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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Supplementary Appendix

An International Randomised Phase 3 Trial of Doxorubicin plus Evofosfamide vs Doxorubicin Alone in Locally Advanced Unresectable or Metastatic Soft Tissue Sarcoma: TH CR-406/SARC 21

William D. Tap*, MD, Prof Zsuzsanna Papai, MD, Brian A.Van Tine, MD, Steven Attia, DO, Kristen N. Ganjoo, MD, Robin L. Jones, MD, Scott Schuetze, MD, Damon Reed, MD, Sant P. Chawla, MD, Richard F. Riedel, MD, Anders Krarup-Hansen, MD, Maud Toulmonde, MD, Isabelle Ray-Coquard, MD, Peter Hohenberger, MD, Giovanni Grignani, MD, Lee D. Cranmer, MD, Scott Okuno, MD, Mark Agulnik, MD, William Read, MD, Christopher W. Ryan, MD, Thierry Alcindor, MD, Xavier F. Garcia del Muro, MD, G. Thomas Budd, MD, Hussein Tawbi, MD, Tillman Pearce, MD, Stew Kroll, MA, Denise K. Reinke, NP, Patrick Schöffski, MD.

*Corresponding author: William D. Tap, MD. Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY. 10065. tapw@mskcc.org.

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Supplementary Online Methods

This was an open-label, randomised, multi-center study. Investigators, patients, and the sponsor were not blinded to treatment assignment. The independent pathology review and the independent radiology review (below) were blinded to treatment arm.

Objectives

The primary objectives of this study were to evaluate the efficacy of evofosfamide in combination with doxorubicin as determined by overall survival in patients with locally advanced unresectable or metastatic soft tissue sarcoma previously untreated with chemotherapy (neoadjuvant and adjuvant chemotherapy permitted) compared with doxorubicin alone and to assess the safety of evofosfamide in combination with doxorubicin in patients with locally advanced unresectable or metastatic soft tissue sarcoma compared with doxorubicin alone.

The secondary objectives of this study were to evaluate the efficacy of evofosfamide in combination with doxorubicin as determined by progression-free survival and response rate in patients with locally advanced unresectable or metastatic soft tissue sarcoma compared with doxorubicin alone and to investigate the pharmacokinetics of evofosfamide, bromo-isophosphoramide mustard (Br-IPM), doxorubicin, and doxorubicinol in plasma.

The tertiary objectives of this study were to evaluate the efficacy of evofosfamide in combination with doxorubicin as determined by overall survival at 6 and 12 months, progression free rate at 3 months and progression-free rate at 6 months, duration of response, stable disease or better rate, change in Eastern Cooperative Oncology Group (ECOG) performance status in patients with locally advanced unresectable or metastatic soft tissue sarcoma compared with doxorubicin alone and to explore and compare quality of life and derive health state utilities as measured by the EQ-5D-5L in patients treated with evofosfamide in combination with doxorubicin and doxorubicin alone.

The exploratory objectives of this study were to explore the association of tumor tissue, radiographic, and serum and plasma hypoxia biomarkers with efficacy and safety endpoints and pharmacokinetic data.

Planned Enrollment

A total of 620 patients with unresectable locally advanced or metastatic soft tissue sarcoma were planned to be enrolled and randomised.

Inclusion and Exclusion Criteria

Male and female patients ≥ 15 years of age who have the ability to understand the purposes and risks of the study and have signed or, if appropriate, the patient's parent or legal guardian have signed a written informed consent form approved by the investigator's IRB/Ethics Committee, with a pathologically confirmed diagnosis of soft tissue sarcoma of the following histopathologic types: synovial sarcoma, high grade fibrosarcoma, undifferentiated sarcoma, sarcoma not otherwise specified (NOS), liposarcoma, leiomyosarcoma, angiosarcoma, malignant peripheral nerve sheath tumor, pleomorphic rhabdomyosarcoma, myxofibrosarcoma, epithelioid sarcoma, undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma (MFH) (including pleomorphic, giant cell, myxoid and inflammatory forms), or other soft tissue sarcomas for which doxorubicin is an appropriate first line therapy. Patients with a gastrointestinal stromal tumor and Kaposi's sarcoma were excluded. Patients were required to have locally advanced unresectable or metastatic disease with no standard curative therapy available and for whom treatment with single agent doxorubicin was considered appropriate, recovered from reversible toxicities of prior therapy, measurable disease by RECIST 1.1 (at least one target lesion outside of previous radiation fields or progressed within a previous radiation field), an ECOG performance status of 0 or 1, a life expectancy of at least 3 months, acceptable liver function (bilirubin 1.5x upper limit of normal (ULN), except in the case of Gilbert's

syndrome; AST (SGOT) and ALT (SGPT) 3.0x ULN); if liver metastases were present then 5x ULN was allowed), acceptable renal function (serum creatinine 1.5x ULN or calculated creatinine clearance ≥ 60ml/min by the Cockcroft Gault formula), acceptable hematologic status (without growth factor support or transfusion dependency, ANC ≥ 1500 cells/µl, platelet count ≥ 100,000/µl, hemoglobin 9.0 g/dL, acceptable cardiac function (normal 12-lead ECG, LVEF normal by MUGA or echocardiogram >50% per CTCAE v4.0). All women of childbearing potential must have had a negative serum pregnancy test and all patients must have agreed to use effective means of contraception (surgical sterilization or the use of barrier contraception with either a condom or diaphragm in conjunction with spermicidal gel or an IUD) with their partner from entry into the study through 6 months after the last dose. Post-menopausal women must have met the criteria of 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels >35 mIU/ml (IU/L).

Patients were not eligible for the trial if they had a low grade tumor according to standard grading systems (e.g., AJCC Grade 1 and 2 or FNCLCC Grade 1), prior systemic therapy for locally advanced or metastatic soft tissue sarcoma (neoadjuvant therapy followed by surgical resection and adjuvant therapy were permitted, palliative radiotherapy to non-target lesions was allowed if completed at least two weeks prior to study entry), prior soft tissue sarcoma therapy with ifosfamide or cyclophosphamide or other nitrogen mustards, prior systemic therapy with an anthracycline or anthracenedione, prior mediastinal/cardiac radiotherapy, current use of drugs with known cardiotoxicity or known interactions with doxorubicin, anti-cancer treatment (radiation therapy, neoadjuvant or adjuvant chemotherapy, targeted therapies, immunotherapy, hormones or other antitumor therapies within 4 weeks prior to study entry and 6 weeks for nitrosoureas or mitomycin C), significant cardiac dysfunction precluding treatment with doxorubicin (e.g., a history of congestive heart failure, myocardial infarction within 6 months of study entry or severe myocardial insufficiency, uncontrolled arrhythmias within 6 months of study entry, angina pectoris requiring antianginal medication within 6 months of study entry, clinically significant valvular heart disease, poorly controlled hypertension), a seizure disorders requiring anticonvulsant therapy unless seizure-free for the last year, known brain metastases (unless previously treated and well controlled for a period of 3 months), previously diagnosed malignancies, except for adequately treated non-melanoma skin cancer, in situ cancer, or other cancer from which the patient has been disease-free for at least 5 years, severe chronic obstructive or other pulmonary disease with hypoxemia (requires supplementary oxygen, symptoms due to hypoxemia or oxygen saturation <90% by pulse oximetry after a 2 minute walk) or in the opinion of the investigator any physiological state likely to cause normal tissue hypoxia, major surgery, other than diagnostic surgery, within 4 weeks prior to Day 1 without complete recovery, an active, uncontrolled bacterial, viral, or fungal infection requiring systemic therapy, prior therapy with a hypoxic cytotoxin, participation in an investigational drug or device study within 28 days prior to study entry, known infection with HIV or active infection with hepatitis B or hepatitis C, exhibited allergic reactions to a structural compound similar to evofosfamide or other drug product excipients, females who were pregnant or breast-feeding, a concomitant disease or condition that would interfere with the conduct of the study, or that would in the opinion of the investigator pose an unacceptable risk to the patient in this study, or an unwillingness or inability to comply with the study protocol for any reason.

Study procedures

After providing written informed consent, patients underwent screening for eligibility to participate within the study. Enrolled patients were randomised 1:1 to one of the two treatment groups. Randomisation was stratified by extent of disease (locally advanced unresectable vs. distant metastases), doxorubicin administration method (bolus injection vs. continuous infusion) and prior systemic therapy (prior adjuvant or neoadjuvant therapy vs. no prior adjuvant or neoadjuvant therapy).

Subjects on both arms would remain on study drug until disease progression, prohibitive toxicity, or completion of six cycles. After six cycles, all patients would have reached the maximum doxorubicin cardiology safety limit of 450 mg/m2. Subjects randomised to the evofosfamide plus doxorubicin arm who had not progressed after 6 cycles could continue to receive additional cycles of evofosfamide alone. All patients were followed regularly until disease progression, initiation of additional anti-tumor therapy or death for up to 36 months after study entry. Subjects in the doxorubicin arm could not crossover to receive evofosfamide after disease progression.

Evofosfamide was administered at a dose of 300 mg/m2 by IV infusion over 30-60 minutes on days 1 and 8 of a 21-day cycle. Doxorubicin could have been delivered as a bolus injection or as a continuous infusion administration; administration schedule must have been specified prior to enrollment. Doxorubicin bolus administration: 75 mg/m2 administered by bolus injection starting on Day 1 of a 21-day cycle. Doxorubicin administration would start between 2 to 4 hours after completion of the evofosfamide infusion when used in combination with evofosfamide. Doxorubicin continuous administration: 75 mg/m2 administered by continuous IV infusion over 6-96 hours starting on Day 1 of a 21-day cycle. Doxorubicin administration would start between 2 to 4 hours after completion of the evofosfamide infusion when used in combination with evofosfamide. Prophylactic growth factor support (filgrastim or pegfilgrastim) would be given on Day 8 or Day 9 of each cycle for patients receiving evofosfamide plus doxorubicin. Growth factor support was not required after Cycle 6 for patients on the evofosfamide plus doxorubicin arm who continued on single agent evofosfamide. Therapeutic use of hematopoietic colony- stimulating factors was permitted following ASCO guidelines for all patients in the doxorubicin arm. Growth factor support could be considered in both treatment arms prior to initiating dose reductions for neutropenia, if not already implemented. Patients were able to receive dexrazoxane or another cardio-protective medication at the investigator's discretion.

Dose modification rules were followed for all haematologic and renal toxicities regardless of causality, and for any other toxicity that was not clearly related to disease progression, intercurrent illness, concomitant medications, or other non-drug intervention.

- If a subject required more than 2 dose level reductions for toxicity, he/she was discontinued from the study.
- Any subject who missed more than 1 cycle (> 3 weeks of Day 1 of a cycle) for treatment-related toxicity was discontinued from the study.

If Day 1 of a cycle for either drug was withheld, the whole cycle was delayed. If Day 8 was withheld, the dose was skipped rather than delayed. Growth factor support was considered in both treatment arms prior to initiating dose reductions for neutropenia, if not already initiated. For febrile neutropenia, defined as ANC < 500/µL and temperature ≥ 38.2ºC (100.8ºF), doxorubicin was reduced up to 25% and evofosfamide was reduced up to 25% in all subsequent cycles.

The following table was followed for evofosfamide dose modifications for haematologic toxicity. If study drug was held at Day 1 of any cycle, counts were repeated weekly and therapy was reinstituted when ANC was ≥ 1000/µL and platelet count was ≥ 100,000/µL.

			Percent of Current Dose for any Cycle	
ANC (/µL)		**Platelets (/µL)**	**Day 1**	**Day 8**
≥1000	AND	≥100,000	100	100
500 – 999	AND/OR	50,000 – 99,999	Hold	100
<500	AND/OR	<50,000	Hold	Hold

The following table was followed for doxorubicin dose modifications for haematologic toxicity.

Nadir ANC (cells/µL)[3]		**Nadir Platelet Count (/µL)**	**Percent of Current Dose for any Cycle**
<500*	AND/OR	<50,000[1]	75-100[2]

ANC = absolute neutrophil count

1) ANC must have been ≥1000 and platelet count ≥100,000 to continue dosing.
2) Percent of current dose must be between 75% and 100%.
3) Growth factor support was considered in both treatment arms prior to initiating dose reductions for neutropenia, if not already initiated.

The following table was followed for evofosfamide and doxorubicin dose modifications for non-haematologic toxicity.

		Evofosfamide and Doxorubicin	
Toxicity	**Details**	**Hold Dose**	**% of Current Dose after Recovery to Grade 0-1**
Grade 1, 2	Serum bilirubin[3]	Grade 1: No Grade 2 or higher: Hold dose until resolution to Grade 0 or 1	75% (doxorubicin) 100% (evofosfamide)
Grade 2[1]	Except for nausea, vomiting, diarrhea, alopecia and fatigue	Hold dose until resolution to Grade 0 or 1	100%
	Intolerable skin toxicity	Hold dose until resolution to Grade 0 or 1	75% (evofosfamide only)
Grade 3[2]	Except nausea and vomiting	Hold dose until resolution to Grade 0 or 1	75%
Grade 4	Life-threatening conditions (study drug-related)	Treatment should be discontinued	NA
Grade 4	Other Grade 4 events such as fatigue and non-life-threatening pulmonary embolism that are adequately treated	Hold dose until resolution to Grade 0 or 1	50%

1) Grade 2 ALT/AST at baseline, treatment should not be held if it remained Grade 2.
2) Grade 2 ALT/AST at baseline, treatment resumed when value returned to Grade 2.
3) Did not apply to subjects with Gilbert's syndrome.

If the subject's post-evofosfamide dose QTc was Grade 3 (> 500 msec), the doxorubicin dose (if dosing that day) was held until the QTc interval was no greater than Grade 1. The subject was retained in the clinic and the QTc interval monitored by ECG at 2.5 hours after the end of the evofosfamide infusion, and then hourly until the QTc interval was no higher than Grade 1 (470 msec or less). The subject's medications were reviewed for drugs that are known to prolong QT interval and to raise the risk of Torsades de Pointe. If the subject's post-evofosfamide dose QTc interval was Grade 4 (> 500 msec with "life threatening signs or symptoms"), study drug was discontinued and the patient monitored and treated as clinically appropriate.

A Schedule of study assessment is provided below.

	Screen[1]	Treatment Period (Cycle 1)			Treatment Period (Cycles 2-6)			Additional Cycles/Maintenance (Cycles 7+)			Treatment Term/ Early Term[15]	Survival Follow up[16]
Assessment		W1	W2	W3	W1	W2	W3	W1	W2	W3		
Informed consent	X											
Determine eligibility	X											
Medical history	X											
Cancer history	X											
Medication history	X											
Archival tumor tissue sample for pathology	X											
Oxygen Saturation	X											
Interim medical history[2]		X										
Complete physical exam[3]	X										X	
Limited physical exam[3]		X			X			X				
Height	X											
Weight[17]	X	X	X		X	X		X	X		X	
ECOG performance status	X	X			X			X			X	
Vital signs & temperature[4]	X	X	X		X	X		X	X		X	
CBC, diff, platelets[14]	X	X	X	X	X	X	X	X	X		X	
Serum chemistry	X	X	X		X	X		X	X		X	
Archival unstained tumor tissue for hypoxia biomarkers	X											
Serum and Plasma hypoxia biomarkers[5]		X			X						X	
Pregnancy test (serum)[6]	X	X			X			X			X	
Urinalysis[7]	X	X			X			X			X	
ECG and MUGA or echocardiogram[8]	X	X[8]	X[8]				X[8]				X	
Tumor assessment[9]	X						X[9]			X[9]	X[9]	X[9]
TH-302 administration[10]		X[10]	X[10]		X[10]	X[10]		X[10]	X[10]			
Doxorubicin administration[11]		X[11]			X[11]							
Filgrastim or pegfilgrastim administration[12]			X			X						
Pharmacokinetic sampling[13]		X										
Concomitant medication		X	X		X	X		X	X		X	
Adverse event assessment		X	X		X	X		X	X		X	
Survival Follow up[16]												X
EQ-5D-5L[18]	X	X			X			X			X	X

BP = blood pressure; CBC = complete blood cell; diff = differential; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HR = heart rate; LVEF = left ventricular ejection fraction; MUGA = multi gated acquisition scan; RR = respiratory rate; TH-302 = evofosfamide.

1) **Screen:** Obtained within 3 weeks prior to Cycle 1 Day 1.
2) **Interim Medical History (Cycle 1 only):** Confirmed subject continued to meet Inclusion/Exclusion criteria; recorded interim medical history since screening visit.
3) **Complete and limited physical examination:** Complete physical exams were done at screening and at termination/early termination visit. Limited physical examinations were performed at the beginning of Cycles 1, 3, and 5 (and every odd cycle for subjects continuing past Cycle 6).
4) **BP, HR, RR and Temperature**
   a) Screening visit
   b) Before and at completion (BP, HR, RR only) of infusion of each dose of evofosfamide and/or doxorubicin
   c) Treatment termination /early termination
5) **Serum and plasma hypoxia biomarkers (required separate consent):** Start of Cycle 1 and 3 (predose) and at termination
6) **Pregnancy Test:** Serum testing at screen and study completion/early termination, and urine or serum testing at pre-dose Cycles 1, 3, and 5 (and every odd cycle for subjects continuing past Cycle 6). Results must have been known prior to dosing.
7) **Urinalysis:** U/A with micro was performed at screen and study completion/early termination. Urine dipstick for glucose and protein was obtained pre-dose on Day 1 of all cycles. If the urine dipstick was positive and a change from baseline or previous cycle for glucose (without elevated blood glucose), RBC or protein, then U/A with micro was performed.
8) **ECG and MUGA or echocardiogram for LVEF determination:** Screening, pre and post- evofosfamide doses at Cycle 1 Days 1 and 8 (ECG only), end of Cycle 4 and end of Cycle 6/Termination (ECG at End of Cycle 6 and Termination and MUGA or echocardiogram at End of Cycle 6 for subjects continuing). The same method of assessment was used for the determination of LVEF throughout the study.
9) **Tumor assessments:** Tumor-appropriate spiral CT of chest, abdomen and pelvis and all other known sites of disease at screening, the end of Cycles 2, 4 and 6 (and every third cycle for subjects continuing to Cycle 7 to Cycle 12 and every third to fifth cycle thereafter), at termination if not done within 6 weeks before termination (before additional anti-tumor therapy was started) and at every 9 weeks post treatment for the first 18 weeks and every 9 to 15 weeks thereafter for subjects who discontinued treatment without documentation of progressive disease and had not started other anti-tumor therapy. After screening tumor assessments should have included all known sites of disease, site of primary, chest and any other clinically indicated sites.
10) **Evofosfamide administration:** Administered evofosfamide on Days 1and 8 for subjects randomized to evofosfamide plus doxorubicin. Assessed whether subject was adequately hydrated prior to administering study drug. Administered appropriate prophylactic anti-emetic regimen.

11) **Doxorubicin administration:** Administered doxorubicin by bolus injection starting on Day 1 of each 3-week cycle or by continuous IV infusion over 6-96 hours starting on Day 1 of a 3-week cycle. Doxorubicin was not to be administered after 6 cycles of treatment. Administered appropriate prophylactic anti-emetic regimen.

12) **Filgrastim or pegfilgrastim administration:** Cycle 1-6 only. Starting on Day 8 or Day 9 after completion of other study procedures.

13) Pharmacokinetic (Cycle 1, Day 1 only):

a) Evofosfamide and Br-IPM sampling for all subjects who received evofosfamide:

i. Draw a blood sample (2.5 mL) for determination of plasma concentrations of evofosfamide and Br-IPM predose, immediately upon completion of evofosfamide infusion, 15 (± 5) minutes post-infusion, one hour (± 0.2 hours) post-infusion and between 2 to 4 hours post-infusion.

b) Doxorubicin sampling (at select sites and in select subjects receiving doxorubicin bolus injection administration (n = 36; approximately 18 per treatment arm):

i. Draw a blood sample (2.5 mL) for determination of plasma concentrations of doxorubicin injection pre-dose, immediately upon completion of doxorubicin infusion and at the following time points after doxorubicin injection completion: 30 (± 5) minutes and 1, 2 and 4 hours (± 0.2 hours) post-infusion, between 6-18 hours and between 24-36 hours post-infusion

14) **CBC, diff, platelets:** PT/INR should have been done for all subjects on anti-coagulation therapy. CBC, diff and platelets were not required on Day 15 for subjects continuing after Cycle 6.

15) **Obtained all required evaluations for early termination as required for the treatment term visit.** Treatment termination visit occurred 1-2 weeks following the last dose of treatment on study. Tumor assessments only required if not done within the past 6 weeks

16) **Survival Follow up:** Subjects were contacted for survival, subsequent cancer therapy information and tumor status (if applicable) every 3 months until up to 3 years from study entry. Subjects who discontinued study treatment without progressive disease had tumor assessments performed every 9 weeks for the first 18 weeks and then every 9 to 15 weeks thereafter or more frequently if required for patient care until disease progression or initiation of additional anti-tumor therapy.

17) **Weight:** Recorded pre-dose on Day 1 for both doxorubicin alone and evofosfamide plus doxorubicin arms. Recorded pre-dose on Day 8 for evofosfamide plus doxorubicin arm only.

18) **EQ-5D-5L:** Completed at screening, Day 1 predose of every cycle, treatment termination, and survival follow up visit.

19) **Oxygen Saturation:** in subjects with known significant pulmonary disease, measured oxygen saturation using pulse oximeter after a 2 minute walk

Note: When multiple assessments were required, the order of procedures and dosing should have been EQ-5D-5L completion, vital signs, blood sample collection, urine sample collection and dosing. If the evofosfamide infusion was not completed in 30-60 minutes, the times of subsequent was adjusted accordingly.

Subjects whose disease was rendered operable after four or more cycles of therapy were able to undergo surgical removal of operable disease. After resection, patients with remaining sites of disease were eligible to continue on study after approval by the medical monitor. Patients who had all sites of disease resected were discontinued from treatment.

Subjects were free to discontinue (withdraw) at any time during this clinical trial. If a subject withdrew from participation in the study during the treatment period, he or she was encouraged to return for an early termination visit for evaluation of safety. The investigator had the right to discontinue any subject from study drug administration or study participation. Reasons for subject study drug administration discontinuation included, but were not limited to:

- Completion of study
- Disease progression
- Clinically significant deterioration of the subject's condition
- Requirement for other anti-tumor therapy
- Resection of all sites of disease
- Noncompliance
- Pregnancy
- Significant AE
- Subject's right to withdraw from the study at any time, with or without a stated reason
- Significant protocol violation
- Lost to follow-up
- Death
- Any other reason that, in the opinion of the principal investigator, would justify the removal of a subject from the study
- The Sponsor's discretion to terminate the study at any time

Safety Evaluation and Parameters

All randomised patients who received study drug were included in the safety analyses and summaries. Safety data were summarized by treatment group. The MedDRA® (Medical Dictionary for Regulatory Activities) thesaurus was used to map the Adverse Event (AE) verbatim to lowest level term (LLT), preferred term (PT) and System Organ Class (SOC) for summary purposes. All AEs including the AE verbatim term and the associated AE thesaurus preferred term was provided in the patient data listings. Analyses of AEs were performed by relationship to study drug, grade, and seriousness. The rate of hospitalization was summarized. Fisher's exact test was used to compare the most frequent AEs (≥5% of patients) between the two treatment groups and the severe AEs (Grade 3 or higher) between the two treatment groups. Severity of AEs or clinically significant laboratory test results were assessed in accordance with the grading scale presented in the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0.

Pharmacokinetics

Blood samples (2.5 mL each) for determination of plasma concentrations of evofosfamide and Br-IPM were collected in all patients receiving evofosfamide in the study at the following time points on Cycle 1, Day 1: Predose, immediately upon completion of the evofosfamide infusion, 15 (+/- 5) minutes post-infusion, one hour (+/- 0.2 hours) post-infusion, and between 2 hours to 4 hours post-infusion.

At select sites and select patients (n=36; approximately 18 per treatment arm) receiving bolus doxorubicin administration, blood samples (2.5 mL each) for determination of plasma concentrations of doxorubicin and doxorubicinol were collected at the following time points on, Day 1 and Day 2 of Cycle 1: Predose, immediately upon completion of doxorubicin infusion, 30 (+/- 5) min, 1, 2 and 4 hours (+/- 0.2 hours) post-infusion, between 6-18 hours post-infusion, and between 24-36 hours post-infusion.

The primary pharmacokinetic parameters (e.g., clearance (Cl) and volume of distribution (V) for evofosfamide) were estimated by means of NONMEM analysis of the sparse pharmacokinetic data. The selection of parameters and the derivation of individual measures of exposure, such as AUC and C_{max}, depended on the final pharmacokinetic model used for this analysis.

Nonlinear mixed effect model building was conducted using NONMEM. Both evofosfamide and its metabolite, Br-IPM, was modeled simultaneously using either a one- or two-compartmental metabolite model with zero-order infusion and first-order elimination to determine the best structural model. The models were parameterized in terms of CL, V and Q (intercompartmental clearance, if needed). Potential covariates (i.e., age, sex gender, race, biochemical and hematological parameters, etc.) were initially identified using visual inspection of the individual parameter estimates versus covariate plots and any potential covariates was then tested for statistical significance using stepwise forward addition followed by stepwise backward elimination. All pharmacokinetic parameters were presented by listings and descriptive summary statistics for AUC and C_{max} and their derived parameters.

The following parameters for evofosfamide and Br-IPM and doxorubicin and doxorubicinol were computed for patients undergoing PK sampling for evofosfamide and/or doxorubicin bolus injection:

- T_{max}: Time to maximum concentration
- C_{max}: Maximum peak observed concentration
- K_{el}: The magnitude of the slope of the linear regression of the log concentration vs. time profile during the terminal phase
- $T_{½}$: Half-life, computed as ln (2)/K_{el}

- AUC_{last}: Area under the concentration-time curve from Hour 0 through the last quantifiable concentration time (LQCT), where LQCT is the time at which the last sample with a quantifiable concentration was drawn
- AUC: Area under the concentration-time curve from 0 to infinity, computed using the linear trapezoidal rule as $AUC_{last} + C_{LQCT} / K_{el}$
- Cl: Clearance computed as Dose divided by AUC (evofosfamide, doxorubicin only)
- Vss: Apparent steady-state volume of distribution, computed as the Dose*AUMC/AUC^2 - Dose*T/(2*AUC), where AUMC is the area under the first moment of the plasma concentration time curve (evofosfamide, doxorubicin only) and T is the duration of infusion
- $V_ß$: Apparent volume of distribution in the post-distributive phase computed as the ratio of Cl to the terminal elimination rate constant, K_{el} (evofosfamide, doxorubicin only)

All calculations used the actual times recorded on the eCRF. In all calculations, zero was substituted for concentrations below the quantification limit (BQL) of the assay. All computed PK parameters were listed by patient (mean, standard deviation, coefficient of variation, minimum, maximum, number of observations). Individual and mean (by time) plasma concentrations versus time were plotted for each dose on both linear and logarithmic scales.

Test Product

Evofosfamide injection was supplied in a 10 mL glass vial with a rubber stopper and aluminum crimped seal containing 650 mg of evofosfamide. Each vial of study medication was labeled clearly, disclosing the lot number, route of administration, required storage conditions, sponsor's name, and appropriate, required precautionary labeling. The evofosfamide drug product was to be stored in a secure area with limited access under controlled conditions at 2-8°C.

Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee was formed to monitor safety and efficacy during the study. The IDMC was comprised of four oncologists and a statistician experienced in clinical trials. A written charter defined the makeup and conduct of the IDMC. The IDMC conducted safety reviews approximately every 3 months. A planned interim analysis for both safety and efficacy was to be performed by the IDMC after 235 survival events at approximately the completion of enrollment.

Independent Pathology Review

An independent central pathology review was conducted to confirm histology. Results from this review were used to explore differences in efficacy based on histology.

An archival tissue samples was required for each patient. These were used to confirm histology via the Independent Pathology Review. The original pathology slide(s) and the corresponding pathology report were collected at the screening visit. If the original pathology slide(s) were not available, either the tissue block or 2-10 unstained slides were requested. Tissue blocks were to be returned to study center after unstained slides have been cut.

Independent Radiology Review

Baseline and follow up radiology studies and other relevant clinical information used for tumor assessment were collected and forwarded to a specified CRO after each tumor assessment for a central review.

Biomarker analyses

Collection of archival tissue samples for testing of hypoxia biomarkers (e.g. Carbonic Anhydrase IX, Neuron Specific Enolase, Osteopontin, Vascular Endothelial Growth Factor) was optional for all patients. Patients must have consented to these procedures in the informed consent prior to collection of archival tissue samples. If the patient gave consent, either the archival tissue block or 2-10 unstained slides were labeled and collected at the screening visit. The corresponding pathology report was also collected.

Collection of serum and plasma samples for testing of hypoxia biomarkers was also optional for patients. Patients must have consented to these procedures in the informed consent prior to collection of blood samples. If the patient gave consent, blood samples were collected at C1D1 (pre-dose), C3D1 (pre-dose) and at treatment termination. Ten milliliters (10 mL) were collected at each time point for a total of 30 mL.

Criteria for Evaluation and Statistical Methods

Subjects were assessed for adverse events before every dose of study drug until 30 days after the last dose of study drug. Tumor assessments were performed at baseline until documentation of disease progression, initiation of other anti-cancer therapy, or death. The assessments were scheduled to occur every 6 weeks for the first 18 weeks, every 9 weeks for the next 18 weeks and then every 9 to 15 weeks. Subjects discontinuing treatment without progressive disease had tumor assessments performed every 9 weeks for the next 18 weeks and then every 9 to 15 weeks until disease progression, initiation of additional anti-tumor therapy, or death. LVEF using either MUGA or echocardiogram and ECG were assessed at baseline, after completion of 4 cycles and at doxorubicin treatment termination. Subjects randomised to the evofosfamide plus doxorubicin arm had additional ECGs performed at pre and post evofosfamide doses on Cycle 1 Days 1 and 8. The EQ-5D-5L questionnaire was completed at day 1 of each cycle and at each follow-up assessment prior to the initiation of any other study activities, treatments or investigator interactions.

When a patient completed the treatment termination or early termination visit, he/she and/or a family member was contacted for survival information every 3 months from study treatment termination until three years from study entry. Anti-tumor therapy (description and dates) since the last contact was collected at each survival follow up if available. In order to capture longer term progression free survival, additional tumor assessments were scheduled every 6 weeks for the first 18 weeks after randomisation, every 9 weeks for the next 18 weeks and then every 9 to 15 weeks for patients who discontinue from the study without progressive disease and without receiving additional anti-tumor therapy until progression or, initiation of additional anti-tumor therapy, or death.

Tests of Hypotheses and Significance Levels

The primary objective of this study was to determine if evofosfamide adds a clinically significant benefit to patients with locally advanced unresectable or metastatic soft tissue sarcoma. This was tested by assessing if there was a significant improvement in overall survival following therapy with evofosfamide in combination with doxorubicin compared to doxorubicin alone. H0 (null): the overall survival in patients with locally advanced unresectable or metastatic soft tissue sarcoma is the same following treatment with evofosfamide in combination with doxorubicin as it is following treatment with doxorubicin alone. HA(alternative): the overall survival in patients with locally advanced unresectable or metastatic soft tissue sarcoma is longer following treatment with evofosfamide in combination with doxorubicin than it is following treatment with doxorubicin alone. The test was conducted using a one-sided alpha level of 2.5% (equivalent to a two-sided 5.0%). The other primary objective was to assess the safety of evofosfamide in combination with doxorubicin in patients with locally advanced unresectable or metastatic soft tissue sarcoma compared with doxorubicin alone.

Sample Size and Power Considerations

A sample size of 620 patients (1:1 randomisation) had 85% power to detect a 33% improvement in overall survival using a one-sided alpha level of 2.5%. The calculation was based on a two-sided log-rank test and compares the overall survival of the evofosfamide in combination with doxorubicin arm to the overall survival of the doxorubicin alone arm. The final analysis of overall survival was to be performed after 434 overall survival events had occurred.

An interim analysis was to be conducted after enrollment of 620 patients was expected to be completed. This interim was to be conducted based on overall survival and planned to occur after 235 deaths. The Lan-DeMets implementation of the O'Brien-Fleming group sequential method was used to determine the stopping boundaries and alpha spending (Lan 1983, O'Brien 1979). A planned one-sided value of 0.0023 based on 235 events would be required to reach statistical significance.

Based on the treatment comparison for the interim analysis at approximately 235 events, the significance level was adjusted to a planned one-sided value of 0.0243 for the final treatment comparison of the primary efficacy parameter after 434 events. The actual significance level depended on the number of events at the time of the interim overall survival analysis.

The primary efficacy analyses were performed on the intent to treat population defined as all randomised patients.

The primary efficacy endpoint was overall survival, which was defined as the duration from date of randomisation to date of death. Kaplan-Meier methods were used to estimate survival. Estimates and confidence intervals were calculated by the product limit method and Greenwood's formula for the variance. In general, durations were summarized by the 25%, 50% (i.e., median), and 75% quartiles and their associated 95% confidence intervals (CIs). Kaplan-Meier estimates and curves are presented for each treatment arm. A two-sided log-rank test with the three randomisation stratification factors was employed to test whether there was a significant difference in the survival between the two treatment arms. The relative risk, standard error, and 95% CI will be presented with adjustment for the stratification factors.

RECIST 1.1 was used to determine objective tumor response, stable disease or better rate, duration of response and progression-free survival. Radiographic examinations were collected to enable an outside independent review facility to assess tumor response including progression. The RECIST response was summarized for all patients by best response (confirmed or unconfirmed). The overall response rate (CR+PR) as well as the rates for the individual categories of response (CR, PR) was estimated as the number of complete or partial responders divided by the number of randomised patients. Interim analyses were based on a more restrictive population to account for on-study patients without a response assessment. The percent of patients with a best response of stable disease was also calculated. Subjects must have had stable disease at their tumor assessment following Cycle 2 (at least 36 days after randomisation) to be classified with at least stable disease. The precision of these estimates was estimated using 95% exact binomial confidence limits. Duration of response (partial and complete responses), defined as time from first response to disease progression was estimated using the Kaplan-Meier method. The primary comparison was a two-sided Cochran-Mantel-Haenszel test using the randomisation strata.

Progression-free survival (PFS) was calculated as time from randomisation to disease progression or death from any cause up to 63 days following the last response assessment (or from start of treatment for patients without a response assessment), whichever occurred first. RECIST 1.1 was used to determine progression at tumor assessments. Subjects who discontinued from study without progression were asked to be followed until disease progression or initiation of additional cancer therapy. Subjects without evidence of progression by the PFS definition were censored at their last response assessment. Subjects undergoing resection were censored for analysis of secondary endpoints related to RECIST response assessments at the time of their last response assessment prior to resection. Progression-free survival analyses followed the methods described for overall survival. The endpoints of progression-free rate at 3 months and 6 months were estimated using the Kaplan-Meier method and reported with its associated 95% confidence interval. For the progression-free rate analyses patients who died prior to 6 months without a RECIST assessment of progression were considered to have progressed at the time of death for the

purpose of this endpoint. Two additional sensitivity analyses were conducted to assess the robustness of the PFS outcome. The first, PFS on-study, included progressive disease or death on active study as a PFS event. Subjects who discontinued from active treatment for reasons other than progressive disease or death were censored at the last response assessment prior to discontinuation. The second, PFS-Extended, allowed a window of three response assessments or 126 days to capture additional death and progressive disease after study discontinuation. PFS-Extended was measured from the start of treatment to the first occurrence of progressive disease or death from any cause up to 126 days following the last response assessment (or from start of treatment for patients without a response assessment).

The three- and six-month progression-free rate comparisons and six- and twelve-month overall survival comparisons were performed from a Z-test using estimates and standard errors derived from the Kaplan-Meier method and Greenwood's formula.

Changes in ECOG performance status were summarized. A paired t-test was used for the test of mean change from baseline to the best assessment and to the last assessment of the study within each treatment group. A two-sample t-test was used to make comparisons between treatment groups for each of the endpoints. The equality of variances was examined using an F-test before applying the two-sample t-test.

The Statistical Analysis Plan did not incorporate the statistical testing of safety adverse events. Although, the Fisher's exact test was specified within the protocol. The provided data allows the reader to perform the associated test. For example, for febrile neutropenia the provided data report 34 subjects with a reported AE of febrile neutropenia (34 of 307 = 11%) in the doxorubicin alone arm compared to 57 subjects with a reported AE of febrile neutropenia (57 of 312 = 18%) in the combination arm. The odds ratio is 0.56 (95% CI: 0.35 – 0.88) with p-value of 0.0125.

The resectability rate was compared between the two treatment groups. Outcomes were categorized based on resected versus not resected and for those resected according to residual disease status (termed "R" factor): R0, no gross or microscopic residual disease; R1, microscopic residual disease (microscopically positive surgical margins with no gross residual disease); and R2, grossly evident residual disease. The percentage of patients with R0/R1 resections were compared between the two groups using Cochran-Mantel-Haenszel test stratifying by extent of disease (unresectable locally advanced vs. metastatic disease). For those patients who underwent resection of all known sites of disease, the overall survival and disease-free survival was compared between the two treatment groups using logrank tests.

EQ-5D-5L item (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) scores, EQ VAS self-rated health and the utility value derived from the individual items was described for each treatment group. Items were summarized by specific category as well as dichotomized for absence or presence of the problem. Changes from baseline were calculated and compared. Paired t-tests were used to explore the mean change from baseline to the best assessment and to the last assessment during the study within each treatment group for each endpoint. Two-sample t-tests were used to make comparisons between treatment groups for each of the endpoints. The equality of variances was examined using an F-test before applying the two-sample t-test.

Replacement of Subjects

If greater than 10 patients were enrolled and then withdraw consent for future follow-up, the sample size was increased by that number of patients to assure that the timing of the primary analysis was preserved. Subject enrollment numbers were unique and would not be re-assigned. Subjects may not be re-randomised once they have entered the study. Subjects who have been terminated from the study could not be re-enroll.

Results

Tertiary outcomes

The Overall Survival (OS) rates at 6 months, 12 months, 18 months, 24 months, and 36 months were similar between the combination arm compared with the doxorubicin alone arm (6 month OS: 85% vs. 83%, p = 0.488; 12 month OS: both 65%, p = 0.974; 18 month OS: 50% vs 53%, p = 0.529; 24 month OS: 40% vs. 43%, p = 0.554; 36 month OS: 19% vs. 29%, p = 0.061).

Similar median Progression-free survival at 3 months was observed in the combination arm and the doxorubicin alone arm; median PFS at 3 months was 191 days and 176 days, respectively (HR: 0.851 [95% CI: 0.701 – 1.034]; p = 0.1041). The 6- and 12-month PFS rate was statistically significantly higher in the combination arm compared with the doxorubicin alone arm (6 month PFS: 55% vs 47%, p = 0.047; 12 month PFS: 25% vs 15%, p = 0.014).

At baseline, the ECOG performance status was either 0 or 1, as required per-protocol, with the exception of 4 subjects who had an ECOG performance status of 2 (3 in the combination arm and 1 in the doxorubicin alone arm). At the lowest assessment excluding the monotherapy period, a similar proportion of subjects in both treatment arms had an ECOG performance status of 0 compared with baseline (59.7% vs. 57.5% for the doxorubicin plus evofosfamide arm and 59.2% vs. 57.8% for the doxorubicin alone arm); with a mean change in ECOG performance status of 0 for both arms, p = 0.387.

Quality of Life and Health Status Assessments

Quality of life and health status were evaluated using the EQ-5D-5L.

Mobility

At baseline, the median mobility scores were 1.0 for both the combination treatment arm and the doxorubicin alone arm. The lowest mean evaluation change from baseline for doxorubicin compared with evofosafamide plus doxorubicin excluding the monotherapy period had a t-test p = 0.655. The highest mean evaluation change from baseline for doxorubicin compared with evofosafamide plus doxorubicin excluding the monotherapy period had a t-test p = 0.682.

Self-care

At baseline, the median self-care scores were 1.0 for both the combination treatment arm and the doxorubicin alone arm. The lowest mean evaluation change from baseline for doxorubicin compared with evofosafamide plus doxorubicin excluding the monotherapy period had a t-test p = 0.055. The highest mean evaluation change from baseline for doxorubicin compared with evofosafamide plus doxorubicin excluding the monotherapy period had a t-test p = 0.070.

Usual Activities

At baseline, the median mobility scores were 1.0 for both the combination treatment arm and the doxorubicin alone arm. The lowest mean evaluation change from baseline for doxorubicin compared with evofosafamide plus doxorubicin excluding the monotherapy period had a t-test p = 0.291. The highest mean evaluation change from baseline for doxorubicin compared with TH-302 plus doxorubicin excluding the monotherapy period had a t-test p = 0.303.

Pain and Discomfort

At baseline, the median scores were 2.0 for both the combination treatment arm and the doxorubicin alone arm. The lowest mean evaluation change from baseline for doxorubicin compared with evofosafamide plus doxorubicin

excluding the monotherapy period had a t-test p = 0.272. The highest mean evaluation change from baseline for doxorubicin compared with evofosafamide plus doxorubicin excluding the monotherapy period had a t-test p = 0.006.

Anxiety and Depression

At baseline, the median scores were 2.0 for both the combination treatment arm and the doxorubicin alone arm. The lowest mean evaluation change from baseline for doxorubicin compared with evofosafamide plus doxorubicin excluding the monotherapy period had a t-test p = 0.467. The highest mean evaluation change from baseline for doxorubicin compared with evofosafamide plus doxorubicin excluding the monotherapy period had a t-test p = 0.361.

Visual Analogue Scale

At baseline, the median scores were 80.0 for both the combination treatment arm and the doxorubicin alone arm. The lowest mean evaluation change from baseline for doxorubicin compared with evofosafamide plus doxorubicin excluding the monotherapy period had a t-test p = 0.797. The highest mean evaluation change from baseline for doxorubicin compared with evofosafamide plus doxorubicin excluding the monotherapy period had a t-test p = 0.740.

EQ-5D-5L health utilities index.

At baseline, the median scores were 0.87 for the combination treatment arm and 0.85 for the doxorubicin alone arm. The lowest mean evaluation change from baseline for doxorubicin compared with TH-302 plus doxorubicin excluding the monotherapy period had a t-test p = 0.483. The highest mean evaluation change from baseline for doxorubicin compared with TH-302 plus doxorubicin excluding the monotherapy period had a t-test p = 0.414.

Table S1: Overall Survival: Primary Analysis Stratification Factor Sensitivity Analyses

	Doxorubicin	Doxorubicin + Evofosfamide	Total
Total Number of Subjects	323	317	640

Randomisation Stratification: Extent of Disease, Prior Systemic Therapy and Doxorubicin Administration
Log-rank statistic, d.f., P-value [a]: 0.40, 1, 0.5267
Log hazard (SE), Relative Risk (95% CI) [b]: 0.062 (0.098), 1.064 (0.878 - 1.289)

Randomisation Stratification: Extent of Disease and Prior Systemic Therapy
Log-rank statistic, d.f., P-value [a]: 0.52, 1, 0.4712
Log hazard (SE), Relative Risk (95% CI) [b]: 0.070 (0.098), 1.073 (0.886 - 1.299)

Randomisation Stratification: Extent of Disease and Doxorubicin Administration
Log-rank statistic, d.f., P-value [a]: 0.42, 1, 0.5168
Log hazard (SE), Relative Risk (95% CI) [b]: 0.063 (0.098), 1.065 (0.880 - 1.291)

Randomisation Stratification: Prior Systemic Therapy and Doxorubicin Administration
Log-rank statistic, d.f., P-value [a]: 0.41, 1, 0.5206
Log hazard (SE), Relative Risk (95% CI) [b]: 0.063 (0.098), 1.065 (0.879 - 1.290)

Randomisation Stratification: Extent of Disease
Log-rank statistic, d.f., P-value [a]: 0.54, 1, 0.4620
Log hazard (SE), Relative Risk (95% CI) [b]: 0.072 (0.098), 1.074 (0.887 - 1.301)

Randomisation Stratification: Prior Systemic Therapy
Log-rank statistic, d.f., P-value [a]: 0.55, 1, 0.4584
Log hazard (SE), Relative Risk (95% CI) [b]: 0.072 (0.097), 1.075 (0.888 - 1.301)

Randomisation Stratification: Doxorubicin Administration
Log-rank statistic, d.f., P-value [a]: 0.45, 1, 0.5045
Log hazard (SE), Relative Risk (95% CI) [b]: 0.065 (0.098), 1.067 (0.881 - 1.292)

No Randomisation Stratification
Log-rank statistic, d.f., P-value [a]: 0.57, 1, 0.4510
Log hazard (SE), Relative Risk (95% CI) [b]: 0.073 (0.097), 1.076 (0.889 - 1.303)

[a] Two-sided log-rank test stratified by randomisation stratification factors.
[b] Relative risk (with associated standard error and 95% CI). CI for relative risk is adjusted to account for interim analysis.

Table S2a: Best Response by Primary (Site) Analysis

	Doxorubicin (N = 323)	**Doxorubicin + Evofosfamide (N = 317)**	**Total (N = 640)**
Evaluable for Confirmed Response (n[%])			
Evaluable [1]	294 (91.0)	296 (93.4)	590 (92.2)
Not Evaluated[2]	29 (9.0)	21 (6.6)	50 (7.8)
Confirmed Response (n[%])			
CR	3 (0.9)	5 (1.6)	8 (1.3)
PR	56 (17.3)	85 (26.8)	141 (22.0)
SD	154 (47.7)	142 (44.8)	296 (46.3)
PD	81 (25.1)	64 (20.2)	145 (22.7)
UE	1 (0.3)	1 (0.3)	2 (0.3)
NA	28 (8.7)	20 (6.3)	48 (7.5)
Stable Disease or Better Response			
Number Responding (n)	213	232	445
Percent Responding (%)	65.9	73.2	69.5
95% CI[3]	60.5,71.1	67.9,78.0	65.8,73.1
95% LCL[3]	61.4	68.8	66.4

[1] Subjects evaluable for best response are off-study or on study with at least 1 response assessment.
[2] No response assessment on study. Subject is classified as PD for analyses.
[3] Exact 95% Binomial Confidence Interval (CI) or Lower Confidence Limit (LCL). In cases for which there are no responses, the Upper Confidence Limit (UCL) is reported in place of LCL; the LCL in this case is 0.0%.

Table S2b: Confirmed Response by Primary Analysis

	Doxorubicin (N = 323)	Doxorubicin + Evofosfamide (N = 317)	Total (N = 640)
Evaluable for Confirmed Response (n[%])			
Evaluable [1]	294 (91.0)	296 (93.4)	590 (92.2)
Not Evaluated[2]	29 (9.0)	21 (6.6)	50 (7.8)
Confirmed Response (n[%])			
CR	3 (0.9)	3 (0.9)	6 (0.9)
PR	43 (13.3)	67 (21.1)	110 (17.2)
SD	167 (51.7)	162 (51.1)	329 (51.4)
PD	81 (25.1)	64 (20.2)	145 (22.7)
UE	0 (0.0)	0 (0.0)	0 (0.0)
NA	29 (9.0)	21 (6.6)	50 (7.8)
Confirmed Partial Response or Better			
Number Responding (n)	46	70	116
Percent Responding (%)	14.2	22.1	18.1
95% CI[3]	10.6, 18.5	17.6, 27.1	15.2, 21.3
95% LCL[3]	11.1	18.3	15.7
Cochran-Mantel-Haenszel P-value[4]	0.0115		
Confirmed Complete Response			
Number Responding	3	3	6
Percent Responding	0.9	0.9	0.9
95% CI[3]	0.2, 2.7	0.2, 2.7	0.3, 2.0
95% LCL[3]	0.3	0.3	0.4
Cochran-Mantel-Haenszel P-value[4]	0.9908		

[1] Subjects evaluable for best response are off-study or on study with at least 1 response assessment.
[2] No response assessment on study. Subject is classified as PD for analyses.
[3] Exact 95% Binomial Confidence Interval (CI) or Lower Confidence Limit (LCL). In cases for which there are no responses, the Upper Confidence Limit (UCL) is reported in place of LCL; the LCL in this case is 0.0%.
[4] Two-sided Cochran-Mantel-Haenszel with stratification factors.

Table S3a: Study Drug Exposure for Evofosfamide

	Doxorubicin + Evofosfamide (N = 313)
Last Cycle Initiated	
Mean (SD)	9.1 (8.72)
Median	6.0
Range	1 – 42
Duration of Exposure (Weeks)[1]	
Mean (SD)	26.8 (27.81)
Median	17.1
Range	0.1 - 144.9
Total Number of Doses	
Mean (SD)	17.6 (17.16)
Median	12.0
Range	1 – 83

SD = standard deviation
1) Weeks from initial dose to last dose.

Table S3b: Study Drug Exposure for Doxorubicin

	Doxorubicin (N = 308)	**Doxorubicin + Evofosfamide (N = 313)**	**Total (N = 621)**
Last Cycle Initiated			
Mean (SD)	4.4 (1.97)	4.6 (1.83)	4.5 (1.90)
Median	6.0	6.0	6.0
Range	1 - 6	0 - 6	0 - 6
Duration of Exposure (Weeks)[1]			
Mean (SD)	10.6 (6.11)	11.4 (5.81)	11.0 (5.97)
Median	15.0	15.1	15.0
Range	0.1 - 21.0	0.0 - 23.4	0.0 - 23.4
Total Number of Doses			
Mean (SD)	4.4 (1.97)	4.5 (1.83)	4.5 (1.90)
Median	6.0	6.0	6.0
Range	1 - 6	0 - 6	0 - 6

SD = standard deviation
1) Weeks from initial dose to last dose.

Table S3c: Doxorubicin Administration Schedule

	Doxorubicin (N = 323)	**Doxorubicin + Evofosfamide (N = 317)**	**Total (N = 640)**
Doxorubicin Administration (n[%])			
Bolus	278 (86.1)	277 (87.4)	555 (86.7)
Continuous	45 (13.9)	40 (12.6)	85 (13.3)
P-value[1] 0.6244			

1) Chi-square-test evofosfamide+doxorubicin vs doxorubicin

Table S4: Subject Disposition

	Doxorubicin (N = 323)	Doxorubicin + Evofosfamide (N = 317)	Total (N = 640)
Study Status (n[%])			
Initiated Treatment	308 (95.4)	313 (98.7)	621 (97.0)
Completed 6 Cycles	170 (52.6)	160 (50.5)	330 (51.6)
Early Termination	153 (47.4)	148 (46.7)	301 (47.0)
Reason for Treatment Discontinuation (n[%])			
Disease Progression by Tumor Evaluation	114 (35.3)	197 (62.1)	311 (48.6)
Completed 6 Cycles	151 (46.7)	5 (1.6)	156 (24.4)
Adverse Event	17 (5.3)	35 (11.0)	52 (8.1)
Subject Decision	17 (5.3)	28 (8.8)	45 (7.0)
Clinical Deterioration	6 (1.9)	13 (4.1)	19 (3.0)
Requirement for Other Antitumor Therapy	3 (0.9)	9 (2.8)	12 (1.9)
Death	5 (1.5)	7 (2.2)	12 (1.9)
Resection of All Sites of Disease	2 (0.6)	7 (2.2)	9 (1.4)
Investigator's Decision	2 (0.6)	4 (1.3)	6 (1.0)
Other	3 (0.9)	2 (0.6)	5 (0.9)
Protocol Violation	3 (0.9)	0 (0.0)	3 (0.5)
Noncompliance	0 (0.0)	1 (0.3)	1 (0.2)

Table S5: Baseline Histology from the Central Pathology Review

Classification	Doxorubicin (N = 323)		Doxorubicin + Evofosfamide (N = 317)		Total (N = 640)	
Synovial sarcoma	11	(3.4%)	17	(5.4%)	28	(4.4%)
Undifferentiated sarcoma	15	(4.6%)	18	(5.7%)	33	(5.2%)
Liposarcoma	50	(15.5%)	59	(18.6%)	109	(17.0%)
Leiomyosarcoma	103	(31.9%)	115	(36.3%)	218	(34.1%)
Angiosarcoma	12	(3.7%)	9	(2.8%)	21	(3.3%)
Pleomorphic/ malignant fibrous	66	(20.4%)	48	(15.1%)	114	(17.8%)
Myxofibrosarcoma	13	(4.0%)	8	(2.5%)	21	(3.3%)
Epithelioid sarcoma	6	(1.9%)	3	(0.9%)	9	(1.4%)
Malignant peripheral nerve sheath tumor	9	(2.8%)	5	(1.6%)	14	(2.2%)
Pleomorphic rhabdomyosarcoma	4	(1.2%)	0	(0.0%)	4	(0.6%)
Sarcoma with Doxorubicin rational treatment	7	(2.2%)	15	(4.7%)	22	(3.4%)
Other[1]	27	(8.4%)	20	(6.3%)	47	(7.3%)

1) Endometrial Stromal Sarcoma (2), Epithelioid hemangioendothelioma (1), Giant Cell Tumor of Soft Tissue (1), Inflammatory Myofibroblastic Tumor (1), Intermediate Grade Sarcoma (1), Intimal Sarcoma (1), Low Grade Myofibroblastic Sarcoma (1), Low Grade Sarcoma (1), Low Grade Tumor (1), Low-grade Endometrial Stromal Sarcoma (1), Malignant Ossifying Fibromyxoid Tumor (1), Malignant PEComa (1), Malignant Phyllodes (3), Malignant Sex Cord Stromal Tumor of the Ovary (1), Malignant Solitary Fibrous Tumor (5), Melanoma (3), Meningeal Hemangiopericytoma (1), Metaplastic (sarcomatoid) Carcinoma (1), Metaplastic Carcinoma (2), Myoepithelial Neoplasm (1), Myxoma (1), Necrotic Tissue (2), No Evidence of Neoplasm (1), Not Eligible Diagnosis (1), Possible Carcinoma (5), Possible Paraganglioma (1), Sclerosing Epithelioid Fibrosarcoma (1), Unclassified Epithelioid Tumor (2), Unclassified Round Cell Neoplasm(1), Undifferentiated High Grade Tumor NOS (1), Undifferentiated Sarcoma (1)

Table S6a: Geometric Mean and Mean (SD) Pharmacokinetic Parameter Estimates for Evofosfamide

PK Parameters	N	Doxorubicin + Evofosfamide Arm	
		Geometric Mean	Mean (SD)
K_{el} (h-1)	215	1.24 (1.198)	1.26 (0.220)
$T_{1/2}$ (h)	215	0.56 (1.198)	0.57 (0.109)
T_{max} (h)	257	0.86 (1.361)	0.90 (0.271)
C_{max} (µg/mL)	257	4.69 (1.570)	5.20 (2.486)
C_{max} adj (µg/mL)	257	6.29 (1.570)	6.94 (3.132)
AUC_{last} (µg-h/mL)	257	4.56 (1.522)	5.00 (2.394)
AUC (µg-h/mL)	215	4.87 (1.504)	5.32 (2.501)
Vss (L/m^2)	215	54.90 (1.521)	59.90 (26.488)
CL ($L/h/m^2$)	215	61.62 (1.504)	66.68 (26.881)

Table S6b: Geometric Mean and Mean (SD) Pharmacokinetic Parameter Estimates for Br-IPM

PK Parameters	N	Doxorubicin + Evofosfamide	
		Geometric Mean	Mean (SD)
K_{el} (h-1)	1	0.73 (NA)	0.73 (NA)
$T_{1/2}$ (h)	1	0.95 (NA)	0.95 (NA)
T_{max} (h)	199	0.90 (1.356)	0.94 (0.280)
C_{max} (µg/mL)	226	0.08 (1.601)	0.08 (0.052)
C_{max} adj (µg/mL)	163	0.12 (1.530)	0.13 (0.056)
AUC_{last} (µg-h/mL)	224	0.06 (2.050)	0.07 (0.055)
AUC (µg-h/mL)	1	0.29 (NA)	0.29 (NA)

AUC = Area under the concentration-time curve from 0 to infinity, computed using the linear trapezoidal rule as $AUC_{last} + CL_{QCT}/ Kel$; AUC_{last} = Area under the concentration-time curve from hour 0 through the last quantifiable concentration time; CL = predicted clearance computed as dose divided by $AUC_{0-\infty}$; C_{max} = maximum peak observed concentration; C_{max} adj = infusion time adjusted C_{max}; K_{el} = the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase; SD = standard deviation; $T_{1/2}$ = Apparent half-life computed as ln(2)/Kel; T_{max} = time to maximum concentration; Vss = predicted steady-state volume of distribution, computed as the $Dose*AUMC/AUC_{0-\infty}^2 - Dose*T/(2*AUC_{0-\infty})$, where AUMC is the area under the first moment of the plasma concentration time curve and T is the duration of infusion

Table S7: Adverse Events (All Grade 3, 4 or 5) Occurring in > 10% of Patients in Either Treatment Arm

	Dox Alone Arm (n=308), No Pts (%)				Dox + TH-302 Arm (n=313), No Pts (%)			
Adverse Event	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Abdominal hernia	1 (0.32)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Abdominal pain	24 (7.79)	7 (2.27)	0 (0)	0 (0)	32 (10.22)	5 (1.6)	0 (0)	0 (0)
Abdominal wall abscess	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)
Activated partial thromboplastin time prolonged	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Acute coronary syndrome	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Adenocarcinoma pancreas	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)
Agranulocytosis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)
Alanine aminotransferase increased	3 (0.97)	0 (0)	0 (0)	0 (0)	10 (3.19)	1 (0.32)	0 (0)	0 (0)
Alopecia	138 (44.81)	0 (0)	0 (0)	0 (0)	153 (48.88)	0 (0)	0 (0)	0 (0)
Anaemia	39 (12.66)	61 (19.81)	4 (1.3)	0 (0)	39 (12.46)	147 (46.96)	3 (0.96)	0 (0)
Anal fistula	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Anal inflammation	1 (0.32)	0 (0)	0 (0)	0 (0)	12 (3.83)	1 (0.32)	0 (0)	0 (0)
Ankle fracture	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Anxiety	14 (4.55)	1 (0.32)	0 (0)	0 (0)	29 (9.27)	1 (0.32)	0 (0)	0 (0)
Appendicitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Arthralgia	17 (5.52)	1 (0.32)	0 (0)	0 (0)	39 (12.46)	1 (0.32)	0 (0)	0 (0)
Arthritis bacterial	1 (0.32)	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Aspartate aminotransferase increased	3 (0.97)	0 (0)	0 (0)	0 (0)	6 (1.92)	2 (0.64)	0 (0)	0 (0)
Asthenia	33 (10.71)	1 (0.32)	0 (0)	0 (0)	37 (11.82)	3 (0.96)	0 (0)	0 (0)
Atrial fibrillation	0 (0)	1 (0.32)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)
Back pain	26 (8.44)	0 (0)	0 (0)	0 (0)	34 (10.86)	5 (1.6)	0 (0)	0 (0)
Bacteraemia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Bladder pain	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	1 (0.32)	0 (0)	0 (0)
Blister	0 (0)	0 (0)	0 (0)	0 (0)	7 (2.24)	1 (0.32)	0 (0)	0 (0)
Blood albumin decreased	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	1 (0.32)	0 (0)	0 (0)
Blood alkaline phosphatase increased	6 (1.95)	0 (0)	0 (0)	0 (0)	16 (5.11)	2 (0.64)	0 (0)	0 (0)
Blood bilirubin increased	4 (1.3)	1 (0.32)	0 (0)	0 (0)	3 (0.96)	0 (0)	0 (0)	0 (0)
Blood pressure increased	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Blood sodium decreased	1 (0.32)	1 (0.32)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)
Blood uric acid increased	1 (0.32)	0 (0)	0 (0)	0 (0)	2 (0.64)	0 (0)	1 (0.32)	0 (0)

Bone pain	11 (3.57)	1 (0.32)	0 (0)	0 (0)	29 (9.27)	2 (0.64)	0 (0)	0 (0)
Brain oedema	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)
Breakthrough pain	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
C-reactive protein increased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Cancer pain	1 (0.32)	0 (0)	0 (0)	0 (0)	1 (0.32)	1 (0.32)	0 (0)	0 (0)
Cardiac failure	1 (0.32)	1 (0.32)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Cardiac failure congestive	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)	1 (0.32)	0 (0)	1 (0.32)
Cardiopulmonary failure	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)
Cataract	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Catheter site infection	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Cellulitis	2 (0.65)	2 (0.65)	0 (0)	0 (0)	11 (3.51)	7 (2.24)	0 (0)	0 (0)
Chest pain	4 (1.3)	2 (0.65)	0 (0)	0 (0)	10 (3.19)	2 (0.64)	0 (0)	0 (0)
Clostridium difficile colitis	0 (0)	1 (0.32)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)
Cognitive disorder	1 (0.32)	2 (0.65)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)
Colitis	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	1 (0.32)	0 (0)	0 (0)
Completed suicide	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)
Confusional state	1 (0.32)	1 (0.32)	0 (0)	0 (0)	5 (1.6)	0 (0)	0 (0)	0 (0)
Conjunctivitis	1 (0.32)	0 (0)	0 (0)	0 (0)	7 (2.24)	1 (0.32)	0 (0)	0 (0)
Constipation	89 (28.9)	0 (0)	0 (0)	0 (0)	130 (41.53)	4 (1.28)	0 (0)	0 (0)
Cough	43 (13.96)	0 (0)	0 (0)	0 (0)	59 (18.85)	0 (0)	0 (0)	0 (0)
Death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)
Decreased appetite	81 (26.3)	1 (0.32)	0 (0)	0 (0)	109 (34.82)	4 (1.28)	0 (0)	0 (0)
Deep vein thrombosis	11 (3.57)	0 (0)	0 (0)	0 (0)	10 (3.19)	1 (0.32)	0 (0)	0 (0)
Dehydration	10 (3.25)	3 (0.97)	0 (0)	0 (0)	21 (6.71)	7 (2.24)	0 (0)	0 (0)
Dental caries	0 (0)	1 (0.32)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)
Dermatitis acneiform	3 (0.97)	0 (0)	0 (0)	0 (0)	8 (2.56)	2 (0.64)	0 (0)	0 (0)
Device related infection	1 (0.32)	2 (0.65)	0 (0)	0 (0)	1 (0.32)	3 (0.96)	0 (0)	0 (0)
Diabetes mellitus	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Diabetic foot	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Diabetic foot infection	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Diarrhoea	67 (21.75)	1 (0.32)	0 (0)	0 (0)	92 (29.39)	4 (1.28)	0 (0)	0 (0)
Diverticulum	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dizziness	20 (6.49)	0 (0)	0 (0)	0 (0)	35 (11.18)	0 (0)	0 (0)	0 (0)
Dry mouth	12 (3.9)	0 (0)	0 (0)	0 (0)	33 (10.54)	0 (0)	0 (0)	0 (0)
Dry skin	16 (5.19)	1 (0.32)	0 (0)	0 (0)	33 (10.54)	1 (0.32)	0 (0)	0 (0)
Dysgeusia	41 (13.31)	0 (0)	0 (0)	0 (0)	70 (22.36)	0 (0)	0 (0)	0 (0)

Dyspepsia	38 (12.34)	1 (0.32)	0 (0)	0 (0)	37 (11.82)	0 (0)	0 (0)	0 (0)
Dysphagia	6 (1.95)	0 (0)	0 (0)	0 (0)	19 (6.07)	1 (0.32)	0 (0)	0 (0)
Dyspnoea	30 (9.74)	3 (0.97)	1 (0.32)	0 (0)	60 (19.17)	6 (1.92)	0 (0)	0 (0)
Dyspnoea exertional	2 (0.65)	0 (0)	0 (0)	0 (0)	5 (1.6)	1 (0.32)	0 (0)	0 (0)
Ejection fraction decreased	28 (9.09)	3 (0.97)	0 (0)	0 (0)	32 (10.22)	7 (2.24)	0 (0)	0 (0)
Electrocardiogram QT prolonged	0 (0)	1 (0.32)	0 (0)	0 (0)	5 (1.6)	1 (0.32)	0 (0)	0 (0)
Embolism	0 (0)	1 (0.32)	0 (0)	0 (0)	2 (0.64)	0 (0)	0 (0)	0 (0)
Epilepsy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Exfoliative rash	0 (0)	0 (0)	0 (0)	0 (0)	4 (1.28)	1 (0.32)	0 (0)	0 (0)
Extravasation	0 (0)	1 (0.32)	0 (0)	0 (0)	2 (0.64)	1 (0.32)	0 (0)	0 (0)
Failure to thrive	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Fatigue	151 (49.03)	11 (3.57)	0 (0)	0 (0)	174 (55.59)	16 (5.11)	0 (0)	0 (0)
Febrile bone marrow aplasia	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Febrile neutropenia	0 (0)	23 (7.47)	11 (3.57)	0 (0)	0 (0)	40 (12.78)	17 (5.43)	0 (0)
Femur fracture	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Fistula	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Flank pain	6 (1.95)	0 (0)	0 (0)	0 (0)	4 (1.28)	1 (0.32)	0 (0)	0 (0)
Fractured sacrum	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Gamma-glutamyltransferase increased	2 (0.65)	4 (1.3)	0 (0)	0 (0)	5 (1.6)	4 (1.28)	0 (0)	0 (0)
Gastroenteritis viral	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Gastrointestinal haemorrhage	0 (0)	0 (0)	1 (0.32)	0 (0)	1 (0.32)	0 (0)	1 (0.32)	0 (0)
General physical health deterioration	2 (0.65)	1 (0.32)	0 (0)	0 (0)	1 (0.32)	5 (1.6)	1 (0.32)	0 (0)
Genital haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Glossitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Glycosuria	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gout	0 (0)	1 (0.32)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)
Groin pain	3 (0.97)	1 (0.32)	0 (0)	0 (0)	7 (2.24)	0 (0)	0 (0)	0 (0)
Haematemesis	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Haematocrit decreased	1 (0.32)	0 (0)	0 (0)	0 (0)	2 (0.64)	2 (0.64)	0 (0)	0 (0)
Haematuria	5 (1.62)	0 (0)	0 (0)	0 (0)	7 (2.24)	0 (0)	1 (0.32)	0 (0)
Haemoglobin decreased	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	4 (1.28)	2 (0.64)	0 (0)
Haemoptysis	0 (0)	3 (0.97)	0 (0)	0 (0)	4 (1.28)	0 (0)	0 (0)	0 (0)
Haemorrhoids	11 (3.57)	0 (0)	0 (0)	0 (0)	42 (13.42)	1 (0.32)	0 (0)	0 (0)
Headache	36 (11.69)	0 (0)	0 (0)	0 (0)	51 (16.29)	1 (0.32)	0 (0)	0 (0)

Hepatic pain	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Herpes zoster	1 (0.32)	1 (0.32)	0 (0)	0 (0)	6 (1.92)	0 (0)	0 (0)	0 (0)
Hip arthroplasty	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Hip fracture	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Hyperglycaemia	6 (1.95)	4 (1.3)	0 (0)	0 (0)	10 (3.19)	5 (1.6)	0 (0)	0 (0)
Hyperkalaemia	1 (0.32)	1 (0.32)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)
Hypertension	4 (1.3)	2 (0.65)	0 (0)	0 (0)	10 (3.19)	1 (0.32)	0 (0)	0 (0)
Hypertensive crisis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Hypertriglyceridaemia	1 (0.32)	1 (0.32)	1 (0.32)	0 (0)	2 (0.64)	0 (0)	0 (0)	0 (0)
Hyperuricaemia	2 (0.65)	0 (0)	0 (0)	0 (0)	3 (0.96)	0 (0)	2 (0.64)	0 (0)
Hypoalbuminaemia	8 (2.6)	2 (0.65)	0 (0)	0 (0)	14 (4.47)	4 (1.28)	0 (0)	0 (0)
Hypocalcaemia	6 (1.95)	4 (1.3)	0 (0)	0 (0)	13 (4.15)	1 (0.32)	0 (0)	0 (0)
Hypokalaemia	11 (3.57)	9 (2.92)	0 (0)	0 (0)	24 (7.67)	10 (3.19)	1 (0.32)	0 (0)
Hyponatraemia	6 (1.95)	4 (1.3)	0 (0)	0 (0)	7 (2.24)	8 (2.56)	0 (0)	0 (0)
Hypophosphataemia	4 (1.3)	4 (1.3)	0 (0)	0 (0)	4 (1.28)	9 (2.88)	0 (0)	0 (0)
Hypotension	7 (2.27)	3 (0.97)	0 (0)	0 (0)	17 (5.43)	0 (0)	0 (0)	0 (0)
Hypoxia	1 (0.32)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ilium fracture	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Incision site infection	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Infusion related reaction	0 (0)	0 (0)	0 (0)	0 (0)	3 (0.96)	1 (0.32)	0 (0)	0 (0)
Insomnia	37 (12.01)	0 (0)	0 (0)	0 (0)	23 (7.35)	0 (0)	0 (0)	0 (0)
International normalised ratio increased	2 (0.65)	2 (0.65)	0 (0)	0 (0)	0 (0)	2 (0.64)	0 (0)	0 (0)
Intertrigo	0 (0)	0 (0)	0 (0)	0 (0)	7 (2.24)	1 (0.32)	0 (0)	0 (0)
Intestinal haemorrhage	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Intestinal perforation	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)
Klebsiella bacteraemia	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Lactic acidosis	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)
Left ventricular dysfunction	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	1 (0.32)	0 (0)
Leg amputation	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Leukopenia	11 (3.57)	13 (4.22)	4 (1.3)	0 (0)	8 (2.56)	8 (2.56)	14 (4.47)	0 (0)
Localised intraabdominal fluid collection	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Lower gastrointestinal haemorrhage	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Lung infection	0 (0)	1 (0.32)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)
Lymphocyte count decreased	5 (1.62)	6 (1.95)	2 (0.65)	0 (0)	4 (1.28)	12 (3.83)	3 (0.96)	0 (0)
Lymphopenia	0 (0)	4 (1.3)	0 (0)	0 (0)	4 (1.28)	3 (0.96)	2 (0.64)	0 (0)
Malignant pleural effusion	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Meningitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)

Mental status changes	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Micturition disorder	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Monoparesis	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Muscular weakness	4 (1.3)	3 (0.97)	0 (0)	0 (0)	9 (2.88)	1 (0.32)	0 (0)	0 (0)
Musculoskeletal chest pain	4 (1.3)	1 (0.32)	0 (0)	0 (0)	9 (2.88)	0 (0)	0 (0)	0 (0)
Myalgia	11 (3.57)	1 (0.32)	0 (0)	0 (0)	19 (6.07)	0 (0)	0 (0)	0 (0)
Myocardial infarction	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Nausea	178 (57.79)	2 (0.65)	0 (0)	0 (0)	205 (65.5)	5 (1.6)	0 (0)	0 (0)
Neck pain	3 (0.97)	1 (0.32)	0 (0)	0 (0)	4 (1.28)	3 (0.96)	0 (0)	0 (0)
Neuropathy peripheral	3 (0.97)	0 (0)	0 (0)	0 (0)	8 (2.56)	1 (0.32)	0 (0)	0 (0)
Neutropenia	4 (1.3)	23 (7.47)	69 (22.4)	0 (0)	13 (4.15)	14 (4.47)	33 (10.54)	0 (0)
Neutrophil count decreased	3 (0.97)	9 (2.92)	32 (10.39)	0 (0)	3 (0.96)	12 (3.83)	19 (6.07)	0 (0)
Non-cardiac chest pain	11 (3.57)	1 (0.32)	0 (0)	0 (0)	10 (3.19)	1 (0.32)	0 (0)	0 (0)
Oedema peripheral	32 (10.39)	4 (1.3)	0 (0)	0 (0)	37 (11.82)	1 (0.32)	0 (0)	0 (0)
Oesophageal obstruction	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Oesophagitis	2 (0.65)	1 (0.32)	0 (0)	0 (0)	2 (0.64)	0 (0)	0 (0)	0 (0)
Oral pain	5 (1.62)	1 (0.32)	0 (0)	0 (0)	11 (3.51)	0 (0)	0 (0)	0 (0)
Oropharyngeal candidiasis	0 (0)	1 (0.32)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)
Osteomyelitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Pain	6 (1.95)	1 (0.32)	0 (0)	0 (0)	13 (4.15)	0 (0)	0 (0)	0 (0)
Pain in extremity	20 (6.49)	2 (0.65)	0 (0)	0 (0)	32 (10.22)	0 (0)	0 (0)	0 (0)
Palmar-plantar erythrodysaesthesia syndrome	2 (0.65)	0 (0)	0 (0)	0 (0)	38 (12.14)	3 (0.96)	0 (0)	0 (0)
Pancytopenia	0 (0)	0 (0)	2 (0.65)	0 (0)	0 (0)	6 (1.92)	9 (2.88)	0 (0)
Partial lung resection	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Pathological fracture	0 (0)	1 (0.32)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)
Pelvic pain	2 (0.65)	0 (0)	0 (0)	0 (0)	2 (0.64)	1 (0.32)	0 (0)	0 (0)
Pelvic venous thrombosis	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.64)	1 (0.32)	0 (0)	0 (0)
Pericardial effusion	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.64)	1 (0.32)	0 (0)	0 (0)
Platelet count decreased	15 (4.87)	4 (1.3)	1 (0.32)	0 (0)	20 (6.39)	3 (0.96)	12 (3.83)	0 (0)
Pleural effusion	1 (0.32)	2 (0.65)	0 (0)	0 (0)	5 (1.6)	0 (0)	0 (0)	0 (0)
Pleuritic pain	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	1 (0.32)	0 (0)	0 (0)
Pneumonia	2 (0.65)	3 (0.97)	0 (0)	1 (0.32)	2 (0.64)	7 (2.24)	0 (0)	0 (0)
Pneumonia respiratory syncytial viral	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)
Pneumonitis	0 (0)	1 (0.32)	0 (0)	0 (0)	1 (0.32)	1 (0.32)	0 (0)	0 (0)
Pneumothorax	2 (0.65)	1 (0.32)	0 (0)	0 (0)	1 (0.32)	3 (0.96)	1 (0.32)	0 (0)
Portal vein thrombosis	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	1 (0.32)	0 (0)	0 (0)

Postoperative wound infection	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Procedural pain	1 (0.32)	0 (0)	0 (0)	0 (0)	7 (2.24)	1 (0.32)	0 (0)	0 (0)
Proctalgia	2 (0.65)	0 (0)	0 (0)	0 (0)	20 (6.39)	2 (0.64)	0 (0)	0 (0)
Proctitis	1 (0.32)	0 (0)	0 (0)	0 (0)	2 (0.64)	1 (0.32)	0 (0)	0 (0)
Prothrombin time prolonged	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pruritus	1 (0.32)	0 (0)	0 (0)	0 (0)	21 (6.71)	2 (0.64)	0 (0)	0 (0)
Pulmonary embolism	0 (0)	17 (5.52)	0 (0)	0 (0)	0 (0)	18 (5.75)	3 (0.96)	0 (0)
Pyelonephritis	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0.96)	0 (0)	0 (0)
Pyrexia	39 (12.66)	2 (0.65)	0 (0)	0 (0)	69 (22.04)	2 (0.64)	0 (0)	0 (0)
Radicular pain	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Rectal fissure	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	1 (0.32)	0 (0)	0 (0)
Renal failure	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.64)	1 (0.32)	0 (0)	0 (0)
Sciatica	1 (0.32)	1 (0.32)	0 (0)	0 (0)	5 (1.6)	0 (0)	0 (0)	0 (0)
Sepsis	0 (0)	0 (0)	3 (0.97)	0 (0)	0 (0)	3 (0.96)	1 (0.32)	3 (0.96)
Septic shock	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)
Sinus tachycardia	1 (0.32)	0 (0)	0 (0)	0 (0)	7 (2.24)	1 (0.32)	0 (0)	0 (0)
Skin hyperpigmentation	1 (0.32)	0 (0)	0 (0)	0 (0)	35 (11.18)	0 (0)	0 (0)	0 (0)
Skin injury	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Skin ulcer	1 (0.32)	1 (0.32)	0 (0)	0 (0)	10 (3.19)	2 (0.64)	0 (0)	0 (0)
Small intestinal obstruction	0 (0)	5 (1.62)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Somnolence	2 (0.65)	1 (0.32)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)
Spinal compression fracture	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	1 (0.32)	0 (0)	0 (0)
Spinal fracture	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	1 (0.32)	0 (0)	0 (0)
Staphylococcal bacteraemia	0 (0)	2 (0.65)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Staphylococcal sepsis	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Stomatitis	99 (32.14)	7 (2.27)	0 (0)	0 (0)	136 (43.45)	26 (8.31)	0 (0)	0 (0)
Streptococcal bacteraemia	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subcutaneous abscess	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Supraventricular tachycardia	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Syncope	1 (0.32)	5 (1.62)	0 (0)	0 (0)	0 (0)	6 (1.92)	0 (0)	0 (0)
Systemic inflammatory response syndrome	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Thrombocytopenia	15 (4.87)	1 (0.32)	3 (0.97)	0 (0)	27 (8.63)	20 (6.39)	25 (7.99)	0 (0)
Thrombophlebitis superficial	1 (0.32)	0 (0)	0 (0)	0 (0)	1 (0.32)	1 (0.32)	0 (0)	0 (0)
Tooth abscess	0 (0)	1 (0.32)	0 (0)	0 (0)	3 (0.96)	0 (0)	0 (0)	0 (0)

Tooth infection	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.64)	1 (0.32)	0 (0)	0 (0)
Transaminases increased	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.64)	1 (0.32)	0 (0)	0 (0)
Troponin increased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Tumour excision	0 (0)	2 (0.65)	0 (0)	0 (0)	2 (0.64)	0 (0)	0 (0)	0 (0)
Tumour haemorrhage	0 (0)	1 (0.32)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)
Tumour pain	2 (0.65)	1 (0.32)	0 (0)	0 (0)	7 (2.24)	0 (0)	0 (0)	0 (0)
Tumour rupture	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Tumour ulceration	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Type 2 diabetes mellitus	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Upper gastrointestinal haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)
Upper respiratory tract infection	7 (2.27)	1 (0.32)	0 (0)	0 (0)	17 (5.43)	3 (0.96)	0 (0)	0 (0)
Urinary tract infection	24 (7.79)	2 (0.65)	0 (0)	0 (0)	41 (13.1)	6 (1.92)	0 (0)	0 (0)
Urinary tract obstruction	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.64)	1 (0.32)	0 (0)	0 (0)
Urine output decreased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.64)	0 (0)	0 (0)
Urticaria	1 (0.32)	0 (0)	0 (0)	0 (0)	5 (1.6)	1 (0.32)	0 (0)	0 (0)
Vaginal haemorrhage	2 (0.65)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Vaginal inflammation	0 (0)	0 (0)	0 (0)	0 (0)	3 (0.96)	1 (0.32)	0 (0)	0 (0)
Vasculitis necrotising	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Vena cava thrombosis	0 (0)	1 (0.32)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Ventricular tachycardia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	0 (0)	0 (0)
Vomiting	61 (19.81)	1 (0.32)	0 (0)	0 (0)	98 (31.31)	2 (0.64)	1 (0.32)	0 (0)
Vulvitis	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.32)	1 (0.32)	0 (0)	0 (0)
Weight decreased	17 (5.52)	1 (0.32)	0 (0)	0 (0)	41 (13.1)	3 (0.96)	0 (0)	0 (0)
White blood cell count decreased	6 (1.95)	12 (3.9)	21 (6.82)	0 (0)	6 (1.92)	14 (4.47)	25 (7.99)	0 (0)
Wound infection	0 (0)	0 (0)	0 (0)	0 (0)	4 (1.28)	2 (0.64)	0 (0)	0 (0)

Table S8: Adverse Events (Any Grade) Occurring in > 10% of Patients in Either Treatment Arm

System Organ Class Preferred Term	Doxorubicin		Doxorubicin + Evofosfamide		Total	
	N	%	N	%	N	%
Overall	308	99.7	313	99.7	621	99.7
Infections and infestations	90	29.2	163	52.1	253	40.7
Urinary tract infection	26	8.4	47	15.0	73	11.8
Blood and lymphatic system disorders	192	62.3	215	68.7	407	65.5
Anaemia	104	33.8	189	60.4	293	47.2
Febrile neutropenia	34	11.0	57	18.2	91	14.7
Neutropenia	96	31.2	60	19.2	156	25.1
Thrombocytopenia	19	6.2	72	23.0	91	14.7
Metabolism and nutrition disorders	119	38.6	170	54.3	289	46.5
Decreased appetite	82	26.6	113	36.1	195	31.4
Hypokalaemia	20	6.5	35	11.2	55	8.9

System Organ Class Preferred Term	Doxorubicin		Doxorubicin + Evofosfamide		Total	
	N	%	N	%	N	%
Psychiatric disorders	61	19.8	76	24.3	137	22.1
Insomnia	37	12.0	23	7.3	60	9.7
Nervous system disorders	111	36.0	152	48.6	263	42.4
Dizziness	20	6.5	35	11.2	55	8.9
Dysgeusia	41	13.3	70	22.4	111	17.9
Headache	36	11.7	52	16.6	88	14.2
Eye disorders	34	11.0	57	18.2	91	14.7
Cardiac disorders	16	5.2	36	11.5	52	8.4
Vascular disorders	46	14.9	71	22.7	117	18.8
Respiratory, thoracic and mediastinal disorders	119	38.6	165	52.7	284	45.7
Cough	43	14.0	59	18.8	102	16.4
Dyspnoea	34	11.0	66	21.1	100	16.1
Gastrointestinal disorders	257	83.4	280	89.5	537	86.5
Abdominal pain	31	10.1	37	11.8	68	11.0
Constipation	89	28.9	134	42.8	223	35.9
Diarrhoea	68	22.1	96	30.7	164	26.4
Dry mouth	12	3.9	33	10.5	45	7.2
Dyspepsia	39	12.7	37	11.8	76	12.2
Haemorrhoids	11	3.6	43	13.7	54	8.7
Nausea	180	58.4	210	67.1	390	62.8
Stomatitis	106	34.4	162	51.8	268	43.2
Vomiting	62	20.1	101	32.3	163	26.2
Skin and subcutaneous tissue disorders	164	53.2	236	75.4	400	64.4
Alopecia	138	44.8	153	48.9	291	46.9
Dry skin	17	5.5	34	10.9	51	8.2
Palmar-plantar erythrodysaesthesia syndrome	2	0.6	41	13.1	43	6.9
Skin hyperpigmentation	1	0.3	35	11.2	36	5.8
Musculoskeletal and connective tissue disorders	101	32.8	138	44.1	239	38.5
Arthralgia	18	5.8	40	12.8	58	9.3
Back pain	26	8.4	39	12.5	65	10.5
Pain in extremity	22	7.1	32	10.2	54	8.7
Renal and urinary disorders	29	9.4	61	19.5	90	14.5
Reproductive system and breast disorders	17	5.5	49	15.7	66	10.6
General disorders and administration site conditions	227	73.7	247	78.9	474	76.3
Asthenia	34	11.0	40	12.8	74	11.9
Fatigue	162	52.6	190	60.7	352	56.7
Oedema peripheral	36	11.7	38	12.1	74	11.9
Pyrexia	41	13.3	71	22.7	112	18.0
Investigations	122	39.6	160	51.1	282	45.4
Ejection fraction decreased	31	10.1	39	12.5	70	11.3
Neutrophil count decreased	44	14.3	34	10.9	78	12.6
Platelet count decreased	20	6.5	35	11.2	55	8.9
Weight decreased	18	5.8	44	14.1	62	10.0

System Organ Class Preferred Term	Doxorubicin		Doxorubicin + Evofosfamide		Total	
	N	%	N	%	N	%
White blood cell count decreased	39	12.7	45	14.4	84	13.5
Injury, poisoning and procedural complications	12	3.9	47	15.0	59	9.5

Table S9: Serious Adverse Events

System Organ Class Preferred Term	Doxorubicin		Doxorubicin + Evofosfamide		Total	
	N	%	N	%	N	%
Overall number of patients that reported a Serious Adverse Event	99/308	32.1	145/313	46.3	244	39.3
Serious Adverse Events Occurring in ≥ 5% of Subjects						
Infections and infestations	21	6.8	38	12.1	59	9.5
Blood and lymphatic system disorders	41	13.3	83	26.5	124	20.0
Anaemia	10	3.2	19	6.1	29	4.7
Febrile neutropenia	27	8.8	56	17.9	83	13.4
Respiratory, thoracic and mediastinal disorders	21	6.8	25	8.0	46	7.4
Gastrointestinal disorders	21	6.8	26	8.3	47	7.6
General disorders and administration site conditions	19	6.2	11	3.5	30	4.8

Table S10a: QTcF by Treatment Arm

	Doxorubicin (N = 308)	Doxorubicin + Evofosfamide (N = 313)	Total (N = 621)
Cycle 4 Week 3			
Change from Baseline			
N	156	169	325
Mean (SD)	11.5 (27.45)	4.0 (25.42)	7.6 (26.64)
Median	9.5	5.8	7.5
Range	-108.5 - 120.8	-105.0 - 98.3	-108.5 - 120.8
P-value[1]	<0.001	0.043	
P-value[2]	0.0108		
≤450 ms, n (%)	143 (91.7%)	150 (87.7%)	293 (89.6%)
>450 – 470 ms, n (%)	6 (3.8%)	15 (8.8%)	21 (6.4%)
>470 – 500 ms, n (%)	4 (2.6%)	5 (2.9%)	9 (2.8%)
>500 ms, n (%)	3 (1.9%)	1 (0.6%)	4 (1.2%)
Cycle 6 Week 3			
Change from Baseline			
N	72	139	211
Mean (SD)	17.3 (26.87)	10.3 (28.80)	12.7 (28.28)
Median	16.3	10.7	13.2
Range	-90.9 - 130.3	-169.3 - 112.6	-169.3 - 130.3
P-value[1]	<0.001	<0.001	
P-value[2]	0.0899		
≤450 ms, n (%)	63 (87.5%)	117 (83.6%)	180 (84.9%)
>450 – 470 ms, n (%)	7 (9.7%)	15 (10.7%)	22 (10.4%)
>470 – 500 ms, n (%)	2 (2.8%)	7 (5.0%)	9 (4.2%)
>500 ms, n (%)	0 (0.0%)	1 (0.7%)	1 (0.5%)
Termination			
Change from Baseline			
N	181	189	370
Mean (SD)	10.1 (30.56)	7.8 (24.64)	8.9 (27.68)
Median	12.0	7.4	8.5
Range	-181.4 - 166.3	-67.6 - 117.2	-181.4 - 166.3
P-value[1]	<0.001	<0.001	
P-value[2]	0.4211		
≤450 ms, n (%)	162 (89.0%)	163 (85.8%)	325 (87.4%)
>450 – 470 ms, n (%)	12 (6.6%)	16 (8.4%)	28 (7.5%)
>470 – 500 ms, n (%)	6 (3.3%)	10 (5.3%)	16 (4.3%)
>500 ms, n (%)	2 (1.1%)	1 (0.5%)	3 (0.8%)

1) Paired t-test vs. screening
2) Two-sample t-test comparing change from baseline between treatment groups

Table S10b: Left Ventricular Ejection Fraction by Treatment Arm

	Doxorubicin (N = 308)	Doxorubicin + Evofosfamide (N = 313)	Total (N = 621)
Cycle 4 Week 3			
Change from Baseline			
N	167	192	359
Mean (SD)	-0.7 (6.23)	-1.4 (5.70)	-1.1 (5.95)
Median	-1.0	-1.0	-1.0
Range	-29.8 - 24.7	-17.0 - 21.0	-29.8 - 24.7
P-value[1]	0.122	0.001	
P-value[2]	0.3210		
≥10% decrease and LVEF <55%, n (%)	5 (3.0%)	10 (5.2%)	15 (4.2%)
LVEF <45%, n (%)	0 (0.0%)	2 (1.0%)	2 (0.6%)
≥20% Decrease, n (%)	1 (0.6%)	0 (0.0%)	1 (0.3%)
Cycle 6 Week 3			
Change from Baseline			
N	81	159	240
Mean (SD)	-2.9 (7.75)	-2.8 (6.32)	-2.9 (6.82)
Median	-4.0	-2.0	-3.0
Range	-24.1 - 19.0	-20.0 - 14.6	-24.1 - 19.0
P-value[1]	0.001	<0.001	
P-value[2]	0.9240		
≥10% decrease and LVEF <55%, n (%)	6 (7.4%)	13 (8.2%)	19 (7.9%)
LVEF <45%, n (%)	0 (0.0%)	4 (2.5%)	4 (1.7%)
≥20% Decrease, n (%)	2 (2.5%)	1 (0.6%)	3 (1.3%)
Termination			
Mean (SD) Dose Day of Termination	100 (39.4)	210 (175.7)	152 (135.7)
Median Dose Day of Termination	122	153	126
Change from Baseline			
N	144	130	274
Mean (SD)	-2.3 (6.58)	-3.6 (8.17)	-2.9 (7.39)
Median	-2.0	-3.0	-2.0
Range	-19.6 - 13.0	-48.6 - 14.9	-48.6 - 14.9
P-value[1]	<0.001	<0.001	
P-value[2]	0.1334		
≥10% decrease and LVEF <55%, n (%)	13 (9.0%)	15 (11.5%)	28 (10.2%)
LVEF <45%, n (%)	3 (2.1%)	5 (3.8%)	8 (2.9%)
≥20% Decrease, n (%)	0 (0.0%)	6 (4.6%)	6 (2.2%)

1) Paired t-test vs. screening
2) Two-sample t-test comparing change from baseline between treatment groups

Table S11: Deaths

	Doxorubicin (N = 323)	**Doxorubicin + Evofosfamide (N = 317)**	**Total (N = 640)**
Primary Cause of Death – All Randomised			
N	208	215	423
Progressive Disease (n[%])	190 (91.3)	194 (90.2)	384 (90.8)
Adverse Event	2 (1.0)	8 (3.7)	10 (2.4)
Other	16 (7.7)	13 (6.0)	29 (6.9)
Primary Cause of Death –Safety Population			
N	200	212	412
Progressive Disease (n[%])	183 (91.5)	191 (90.1)	374 (90.8)
Adverse Event	2 (1.0)	8 (3.8)	10 (2.4)
Other	15 (7.5)	13 (6.1)	28 (6.8)

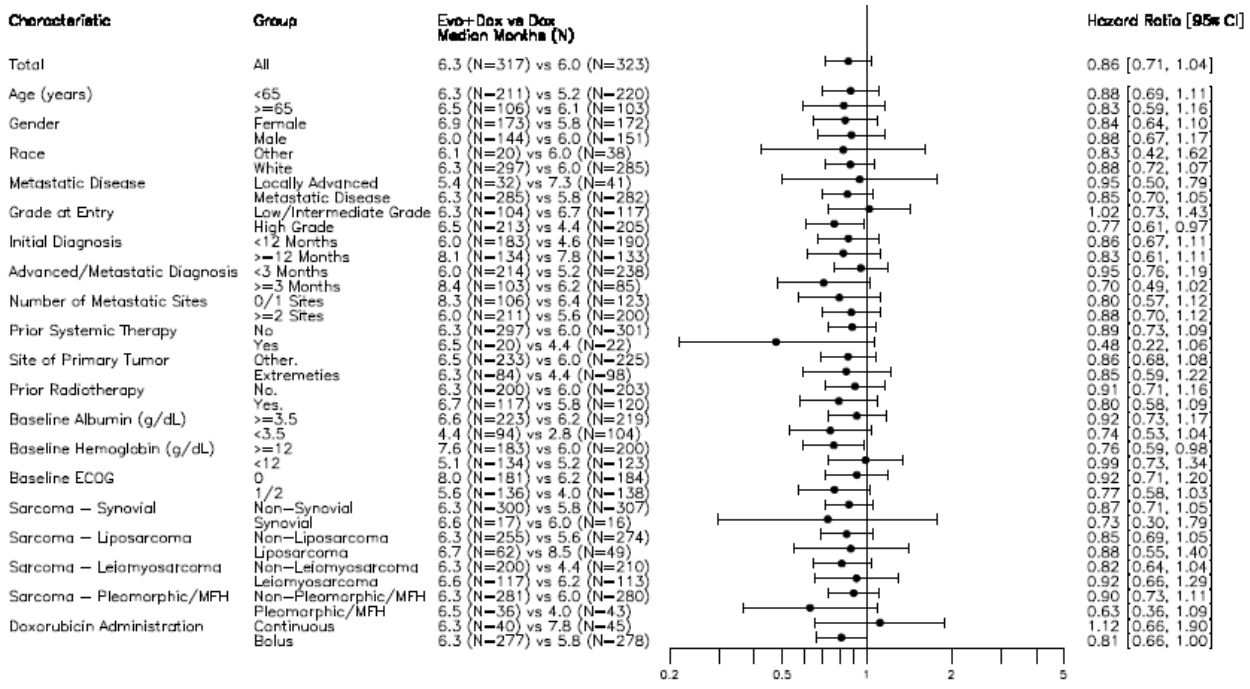
Table S12: Overall Survival Cox Proportion Hazards Model: Univariate Analyses: Serum Biomarker

Characteristic	Doxorubicin		Doxorubicin + Evofosfamide		Hazard Ratio (95% CI) [a]	P-value [a]
	Number of Subjects	Median (95% CI)	Number of Subjects	Median (95% CI)		
CAIX (pg/mL)						
<=64.9	94	610 (488 - 879)	105	561 (419 - 718)	1.06 (0.740, 1.504)	0.7665
> 64.9	103	488 (389 - 681)	97	539 (414 - 711)	1.01 (0.724, 1.416)	0.9422
Within Treatment Arm [b]	1.18	(0.832, 1.668), 0.356	1.07	(0.766, 1.506), 0.679		
Treatment Biomarker Interaction [c]	0.92	(0.567, 1.496), 0.739				
LD-1 (%)						
<=22.35	102	450 (326 - 569)	109	395 (320 - 487)	1.07 (0.775, 1.489)	0.6652
> 22.35	102	822 (557 - 946)	111	798 (651 - 928)	1.00 (0.701, 1.428)	0.9966
Within Treatment Arm [b]	0.60	(0.422, 0.841), 0.003	0.55	(0.393, 0.773), 0.000		
Treatment Biomarker Interaction [c]	0.95	(0.589, 1.531), 0.832				
LD-2 (%)						
<=31.4	108	454 (340 - 572)	105	398 (318 - 524)	1.05 (0.760, 1.437)	0.7853
> 31.4	96	759 (530 - 979)	115	781 (651 - 928)	1.04 (0.728, 1.494)	0.8173
Within Treatment Arm [b]	0.60	(0.424, 0.851), 0.004	0.58	(0.419, 0.809), 0.001		
Treatment Biomarker Interaction [c]	0.97	(0.604, 1.570), 0.912				
LD-3 (%)						
<=24.3	104	628 (488 - 935)	115	674 (524 - 858)	0.96 (0.681, 1.349)	0.8083
> 24.3	100	509 (389 - 623)	105	474 (364 - 647)	1.09 (0.784, 1.518)	0.6035
Within Treatment Arm [b]	1.19	(0.845, 1.676), 0.320	1.36	(0.980, 1.890), 0.065		
Treatment Biomarker Interaction [c]	1.14	(0.712, 1.833), 0.582				
LD-4 (%)						
<=10.3	107	681 (517 - 979)	114	731 (585 - 921)	0.99 (0.697, 1.397)	0.9393
> 10.3	97	429 (340 - 604)	106	411 (327 - 487)	1.05 (0.758, 1.457)	0.7640
Within Treatment Arm [b]	1.58	(1.124, 2.232), 0.008	1.68	(1.211, 2.341), 0.002		
Treatment Biomarker Interaction [c]	1.06	(0.659, 1.701), 0.814				
LD-5 (%)						
<=11	108	648 (517 - 879)	109	718 (553 - 928)	0.99 (0.704, 1.405)	0.9750
> 11	96	428 (319 - 604)	111	470 (350 - 604)	0.99 (0.712, 1.376)	0.9517
Within Treatment Arm [b]	1.51	(1.072, 2.137), 0.018	1.51	(1.089, 2.103), 0.013		
Treatment Biomarker Interaction [c]	1.01	(0.626, 1.622), 0.975				
Neuron-specific enolase (ng/mL)						

<=11.5	95	823 (558 -	1E3)	118	655 (473 -	798)	1.23 (0.864, 1.760)	0.2472
> 11.5	1	487 (366 -	569)	99	487 (352 -	672)	0.86 (0.619, 1.184)	0.3454
Within Treatment Arm [b]	1.74 (1.224, 2.460),		0.002	1.23 (0.882, 1.711),		0.222		
Treatment Biomarker Interaction [c]	0.70 (0.431, 1.122),		0.137					
Osteopontin(ng/mL)								
<=104.15	101	823 (604 -	979)	111	821 (655 -	928)	1.05 (0.735, 1.507)	0.7812
> 104.15	121	487 (380 -	592)	117	364 (299 -	487)	1.18 (0.867, 1.596)	0.2975
Within Treatment Arm [b]	1.47 (1.051, 2.061),		0.024	1.77 (1.283, 2.454),		0.000		
Treatment Biomarker Interaction [c]	1.20 (0.751, 1.908),		0.451					
Vascular Endothelial Growth Factor (pg/mL)								
<=67	102	946 (699 -	.)	111	821 (655 -	971)	1.22 (0.837, 1.768)	0.3035
> 67	120	448 (348 -	572)	118	375 (302 -	482)	1.07 (0.799, 1.440)	0.6387
Within Treatment Arm [b]	2.16 (1.524, 3.056),		0.000	2.00 (1.445, 2.775),		0.000		
Treatment Biomarker Interaction [c]	0.92 (0.572, 1.474),		0.724					

Note: Hazard ratio compares the first characteristic to second characteristic.
[a] Relative risk/Chi-square test of treatment effect within biomarker subgroup (stratified by extent of disease). [b] Relative risk/Chi-square test of biomarker effect within treatment arm (stratified by extent of disease)
[c] Relative risk/Chi-square test of treatment-biomarker interaction (stratified by extent of disease)

Figure S1: Forrest Plot for Progression-Free Survival Subgroup Analyses



Independent Pathology Review Charter

Project Charter Purpose
To define the process and procedure whereby all patients enrolled in Study TH-CR-406/SARC021 had pathology centrally reviewed to assess study eligibility for the appropriate sarcoma diagnosis and tumor grade by expert sarcoma pathologists.

This charter described the procedures and processes for specimen handling, independent pathology review, and data management as well as defined the roles and responsibilities of each group involved.

Contributors

Contributors, Organization
Brian Rubin, MD, PhD, Cleveland Clinic
Jean Michel Coindre, MD, PhD, Institut Bergonie, Bordeaux France
Alexander Lazar, MD, PhD, The University of Texas MD Anderson Cancer Center
Torsten Nielsen, MD, PhD, University of British Columbia, Vancouver, Canada
Tillman Pearce, MD, Threshold
Stew Kroll, Threshold
Larissa Felt, Threshold
Brenda Steltzriede, SARC
Denise Reinke, SARC
William Tap, MD, Memorial Sloan Kettering Cancer Center

Specimen Handling and Storage
Pathology samples and reports were shipped from the clinical site to Covance Labs. Once received at Covance, the reports and samples were logged into their system and QC'ed to ensure alignment of the sample and report accession numbers for each patient.

Covance would query the sites for missing or incorrect information. Specimens and reports were not released to Nationwide until all queries were resolved.

Pathology reports requiring translation were provided to Threshold; who worked with a translation vendor. Once translated, Threshold provided the reports back to Covance.

Covance batch shipped QC specimens and reports to Nationwide Children's Hospital/RINCH for preparation and presentation to the central pathology reviewers. Translated reports were sent with the accompanying non-translated reports.

Nationwide Children's Hospital/RINCH verified that all specimens matched the accompanying paperwork, and entered information into their tracking systems.

Nationwide reviewed specimen cut sections from tissue blocks (if appropriate), stain (H&E) and QC slides for adequacy for imaging, and images were digitally scanned into the Aperio system.

Nationwide identified and provided any issues to Threshold/SARC for follow up and resolution. If Nationwide identified that additional specimen(s) or report(s) were needed this was communicated to Threshold/SARC. Additional specimens were shipped to Covance who performed their QC prior to shipping to Nationwide.

Nationwide retained all specimens and reports until everything had been reviewed by the pathologists and only then returned items at the request of Threshold. Threshold provided a list of subjects for whom samples needed to be returned to their respective sites.

Physician Training
Training was completed by all pathologists on the central pathology process, systems and guidelines prior to initiating any review.

Nationwide Children's Hospital/RINCH team provided training on the Aperio, eSlideManager system. The pathology review application was "eSlideManager", developed by Aperio ePathology Solutions. eSlideManager presented reviewed information for each patient as a 'Case'. Each case consisted of one or more tissue specimens, and each tissue specimen had one or more digital slide images. The digital slide images were obtained by preparing a stained glass slide from the tissue specimen that was fed into an Aperio digital slide scanner. eSlideManager provided an orderly hierarchical view of the case/specimen/slide relationship along with an electronic copy of the institution pathology report to allow a pathologist to review the slide specimen with all relevant information conveniently at-hand.

Threshold trained the pathologists on the Datalabs EDC system.

NCIC was responsible for ensuring the pathologist reviewing Canadian patients completed required training on any of the systems.

Pathology Review Process
The pathologists received an email notification after pathology samples and reports had been scanned and images were uploaded to the eSlide manager system electronic case report form. Completion guidelines were created and provided to the pathologists. Pathologist read images on an ongoing basis with a target to read images within 2-3 weeks of notification of upload. Pathologists were assigned cases by their country of origin with all US cases being assigned to two pathologists and the rest of world cases being assigned to another.

Upon review of the images, the pathologists completed the Central Pathology Review eCRF (see Reference documents)

The pathologists documented their analyses electronically on an electronic case report form (eCRF) in the DataLabs system.

DataLabs allowed flagging of controversial diagnoses. Controversial diagnoses were those in which a single reviewer wanted to review in collaboration with the pathology team for consensus. The flagged controversial cases in DataLabs were batched and the pathologists held a teleconference (adjudication) to review by simultaneously viewing the images, if available, and pathology report(s) in the Aperio system during the teleconference.

DataLabs also flagged specimens determined to not be an eligible subtype or grade required for study enrollment and Threshold contacted the site to determine if additional documentation or pathology was available and requested for these to be sent to Covance.

If slides did not contain adequate tissue, the reviewing pathologist indicated this on the eCRF; Threshold contacted the site to request resubmission to Covance of a representative specimen.

If there were no available remaining slides or blocks, the reviewing pathologists reviewed the available pathology reports and made a final assessment. The basis for confirming eligible pathology was captured from whatever pathology specimen and/or pathology report was available.

Data Management
System queries were generated in the clinical database for missing data. Pathologists must have reviewed system queries and resolved any discrepancies. Parexel Data Management team reviewed query responses and action generated system queries as appropriate.

Threshold Clinical and Data Management team received email alert notifications and would follow-up as appropriate. If adjudication was warranted Threshold/SARC contacted the pathologists to arrange and execute.

eCRF completion guidelines were created and provided by Threshold to the pathologists.

Pathology Confirmation for Canadian Samples
NCIC was responsible for the collection and storage of samples obtained from all Canadian sites per their established processes. NCIC was responsible for the establishment and management of specimens and samples for inclusion into a system by which the central pathologist was able to view these specimens and reports to complete the case report form.

The reviewing pathologist for the specimens collected from Canadian investigation sites was responsible per NCIC processes for reviewing subject samples and reports in the NCIC established system.

The case report form in DataLabs was completed by the pathologist using the completion guidelines. The data inputted by the pathologist was reviewed by Threshold using the same guidelines used for non- Canadian subjects. Any issues were communicated to NCIC for follow up and resolve.

The contract between NCIC and Threshold was referenced for delegation responsibilities. NCIC held all procedures and processes.

Investigational Sites (from greatest to least in patient recruitment):

Site	Investigator	# of patients
298-Memorial Sloan-Kettering Cancer Center	Tap	45
469-Allami Egeszsegugyi Kozpont (AEK) (State Health Center)	Pápai	34
191-Washington University School of Medicine	Van Tine	30
330-Mayo Clinic Florida	Attia	29
471-UZ Leuven - Campus Gasthuisberg	Schöffski	27
194-Stanford University Department of Medicine Divison Of Oncology	Ganjoo	26
321-University of Washington[Cancer Center]/Seattle Cancer Care Alliance	Jones	24
320-University of Michigan Cancer Center	Schuetze	19
182-Moffitt Cancer Center	Reed	17
198-Duke University Medical Center	Riedel	15
200-Sarcoma Oncology Center	Chawla	15
781-Herlev Hospital	Krarup-Hansen	14
511-Institut Bergonié	Nguyen	13
113-The University of Arizona Cancer Center	Cranmer	12
219-Mayo Clinic-MN	Okuno	12
507-Centre Léon Bérard	Ray-Coquard	12
619-IRCC - Presidio Ospedaliero di Candiolo	Aglietta	12
685-Universitätsklinikum Mannheim	Hohenberger	12
331-Robert H. Lurie Comprehensive Cancer Center of Northwestern University	Agulnik	11
326-Winship Cancer Institute, Emory University	Read	10
328-Oregon Health and Science University	Ryan	10
228-University of Pittsburgh Medical Center	Tawbi	9
329-Cleveland Clinic Foundation	Budd	9
411-ICO Hospital Duran i Reynals	García del Muro Solans	9
967-McGill University - Dept. Oncology	Alcindor	9
409-H.Sta.Creu i St.Pau	López Pousa	8
584-GUZ Russian Oncology Research Center n.a. N.N.Blokhin RAMN	Aliev	8
722-Centrum Onkologii Instytut im. M. Sklodowskiej-Curie	Rutkowski	8
193-PENN Cancer Network	Staddon	7
225-Roswell Park Cancer Institute	Khushalani	7
297-MUSC - Hollings Cancer Center	Wrangle	7
682-Universitätsklinikum Essen	Bauer	7
683-Medizinische Hochschule Hannover	Gruenwald	7
858-Hadassah Medical Organisation_Ein Karem	Katz	7
112-Indiana University Simon Cancer Center	Rushing	6
294-Carolinas Hematology-Oncology Associates	Livingston	6
509-L'Institut de Cancerologie de l'Ouest - Rene Gauducheau	Bompas	6
587-Clinical Oncology Dispensary [Chemotherapy]	Mukhametshina	6
680-Universitätsklinikum Münster	Keßler	6
234-Massachusetts General Hospital	Demetri	5
319-University of Iowa Hospitals and Clinics	Milhem	5
336-University of Vermont	Verschraegen	5
338-Fox Chase Cancer Center	Movva	5

Site	Investigator	# of patients
468-Csoszi Endoszkopos KFT	Csoszi	5
299-Montefiore Medical Center	Packer	4
332-Rush University Medical Center	Batus	4
337-Oncology Specialists, S. C.	Kaiser	4
344-University Hospitals Seidman Cancer Center	Koon	4
412-C.H.U. de Canarias	Cruz Jurado	4
512-Centre Georges-François Leclerc	Isambert	4
723-Centrum Onkologii Instytut im M. Sklodowskiej-Curie	Cedrych	4
217-Dana Farber Cancer Center	Demetri	3
296-Kootenai Cancer Center	Mulvey	3
841-Allgemeines Krankenhaus Wien	Brodowicz	3
842-LKH-Univ. Klinikum Graz	Samonigg	3
969-Cross Cancer Institute	Mulder	3
971-Ottawa Health Research Institute - General Division	Tim	3
972-Juravinski Cancer Centre at Hamilton Health Sciences	Tozer	3
199-Mayo Clinic Arizona	Curtis	2
322-Vanderbilt University Medical Center	Keedy	2
335-VCU Massey Cancer Center	Poklepovic	2
341-Ohio State University Comprehensive Cancer Center	Chen	2
342-John Hopkins Hospital	Meyer	2
408-H.U. 12 de Octubre	López Martín	2
413-H.U. R. y Cajal	Vaz Salgado	2
506-CHU La Timone	Salas	2
585-FGU Moscow Research Institute of Oncology named after P.A. H	Bolotina	2
686-HELIOS Klinikum Bad Saarow	Reichardt	2
724-Wojewodzkie Centrum Onkologii w Gdansku	Pikiel	2
976-Tom Baker Cancer Centre	Henning	2
323-Wake Forest Baptist Health	Savage	1
327-Columbia University Medical Center	Kalinsky	1
339-USC/Norris Comprehensive Cancer Center and Hospital	Hu	1
340-Medical College of Wisconsin	Charlson	1
343-Washington Cancer Institute	Priebat	1
513-Centre Antoine Lacassagne	Thyss	1
617-PO G.Rodolico, AOU Policlinico-Vittorio Emanuele di Catania	Soto Parra	1
687-Helios Klinikum Berlin-Buch	Reichardt	1
968-BCCA - Vancouver Cancer Centre	Knowling	1
973-Univ. Health Network-Princess Margaret Hospital	Gupta	1
975-CancerCare Manitoba	Wong	1