures

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Authors' Contributions

J. Martín-Broto: Investigation, writing-review and editing. **A. Lopez Pousa:** Investigation, writing-review and editing. **A. Brohl:** Investigation, writing-review and editing. **B. Van Tine:** Investigation, writing-review and editing. **B. Powers:** Investigation, writing-review and editing. **S. Stacchiotti**: Investigation, writing-review and editing. **J.-Y. Blay:** Investigation, writing-review and editing. **J. Hu:** Investigation, writing-review and editing. **G. Oakley III:** Formal analysis, visualization, methodology, writing-original draft, writing-review and editing.

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