EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 20 of Regulation (EC) No 726/2004

Lartruvo

Procedure number: EMEA/H/A-20/1479/C/4216/015

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

Lartruvo was granted a conditional marketing authorisation under Article 14(7) of Regulation (EC) No. 726/2004, valid throughout the European Union, on 9 November 2016. The therapeutic indication of Lartruvo is:

'*in combination with doxorubicin, for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin*'.

Lartruvo was authorised based on a single open-label, randomised phase 1b/2 clinical trial which enrolled doxorubicin-naïve subjects with advanced soft tissue sarcoma not amenable to treatment with surgery and radiotherapy (study JGDG). In this trial, treatment with olaratumab in combination with doxorubicin resulted in an improvement in progression-free survival (PFS) (8.2 vs. 4.4 months according to independent assessment; 6.6 vs. 4.1 months, hazard ratio (HR) 0.672 [95% CI: 0.442, 1.021], p = 0.0615 according to investigator assessment) and overall survival (OS) (26.5 months vs. 14.7 months, HR = 0.463; p = 0.0003).

In order to confirm the efficacy and safety of olaratumab, the marketing authorisation holder was required to submit as specific obligation, by January 2020, the clinical study report of a phase III randomised double-blind confirmatory study comparing doxorubicin plus olaratumab versus doxorubicin in patients with advanced or metastatic soft tissue sarcoma (Study I5B-MCJGDJ [JGDJ]; ANNOUNCE), including exploratory biomarker data.

In January 2019, the marketing authorisation holder communicated to the European Medicines Agency high level preliminary results of the JGDJ study. In total, 509 patients were randomised to treatment either with Lartruvo + doxorubicin (followed by Lartruvo monotherapy until progression) or with placebo + doxorubicin (followed by placebo monotherapy until progression).

The study gave rise to concerns about lack of efficacy, because it did not meet the primary objective to prolong survival in the overall population or in the leiomyosarcoma sub-population. Furthermore, there was no clinical benefit in key secondary efficacy endpoints.

On 25 January 2019 the European Commission (EC) triggered a procedure under Article 20 of Regulation (EC) No 726/2004, and requested the CHMP to assess the above concerns and their impact on the benefit-risk balance of Lartruvo. The EC requested the CHMP to give its opinion on whether the marketing authorisation for this product should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Olaratumab is a PDGFR-α antagonist. Olaratumab is a recombinant fully human IgG subclass 1 monoclonal antibody that specifically binds to PDGFR-α and blocks PDGF-AA, -BB, and –CC induced downstream signalling. In addition to blocking ligand-induced cell mitogenesis and receptor autophosphorylation, olaratumab inhibits ligand-induced phosphorylation of the downstream signalling molecules Akt and mitogen-activated protein kinase. Platelet-derived growth factor/ platelet-derived growth factor receptor alpha receptor (PDGF/PDGFR-α) signalling plays a role in both organ and tissue development, as well as in pathogenesis of non-malignant diseases (for example, pulmonary fibrosis) and malignant cancers.

Lartruvo was granted a conditional marketing authorisation under Article 14(7) of Regulation (EC) No. 726/2004, valid throughout the European Union, on 9 November 2016.

The main study included in the application was an open-label, multicentre, Phase 1b/2 trial to evaluate the safety and efficacy of olaratumab in combination with doxorubicin in patients with advanced soft tissue sarcoma (STS). Trial results were positive and seemed compelling from the clinical point of view. Treatment with olaratumab on top of doxorubicin nearly doubled PFS (8.2 vs 4.5 months; according to the IRC; 6.6 vs. 4.1 months, HR 0.672 [95% CI: 0.442, 1.021], p = 0.0615 according to investigator assessment). The improvement in OS was even more important. Olaratumab reduced the risk of death by 53.7% (HR = 0.463; p=0.0003), representing 80% longer median survival in the investigational arm (26.5 months vs. 14.7 months). In addition, Kaplan-Meier curves showed an unusual early separation and a persistence of the OS benefit over time.[1]

In order to confirm the efficacy and safety of olaratumab, the marketing authorisation holder (MAH) was required to submit, by January 2020, the clinical study report of a Phase 3, randomised, double-blind confirmatory study comparing doxorubicin plus olaratumab versus doxorubicin in patients with advanced or metastatic soft tissue sarcoma (STS; Study I5B-MCJGDJ [JGDJ]; ANNOUNCE), including exploratory biomarker data.

In January 2019, the marketing authorisation holder communicated to the European Medicines Agency high level preliminary results of the JGDJ study. In March 2019, the clinical study report was submitted for assessment.

Table 1 Overview of data submitted

Study id and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment	Main efficacy results
Therapeutic indication: advanced or metastatic soft tissue sarcoma not amenable to treatment with surgery or radiotherapy with curative intent					
Study I5B-MC-JGDJ (ANNOUNCE) phase 3, randomized, double blind, placebo controlled, parallel group, multicenter	Primary objective: OS in STS (ITT population) and leiomiosarcoma (LMS) population. Secondary objectives: PFS (by inv), ORR (by inv), DCR, DoR, DDC, PFS2, TTP, time to any new *metastases*, nMFS, Time to any progression based on increased sum of target lesions, Time to first worsening of ECOG PS, PROs: Pain, HRQoL, and health status, Safety and tolerability, PK and immunogenicity. Prespecified Exploratory Objective: Association between biomarkers and clinical outcomes	Planned: 460 (of those 200 LMS) Randomized: 509 (ITT population) [258 investigational arm (257 treated at least 1 dose); 251 control arm (249 at least 1 dose)] 234 (LMS population) [119 investigational arm (all received at least 1 dose); 115 control arm (114 at least 1 dose)]	Age≥18 years; locally advanced unresectable or metastatic STS for whom treatment with single-agent doxorubicin was considered appropriate, and not amenable to curative treatment with surgery or radiotherapy; any number of prior lines of therapy allowed (but no anthracyclines); life expectancy ≥3 months; measurable or non-measurable but evaluable disease by RECIST v1.1; ECOG PS 0 or 1; normal organ function; LVEF≥50%; available tumour tissue. Excluded Kaposi sarcoma and GIST; untreated CNS metastases or a recent history of cardiac disease.	Investigational arm: Olaratumab 20 mg/kg IV infusion over approximately 1 hour on Days 1 and 8 in Cycle 1 (loading doses) followed by olaratumab 15 mg/kg IV infusion over approximately 1 hour on Days 1 and 8 in all subsequent cycles; Doxorubicin 75 mg/m2 IV injection on Day 1 of Cycles 1 to 8 (administered after olaratumab) – 21 day cycle Investigational arm:Placebo (equivalent volume) IV infusion over approximately 1 hour on Days 1 and 8 in all cycles; Doxorubicin 75 mg/m2 IV injection on Day 1 of Cycles 1 to 8 (administered after placebo) - 21 day cycle (Cardioprotective Therapy: Starting	OS (ITT): median OS 20.37 (95%CI 17.84, 22.90) vs 19.75 (95%CI 16.49, 23.75) months, HR=1.047 (95% CI: 0.841, 1.303), p=0.6945. OS (LMS): median OS 21.55 (95%CI 18.63, 27.63) vs 21.88 (95%CI 17.54, 25.07) months, HR=0.951 (95% CI: 0.690, 1.312), p=0.7618. PFS (ITT): median PFS 5.42 (95%CI 4.11, 6.70) vs 6.77 (95%CI 5.49, 8.08) months, HR=1.231 (95% CI: 1.009, 1.502), p=0.0422. PFS (LMS population): median PFS 4.34 (95%CI 2.69, 6.97) vs 6.93 (95%CI 5.55, 8.41) months, HR=1.223 (95% CI:

[1] European Public Assessment Report for Lartruvo: https://www.ema.europa.eu/en/documents/assessment-report/lartruvo-epar-public-assessment-report_en.pdf

				with Cycle 1, dexrazoxane (in a 10:1 ratio to the doxorubicin dose) to mitigate cardiotoxicity with doxorubicin was allowed at investigator's discretion and was recommended for all patients who received 5 or more cycles of doxorubicin.)	0.918, 1.628), p=0.1713. ORR (ITT population): 14% (95%CI 9.7, 18.2) vs 18.3% (95%CI 13.5, 23.1) ORR (LMS population): 13.4 (95%CI 7.3, 19.6) vs 22.6% (95%CI 15.0, 30.3)
Abbreviations: OS= overall survival; PFS=progression free survival; ORR= objective response rate (Complete response [CR] + partial response [PR]); partial response [PR]); DCR=Disease control rate (CR + PR + stable disease [SD]); LMS=leiomiosarcoma; ITT= intention-to-treat; STS=soft tissue sarcoma; MFS= new metastasis free survival; DoR=Duration of response; DDC=Duration of disease control; PFS2=progression-free survival following subsequent anti-cancer therapy; TTP=Time to any progression; nMFS=New metastasis-free survival; ECOG PS=Eastern Cooperative Oncology Group performance status; PROs=Patient-reported outcomes; HRQoL=health-related quality of life; PK=Pharmacokinetics; LVEF=left ventricular ejection fraction; GIST=gastrointestinal stromal tumour; CNS=central nervous system; IV=intravenous					

2.2. Data on efficacy

Methods

- **Study participants**

The study enrolled male and female patients with histologically-confirmed diagnosis of locally advanced unresectable or metastatic STS (excluding Kaposi sarcoma and gastrointestinal stromal tumour [GIST]) for whom treatment with single-agent doxorubicin was considered appropriate, and who were not amenable to curative treatment with surgery or radiotherapy. The protocol did not restrict patients who had received any number of prior lines of therapy, with the exception of those containing anthracyclines.

Main inclusion criteria

- Have a histologically-confirmed diagnosis of locally advanced unresectable or metastatic STS
- Have measurable or non-measurable but evaluable disease as defined by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1
- Have an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 to 1 at study entry
- May have had any number of prior systemic cytotoxic therapies but not received any previous treatment with anthracyclines
- Have a left ventricular ejection fraction (LVEF) ⩾50% assessed at baseline

Main exclusion criteria

- GIST or Kaposi sarcoma
- Untreated central nervous system metastases
- Recent history of cardiac disease
- Received prior treatment with doxorubicin, epirubicin, idarubicin, and/or other anthracyclines and anthracenediones
- Received prior treatment with olaratumab or participated in a prior olaratumab trial

- Received prior radiation therapy to the mediastinal/pericardial area or whole pelvis radiation

- **Treatments**

Patients assigned to the investigational arm received the following according to a 21-day cycle:

- Olaratumab 20 mg/kg intravenous (IV) infusion over approximately 1 hour on Days 1 and 8 in Cycle 1 (loading doses) followed by olaratumab 15 mg/kg IV infusion over approximately 1 hour on Days 1 and 8 in all subsequent cycles
- Doxorubicin 75 mg/m^2 IV injection on Day 1 of Cycles 1 to 8 (administered after olaratumab)

Patients assigned to the control arm received the following according to a 21-day cycle:

- Placebo (equivalent volume) IV infusion over approximately 1 hour on Days 1 and 8 in all cycles
- Doxorubicin 75 mg/m^2 IV injection on Day 1 of Cycles 1 to 8 (administered after placebo)

Patients received combination treatment for 8 cycles followed by olaratumab monotherapy (in the investigational arm) or placebo (in the control arm) until evidence of progressive disease (PD), unacceptable toxicity, death, or other withdrawal criteria were met.

Starting with Cycle 1, dexrazoxane (in a 10:1 ratio to the doxorubicin dose) to mitigate cardiotoxicity during treatment with doxorubicin was allowed at the investigator's discretion and was recommended for all patients who received 5 or more cycles of doxorubicin.

Premedication to be given prior to olaratumab/placebo administration was initially recommended in the study protocol and required beginning with Protocol Amendment (b). Recommended/required premedication (or equivalents) was as follows:

- A histamine H1 antagonist (for example, diphenhydramine) and dexamethasone IV 30 to 60 minutes prior to olaratumab/placebo doses on Days 1 and 8 of Cycle 1.
- For subsequent cycles, a histamine H1 antagonist IV 30 to 60 minutes prior to each dose of olaratumab/placebo.

Additional premedication was permitted at the investigator's discretion.

A 1-hour observation period for monitoring for evidence of infusion-related reactions (IRRs) was required following study drug administration in the first 2 cycles, and thereafter only if a patient experienced an IRR.

- **Objectives**

Primary Objective

The primary objective was to compare olaratumab plus doxorubicin versus placebo plus doxorubicin with respect to OS in 2 populations:

(1) Patients with advanced or metastatic STS not amenable to treatment with surgery or radiotherapy with curative intent (intent-to-treat [ITT] population)

(2) Patients with advanced or metastatic leiomyosarcoma (LMS) not amenable to treatment with surgery or radiotherapy with curative intent (LMS population)

The study was to be considered positive if either population (or both) showed a statistically significant improvement in OS.

Secondary Objectives

The secondary objectives were to compare olaratumab plus doxorubicin versus placebo plus doxorubicin as follows:

- PFS (time from date of randomization to the first date of radiologic disease progression based on investigator assessment or death due to any cause).
- ORR (portion of randomized patients achieving a best overall response of PR or CR).
- DCR (portion of randomized patients achieving a best overall response of CR, PR, or SD).
- DoR (defined for each patient with a best response of CR or PR as the duration from first date of CR or PR to first date of radiologic disease progression or death due to any cause).
- DDC (defined for each patient with a best response of CR, PR, or SD as time from randomization to first date of radiologic disease progression or death due to any cause).
- PFS2 (time from randomization to the date of disease progression on next-line treatment, or death due to any cause, whichever occurred first).
- TTP (defined identically to PFS, except that TTP was censored at the date of death if there was no prior or concurrent radiologic disease progression).
- Time to any new metastasis (time from randomization to first date of radiographic documentation of 1 or more new lesions).
- nMFS (time from randomization to first date of radiographic documentation of 1 or more new lesions, or to date of death from any cause, whichever occurred first).
- Time to any progression based on increased sum of target lesions (time from randomization to first date of radiologic disease progression based solely on an increased sum of target lesions).
- Time to first worsening in ECOG PS (time from randomization to first date of observing a 1-point (or greater) deterioration from baseline).

(Radiographic assessments were performed according to RECIST v1.1 criteria every 6 weeks until radiographic documentation of PD.)

- Patient-reported outcomes (PROs): Pain, health-related quality of life (HRQoL), and health status
- Safety and tolerability
- Pharmacokinetics (PK) and immunogenicity

- **Sample size**

The study planned to enrol 460 patients in 1:1 randomization (230 patients in the investigational arm and 230 patients in the control arm). Enrolment was conducted so that approximately 200 patients with LMS and 260 patients with other (non-LMS) histology would be randomized. The final analysis was to occur only when both a minimum of 131 OS events had been observed in randomized patients with LMS, and a minimum of 322 OS events had been observed in randomized patients overall.

- **Statistical methods**

The study was designed to achieve one or the other of the 2 primary outcomes (OS). Achieving both primary outcomes was not required. The study was to be considered "positive" if either the ITT or LMS populations (or both) showed a statistically significant improvement in OS.

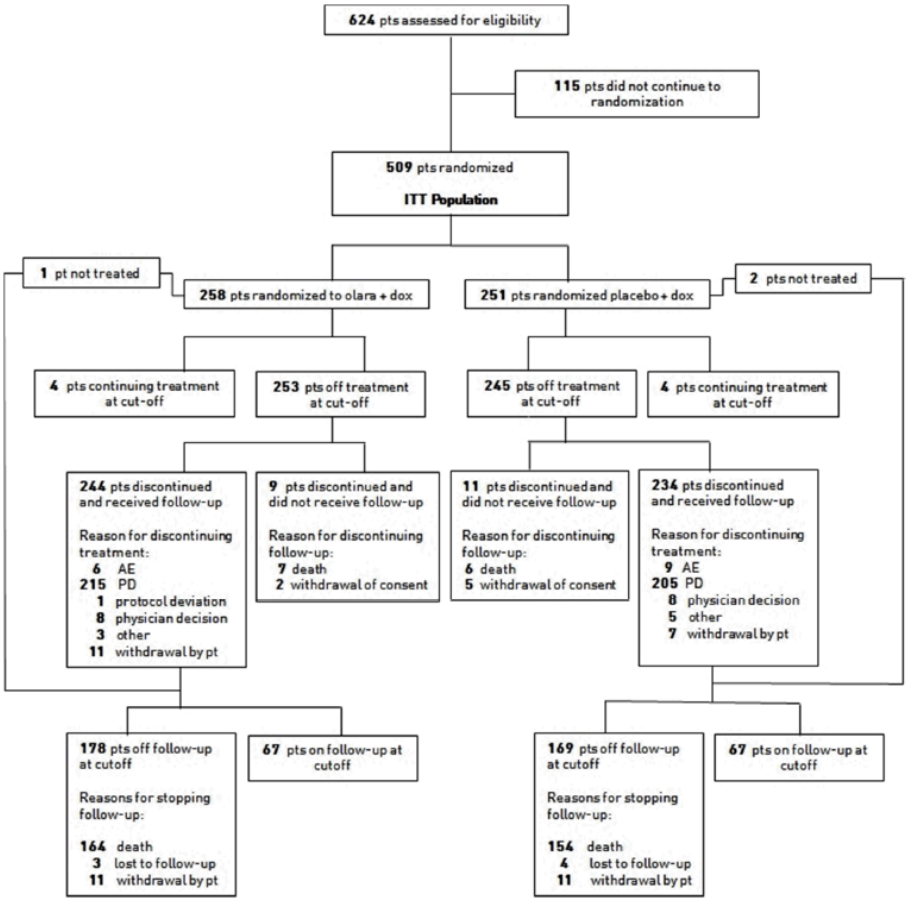
Statistical testing was planned to be conducted according to the graphical method of Maurer and Bretz (2013) to control the overall type I error rate at 0.025 (1-sided). The hypotheses primary objectives were OS in the ITT population and OS in the LMS population. The hypotheses secondary objectives were PFS in the ITT population and ORR in the ITT population. Initially, the overall 1-sided alpha of 0.025 was split between the primary objectives, with OS in the ITT population tested at an alpha of 0.02 and OS in the LMS population tested at an alpha of 0.005. Zero alpha was initially assigned to the other hypotheses.

All tests of treatment effects were conducted at a 2-sided alpha level of 0.05 unless otherwise stated, and all confidence intervals (CIs) were given at a 2-sided 95% level, unless otherwise stated. OS survival curves, the median with 95% CI and survival rates at various time points for each treatment group were estimated using the Kaplan-Meier method. The hazard ratio (HR) was estimated using a stratified Cox regression model, stratified by randomization strata. All randomized patients, according to the ITT principle, were included in the analysis of OS. An unstratified log-rank test was performed as a sensitivity analysis. Stratification was based on interactive web response system (IWRS) data used for randomization. Stratification factors were number of prior systemic therapies for advanced/metastatic disease (0 versus $\geqslant$1), histological tumour type (LMS versus LPS versus undifferentiated pleomorphic sarcoma versus other STS types), and ECOG PS (0 versus 1). Time-to-event analyses were based on the log-rank test, stratified by the randomization strata.

Results

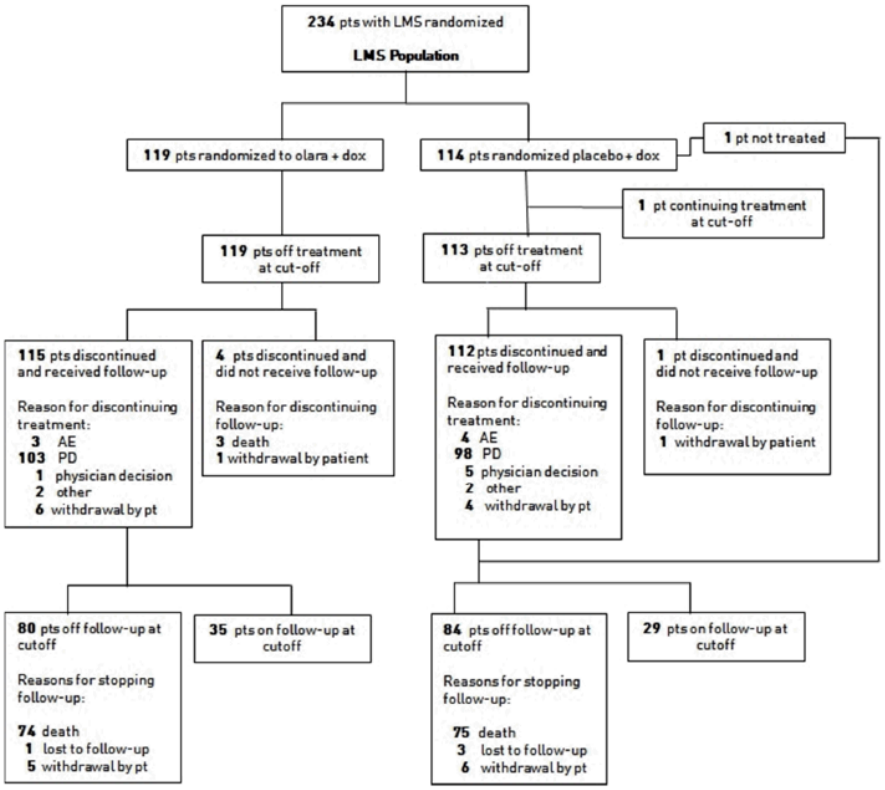
This multicentre study was conducted at 110 study centres in 25 countries. First patient was enrolled on 16 September 2015. Data cut-off is 5 December 2018.

- **Participant flow**



Abbreviations: AE = adverse event(s); dox = doxorubicin; ITT = intent-to-treat; olara = olaratumab; PD = progressive disease; pts = patients.
Note: Data cutoff 05 December 2018.
Sources: lillyce/prd/ly3012207/i5b_mc_jgdj/csr1/output/shared/scrnf_o_ds.rtf; itt_o_ds.rtf; lds.rtf.

Figure 1 Patient disposition, all patients



Abbreviations: AE = adverse event(s); dox = doxorubicin; LMS = leiomyosarcoma; olara = olaratumab; PD = progressive disease; pts = patients.
Note: Data cutoff 05 December 2018.
Source: lillyce/prd/ly3012207/i5b_mc_jgdj/csr1/output/shared/itt_o_ds_lms.rtf; lds.rtf; lptdc.rtf.

Figure 2 Patient disposition, all patients with LMS

Protocol amendments: four protocol amendments and 10 protocol addendums were released throughout the study.

Protocol deviations: Important protocol deviations occurred in 67 (26%) vs 58 (23.1%) patients in the investigational vs control arm, respectively. Protocol deviations were reviewed by the sponsor and were considered unlikely to have affected the results or conclusions.

- **Baseline data**

Below is baseline data for the ITT and LMS populations.

Table 2 Demographics ANNOUNCE ITT population

	Investigational Arm N = 258 n (%)	Control Arm N = 251 n (%)
Sex		
Male	114 (44.2)	99 (39.4)
Female	144 (55.8)	152 (60.6)
Race		
American Indian or Alaska native	3 (1.2)	3 (1.2)
Asian	50 (19.4)	48 (19.1)
Black or African American	12 (4.7)	2 (0.8)
Native Hawaiian or Other Pacific Islander	1 (0.4)	0 (0.0)
White	186 (72.1)	193 (76.9)
Multiple	5 (1.9)	4 (1.6)
Not reported	1 (0.4)	1 (0.4)
Age (years)		
Mean (SD)	56.7 (12.4)	57.1 (11.6)
Median	57.0	57.0
Minimum - Maximum	23 - 84	20 - 82
Age group		
<65 years	180 (69.8)	180 (71.7)
≥65 years	78 (30.2)	71 (28.3)
Age group		
<75 years	241 (93.4)	236 (94.0)
≥75 years	17 (6.6)	15 (6.0)
Age group		
<85 years	258 (100.0)	251 (100.0)
≥85 years	0 (0.0)	0 (0.0)

Abbreviations: ITT = intent-to-treat; N = number of randomized patients; SD = standard deviation.

Table 3 Baseline Characteristics ANNOUNCE ITT Population

	Investigational Arm N = 258		Control Arm N = 251	
Duration of disease (months)[a]				
N	257[b]		251	
Mean (SD)	26.2 (39.10)		26.9 (36.28)	
Median	11.3		11.8	
Minimum – Maximum	0 - 260		0 - 192	
	n	**%**	**n**	**%**
Stage of disease at randomization				
Locally advanced	42	16.3	45	17.9
Metastatic	216	83.7	206	82.1
Histological tumor type (from eCRF)				
Leiomyosarcoma	119	46.1	115	45.8
Liposarcoma	48	18.6	43	17.1
Pleomorphic sarcoma	34	13.2	30	12.0
Other[c]	57	22.1	63	25.1
Number of prior systemic therapies (from eCRF)				
0	190	73.6	191	76.1
≥1	68	26.4	60	23.9
Prior systemic treatment in neoadjuvant or adjuvant setting				
No	249	96.5	240	95.6
Yes	9	3.5	11	4.4
Lesions				
Liver	68	26.4	67	26.7
Lung	160	62.0	160	63.7
Bone	33	12.8	47	18.7
Prior radiation therapy				
No	171	66.3	166	66.1
Yes	87	33.7	85	33.9
Geographic location (from eCRF)				
North America	88	34.1	85	33.9
Europe	108	41.9	106	42.2
Rest of world	62	24.0	60	23.9
ECOG Performance Status				
0	153	59.3	150	59.8
1	105	40.7	101	40.2

Abbreviations: ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; ITT = intent-to-treat; LMS = leiomyosarcoma; N = number of randomized patients; n = number of patients in category; SD = standard deviation.

a Duration of disease was defined as the number of months from the first diagnosis of cancer to randomization.

b The date of initial pathological diagnosis was missing for 1 patient. Thus, duration of disease could not be calculated for this patient.

c One patient in the "other tumor type" category had lymphoma, which is not a type of soft tissue sarcoma. Enrollment of this patient was a protocol violation.

Table 4 Demographics ANNOUNCE LMS Population

	Investigational Arm N = 119 n (%)	Control Arm N = 115 n (%)
Sex		
Male	28 (23.5)	26 (22.6)
Female	91 (76.5)	89 (77.4)
Race		
American Indian or Alaska native	0 (0.0)	3 (2.6)
Asian	15 (12.6)	20 (17.4)
Black or African American	10 (8.4)	2 (1.7)
Native Hawaiian or Other Pacific Islander	1 (0.8)	0 (0.0)
White	90 (75.6)	88 (76.5)
Multiple	2 (1.7)	2 (1.7)
Not reported	1 (0.8)	0 (0.0)
Age (years)		
Mean (SD)	56.9 (11.1)	57.6 (9.8)
Median	58.0	56.0
Minimum - Maximum	29 - 77	34 - 82
Age group		
<65 years	85 (71.4)	85 (73.9)
≥65 years	34 (28.6)	30 (26.1)
Age group		
<75 years	115 (96.6)	108 (93.9)
≥75 years	4 (3.4)	7 (6.1)
Age group		
<85 years	119 (100.0)	115 (100.0)
≥85 years	0 (0.0)	0 (0.0)

Abbreviations: N = number of randomized patients; SD = standard deviation; LMS = leiomyosarcoma.

Table 5 Baseline Characteristics ANNOUNCE LMS Population

	Investigational Arm N = 119		Control Arm N = 115	
Duration of disease (months)[a]				
n	118		115	
Mean (SD)	26.3 (35.35)		23.4 (32.47)	
Median	9.9		11.8	
Minimum – Maximum	0 -165		1-183	
	n	**%**	**n**	**%**
Stage of disease at randomization				
Locally advanced	12	10.1	15	13.0
Metastatic	107	89.9	100	87.0
Number of prior systemic therapies (from eCRF)				
0	81	68.1	84	73.0
≥1	38	31.9	31	27.0
Prior systemic treatment in neoadjuvant or adjuvant setting				
No	116	97.5	107	93.0
Yes	3	2.5	8	7.0
Lesions				
Liver	48	40.3	38	33.0
Lung	84	70.6	89	77.4
Bone	15	12.6	22	19.1
Prior radiation therapy				
No	86	72.3	78	67.8
Yes	33	27.7	37	32.2
Primary tumor location				
Gastrointestinal system	6	5.0	5	4.3
Retroperitoneal	21	17.6	26	22.6
Uterus	46	38.7	48	41.7
Vascular system	8	6.7	3	2.6
Other	38	31.9	33	28.7
Geographic location (from eCRF)				
North America	56	47.1	51	44.3
Europe	42	35.3	43	37.4
Rest of world	21	17.6	21	18.3
ECOG Performance Status				
0	70	58.8	71	61.7
1	49	41.2	44	38.3

Abbreviations: ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; LMS = leiomyosarcoma; N = number of randomized patients; n = number of patients in category; SD = standard deviation.

a Duration of disease was defined as the number of months from the first diagnosis of cancer to randomization.

- **Outcomes and estimation**

Primary Endpoint: Overall Survival – ITT Population

There was no significant difference in OS between the treatment arms. The median OS was 20.37 months in the investigational arm and 19.75 months in the control arm (HR=1.047 [95% CI: 0.841, 1.303]; p=0.6945).

Table 6 Overall Survival ANNOUNCE ITT Population

	Investigational Arm (N = 258)	Control Arm (N = 251)	Treatment Difference[a]
Number of deaths, n (%)	171 (66.3)	160 (63.7)	
Number censored, n (%)	87 (33.7)	91 (36.3)	
Median survival – months (95% CI)	20.37 (17.84, 22.90)	19.75 (16.49, 23.75)	0.62
Log-rank p-value (2-sided)			
Stratified[b]			0.6945
Unstratified			0.7885
Hazard ratio (95% CI)			
Stratified[b]			1.047 (0.841, 1.303)
Unstratified			1.030 (0.830, 1.278)
Survival rate, % (95% CI)[c]			
3-month	94.1 (90.4, 96.4)	94.0 (90.2, 96.3)	0.1 (-4.0, 4.3)
6-month	86.8 (82.0, 90.5)	86.5 (81.6, 90.2)	0.3 (-5.7, 6.3)
9-month	79.5 (74.0, 84.0)	76.9 (71.1, 81.8)	2.6 (-4.7, 9.9)
12-month	67.3 (61.0, 72.7)	66.4 (60.0, 72.0)	0.9 (-7.5, 9.2)
15-month	60.3 (53.9, 66.1)	60.4 (53.8, 66.3)	-0.1 (-8.8, 8.6)
18-month	55.3 (48.9, 61.3)	53.0 (46.5, 59.2)	2.3 (-6.6, 11.2)

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; ITT = intent-to-treat; IWRS = Interactive Web Response System; N = number of randomized patients; n = number of patients in category.

[a] Treatment effect/difference/p-values are computed based on comparator placebo+doxorubicin.

[b] Stratified by Strata: ECOG PS at baseline (IWRS), number of prior systemic therapies (IWRS), histological tumor type (IWRS).

[c] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation.

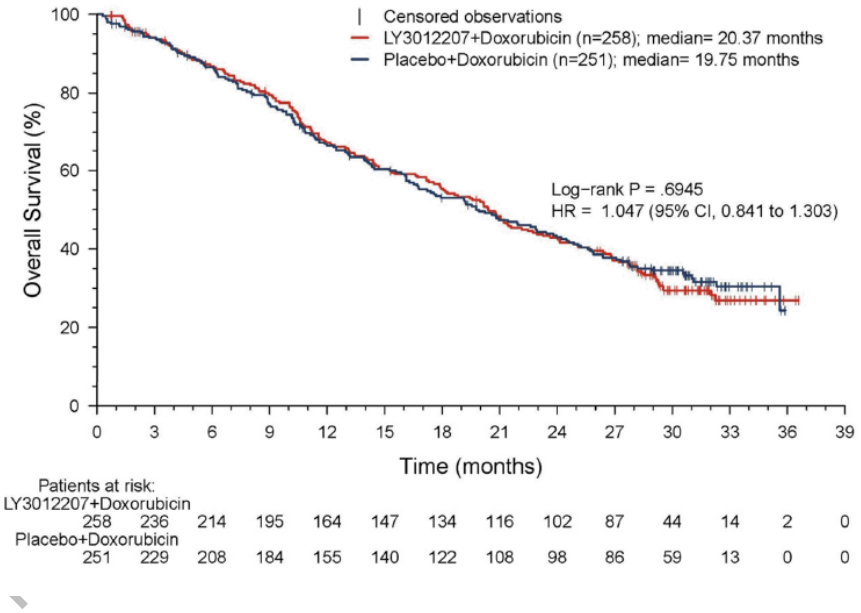
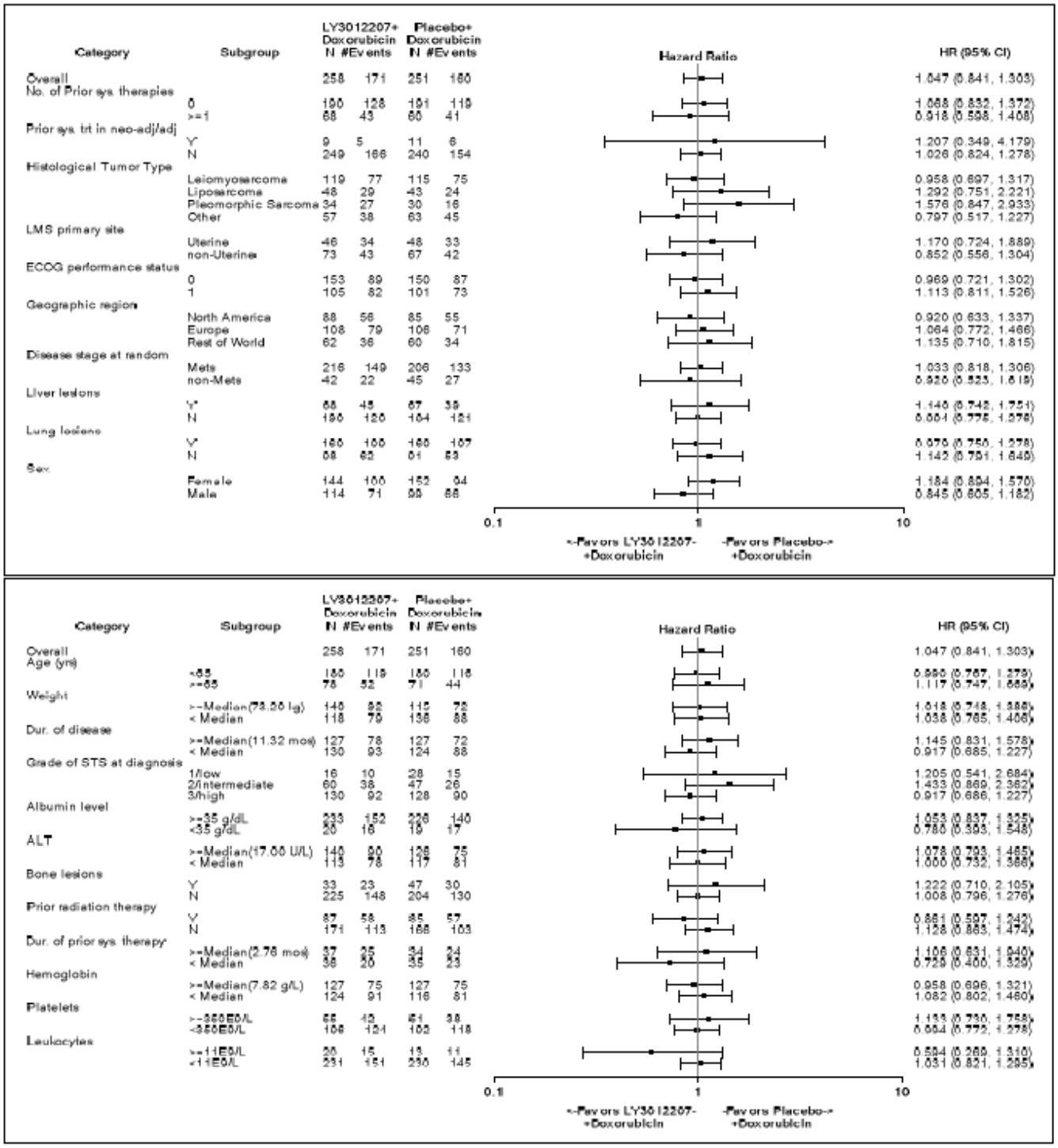


Figure 3 Kaplan-Meier curve for OS of investigational arm versus control arm in ANNOUNCE ITT population.

Multiple sensitivity analyses were conducted on the primary OS endpoint. None of the sensitivity analyses demonstrated a difference between the treatment arms.



Abbreviations: ALT = alanine aminotransferase; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; ITT = intent-to-treat; OS = overall survival; STS = soft tissue sarcoma.

Note: Hazard ratio and 95% CI (Wald) were estimated using Stratified Cox model for overall and unstratified Cox models for subgroups.

Figure 4 Forest plot for unstratified subgroup analysis of OS in ANNOUNCE ITT population.

Following study treatment discontinuation, patients could receive additional anticancer therapies at the discretion of the investigator. To investigate whether the survival advantage observed in either of the treatment arms could be driven by post-study therapies effect, anticancer therapies received following discontinuation of study treatment were evaluated. As seen in following table, post-discontinuation

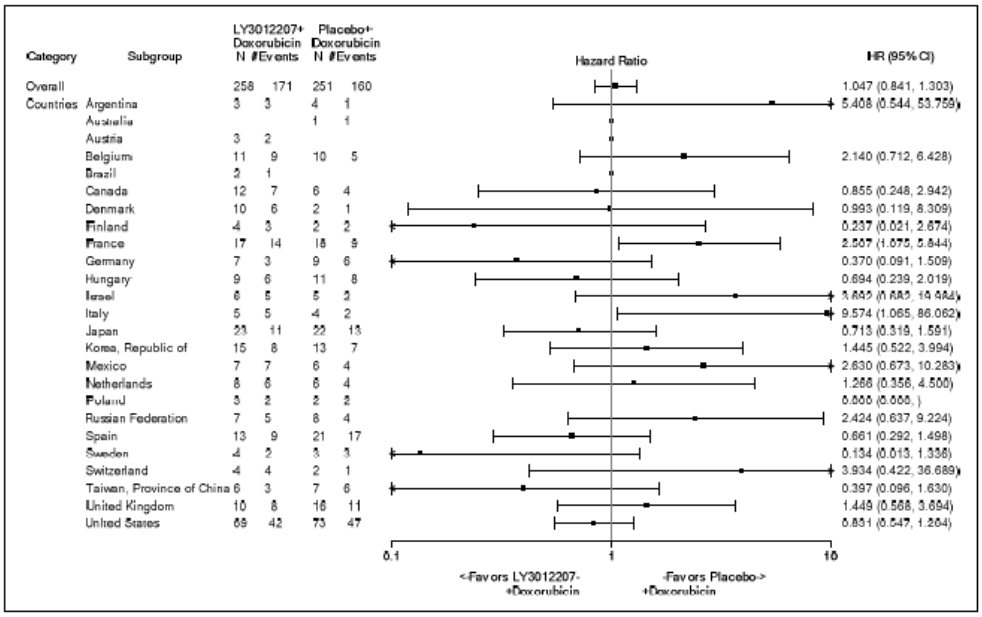
systemic therapy agents were generally well balanced between treatment arms, however post-discontinuation radiation therapy was administered more commonly in the control arm (27.9%) than in the investigational arm (15.1%).

Table 7 Post-discontinuation Therapy, Including Systemic Therapy Received by ≥10% of Patients in Either ANNOUNCE ITT Population

Parameter	Investigational Arm N = 258 n (%)	Control Arm N = 251 n (%)
Surgical procedure	32 (12.4)	28 (11.2)
Radiotherapy	39 (15.1)	70 (27.9)
Systemic therapy		
Overall	178 (69.0)	169 (67.3)
Gemcitabine	72 (27.9)	82 (32.7)
Trabectedin	65 (25.2)	67 (26.7)
Pazopanib	55 (21.3)	57 (22.7)
Docetaxel	40 (15.5)	48 (19.1)
Dacarbazine	31 (12.0)	35 (13.9)
Ifosfamide	25 (9.7)	26 (10.4)

Abbreviations: ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category.

In addition to the broad geographic regions of North America, Europe, and Rest of World that were considered stratification factors, a by-country analysis of OS was performed.



Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; LY3012207 = olaratumab; OS = overall survival.

Figure 5 Forest plot of unstratified analysis of OS by country in ANNOUNCE ITT population

Primary Endpoint: Overall Survival – LMS Population

There was no difference, statistical or clinically meaningful, in OS between the treatment arms. The median OS was 21.55 months in the investigational arm and 21.88 months in the control arm (HR=0.951 [95% CI: 0.690, 1.312]; p=0.7618).

Table 8 Overall Survival ANNOUNCE LMS Population (data cut-off 05 December 2018)

	Investigational Arm N = 119	Control Arm N = 115	Treatment Difference[a]
Number of deaths, n (%)	77 (64.7)	75 (65.2)	
Number censored, n (%)	42 (35.3)	40 (34.8)	
Median survival – months (95% CI)	21.55 (18.63, 27.63)	21.88 (17.54, 25.07)	-0.33
Log-rank p-value (2-sided)			
Stratified[b]			0.7618
Unstratified			0.7909
Hazard ratio (95% CI)			
Stratified[b]			0.951 (0.690, 1.312)
Unstratified			0.958 (0.697, 1.317)
Survival rate, % (95% CI)[c]			
3-month	93.2 (86.9, 96.5)	95.6 (89.7, 98.1)	-2.4 (-8.3, 3.5)
6-month	88.0 (80.5, 92.7)	87.5 (79.8, 92.4)	0.5 (-8.1, 9.0)
9-month	84.5 (76.5, 89.9)	81.2 (72.6, 87.3)	3.3 (-6.5, 13.1)
12-month	73.9 (64.8, 80.9)	70.2 (60.7, 77.8)	3.7 (-8.0, 15.4)
15-month	65.9 (56.4, 73.8)	65.5 (55.8, 73.6)	0.4 (-12.1, 12.8)
18-month	62.2 (52.7, 70.4)	58.0 (48.2, 66.6)	4.2 (-8.6, 17.1)

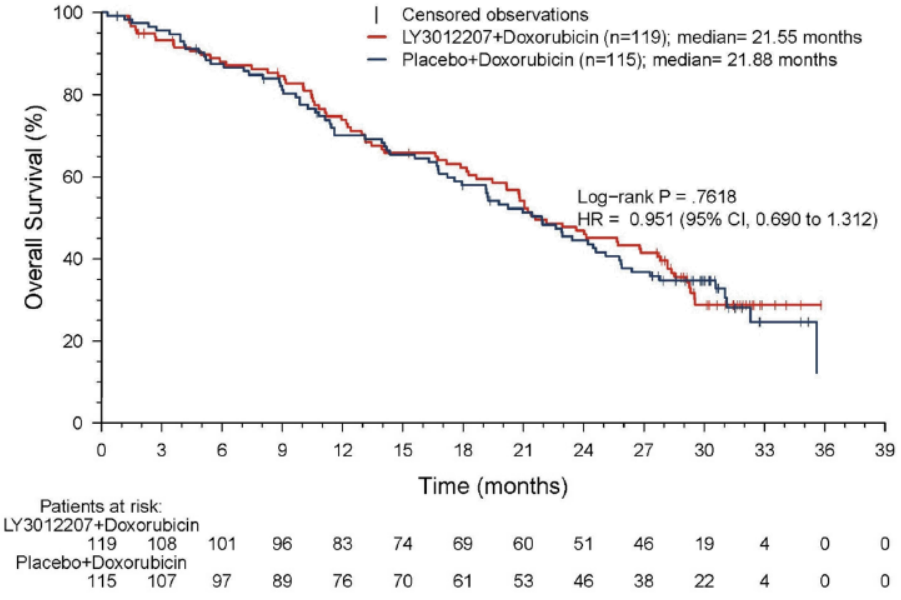
Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; IWRS = interactive web response system; LMS = leiomyosarcoma; N = number of randomized patients; n = number of patients in category; OS = overall survival.

Note: Quartiles and OS rates were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley (1982), and Greenwood (1926), respectively.

[a] Treatment difference/p-values are computed based on comparator placebo plus doxorubicin.

[b] Stratified by Strata: ECOG PS at baseline (IWRS), number of prior systemic therapies (IWRS), histological tumor type (IWRS).

[c] 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation.



Abbreviations: CI = confidence interval; HR = hazard ratio; LMS = leiomyosarcoma; LY3012207 = olaratumab; OS = overall survival.

Figure 6 Kaplan-Meier curve for OS of investigational arm versus control arm in ANNOUNCE LMS population.

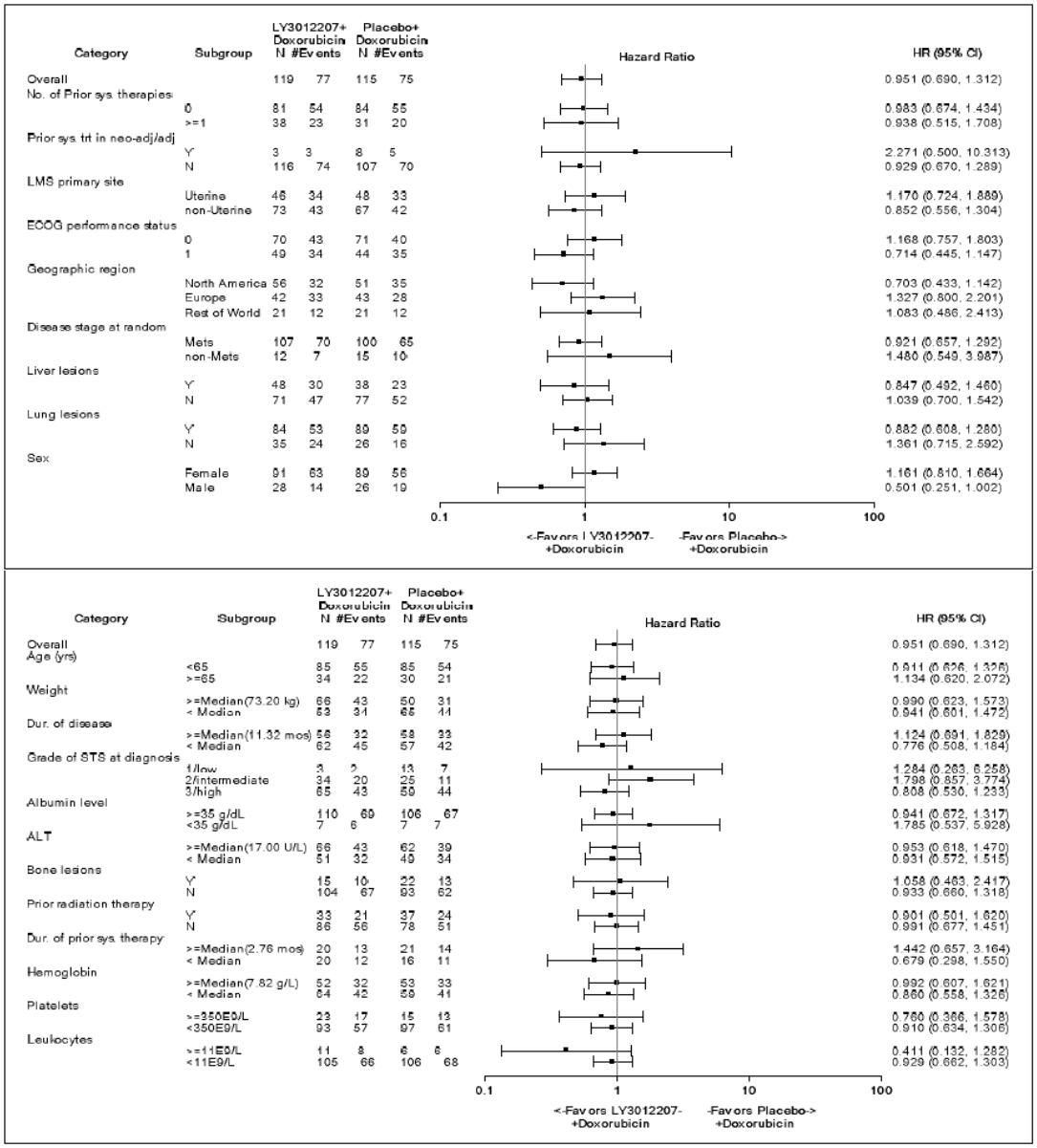


Figure 7 Forest plot of unstratified subgroup analyses of OS in ANNOUNCE LMS population.

<u>Secondary Endpoint - Progression-Free Survival – ITT Population</u>

There was a significant difference in PFS between the treatment arms in favour of the control arm. The median PFS was 5.42 months in the investigational arm and 6.77 months in the control arm (HR=1.231 [95% CI: 1.009, 1.502]; p=0.0422).

Table 9 Progression-Free Survival ANNOUNCE ITT Population (data cut-off 05 December 2018)

	Investigational Arm (N = 258)	Control Arm (N = 251)	Treatment Difference[a]
Number of events, n (%)	219 (84.9)	217 (86.5)	
Number censored, n (%)	39 (15.1)	34 (13.5)	
Median PFS – months (95% CI)	5.42 (4.11, 6.70)	6.77 (5.49, 8.08)	-1.35
Log-rank p-value (2-sided)			
Stratified[b]			0.0422
Unstratified			0.1703
Hazard ratio (95% CI)			
Stratified[b]			1.231 (1.009, 1.502)
Unstratified			1.142 (0.946, 1.378)
PFS rate, % (95% CI)[c]			
3-month	61.9 (55.6, 67.7)	69.8 (63.6, 75.2)	-7.9 (-16.3, 0.5)
6-month	45.8 (39.4, 52.0)	51.9 (45.4, 58.0)	-6.1 (-15.1, 2.9)
9-month	29.2 (23.5, 35.3)	34.5 (28.4, 40.6)	-5.2 (-13.8, 3.3)
12-month	19.9 (14.9, 25.4)	20.9 (15.8, 26.5)	-1.0 (-8.6, 6.5)
15-month	13.4 (9.2, 18.4)	13.6 (9.4, 18.6)	-0.2 (-6.7, 6.3)

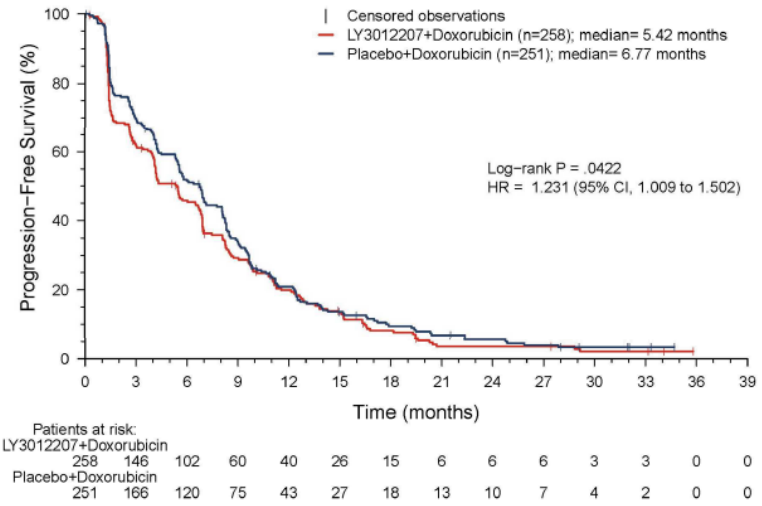
Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; ITT = intent-to-treat; IWRS = interactive web response system; N = number of randomized patients; n = number of patients in category; PFS = progression-free survival.

Note: Quartiles and PFS rates, along with 95% CIs, were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley (1982), and Greenwood (1926), respectively.

a Treatment difference/p-values are computed based on comparator placebo plus doxorubicin.

b Stratified by ECOG PS at baseline (IWRS), number of prior systemic therapies (IWRS), histological tumor type (IWRS).

c 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation.

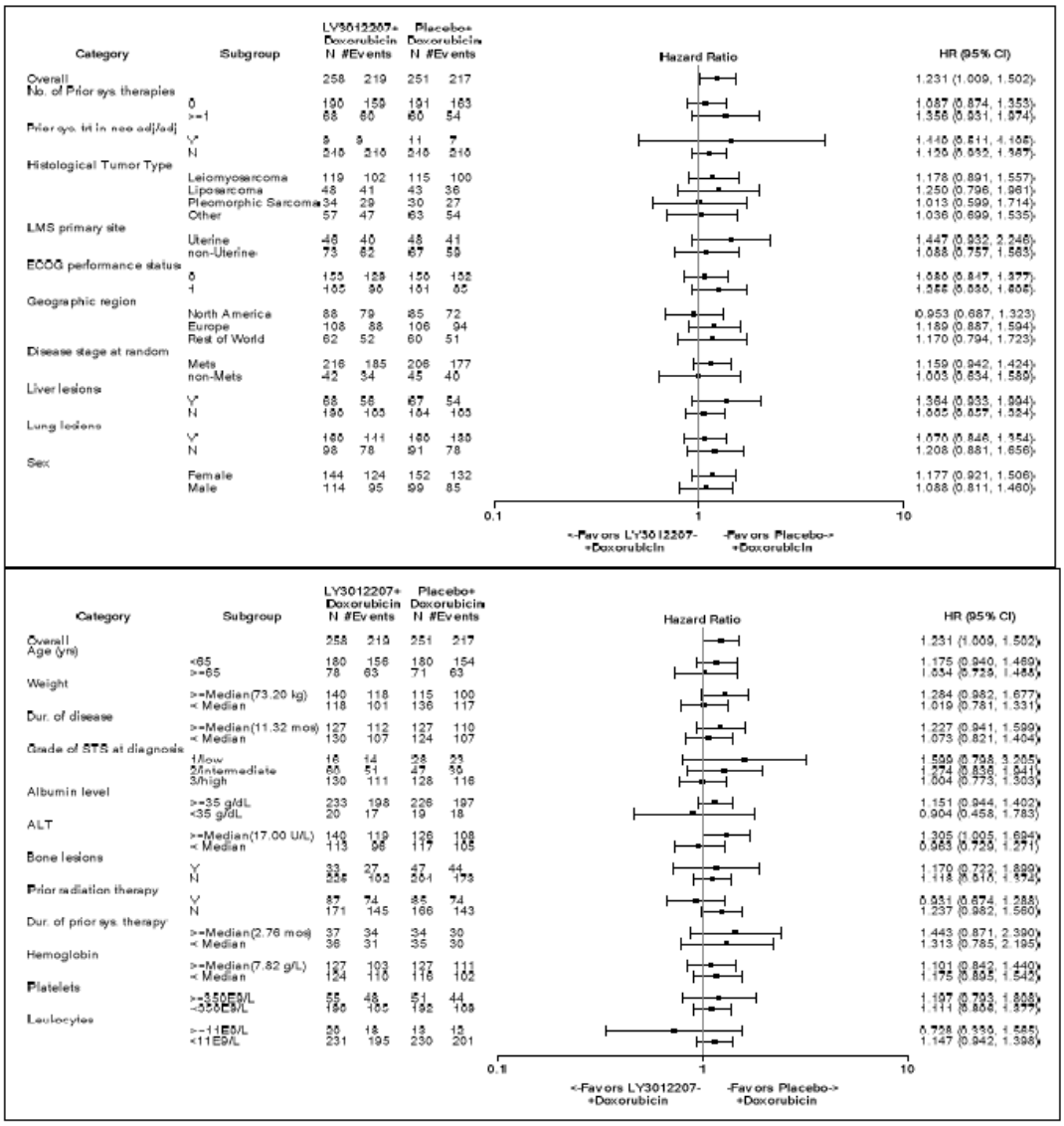


Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; LY3012207 = olaratumab; PFS = progression-free survival.

Figure 8 Kaplan-Meier curve for investigator-assessed PFS of investigational arm versus control arm in ANNOUNCE ITT population.

The results of multiple sensitivity analyses and a multivariate analysis conducted on the PFS endpoint were consistent with the main PFS analysis.

The estimate of PFS treatment effect (as assessed by the stratified HR) on the majority of prespecified subgroups slightly favoured the control arm, consistent with the overall PFS results.



Abbreviations: ALT = alanine aminotransferase; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; LMS = leiomyosarcoma; PFS = progression-free survival; STS = soft tissue sarcoma.
Note: Hazard ratio and 95% CI (Wald) were estimated using a stratified Cox model for overall and unstratified Cox models for subgroups.

Figure 9 Forest plot for unstratified subgroup analysis of PFS in ANNOUNCE ITT population.

Secondary Endpoint - Progression-Free Survival LMS Population

There was no significant difference in PFS between the treatment arms. The median PFS was 4.34 months in the investigational arm and 6.93 months in the control arm (HR=1.223 [95% CI: 0.918, 1.628]; p=0.1713).

Table 10 Progression-Free Survival ANNOUNCE LMS Population (data cut-off 05 December 2018)

	Investigational Arm (N = 119)	Control Arm (N = 115)	Treatment Difference[a]
Number of events, n (%)	102 (85.7)	100 (87.0)	
Number censored, n (%)	17 (14.3)	15 (13.0)	
Median PFS – months (95% CI)	4.34 (2.69, 6.97)	6.93 (5.55, 8.41)	-2.60
Log-rank p-value (2-sided)			
Stratified[b]			0.1713
Unstratified			0.2532
Hazard ratio (95% CI)			
Stratified[b]			1.223 (0.918, 1.628)
Unstratified			1.178 (0.891, 1.557)
PFS rate, % (95% CI)[c]			
3-month	58.5 (49.0, 66.9)	76.3 (67.1, 83.2)	-17.7 (-29.7, -5.7)
6-month	47.9 (38.4, 56.8)	57.5 (47.6, 66.2)	-9.5 (-22.7, 3.6)
9-month	30.7 (22.2, 39.7)	36.8 (27.7, 46.0)	-6.1 (-18.9, 6.7)
12-month	20.6 (13.2, 29.1)	15.0 (8.8, 22.8)	5.6 (-5.1, 16.4)
15-month	11.4 (6.0, 18.9)	8.6 4.0, 15.2)	2.9 (-5.7, 11.5)

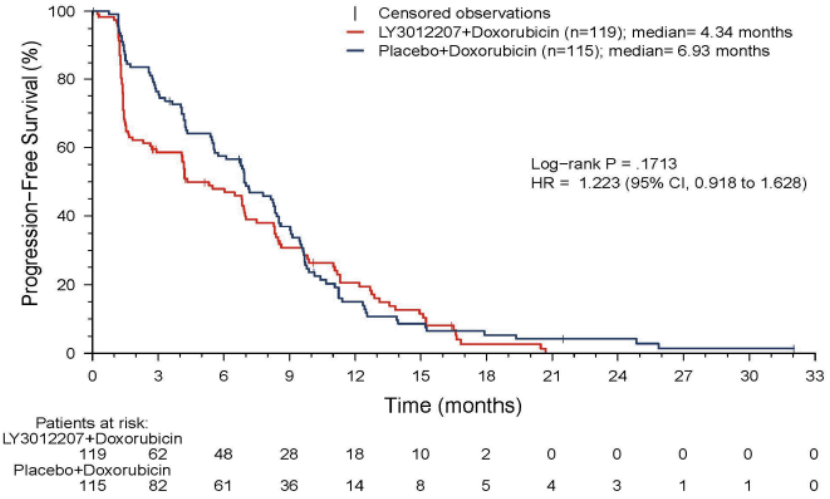
Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; IWRS = interactive web response system; LMS = leiomyosarcoma; N = number of randomized patients; n = number of patients in category; PFS = progression-free survival.

Note: Quartiles and PFS rates, along with 95% CIs, were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley (1982), and Greenwood (1926), respectively.

a Treatment difference/p-values are computed based on comparator placebo plus doxorubicin.

b Stratified by ECOG PS at baseline (IWRS), number of prior systemic therapies (IWRS), histological tumor type (IWRS).

c 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation.



Abbreviations: CI = confidence interval; HR = hazard ratio; LMS = leiomyosarcoma; LY3012207 = olaratumab; PFS = progression-free survival.

Figure 10 Kaplan-Meier curve for investigator-assessed PFS of investigational arm versus control arm in ANNOUNCE LMS population

Secondary Endpoint - ORR and DCR ITT Population

No statistically significant difference in ORR or DCR was observed between the investigational arm and control arms, and both rates favoured the control arm.

Table 11 Objective Response Rate ANNOUNCE ITT Population

	Investigational Arm N = 258 n (%)	Control Arm N = 251 n (%)	Stratified Odds Ratio (95% CI)[a]	p-value[b]
Best Overall Response, n %				
Complete response (CR)	2 (0.8)	1 (0.4)		
Partial response (PR)	34 (13.2)	45 (17.9)		
Stable disease (SD)	138 (53.5)	144 (57.4)		
Progressive disease (PD)	70 (27.1)	52 (20.7)		
Not evaluable	14 (5.4)	9 (3.6)		
Objective response rate (CR+PR)	36 (14.0)	46 (18.3)	0.7	0.1837
95% CI for response rate[c]	(9.7, 18.2)	(13.5, 23.1)	(0.4, 1.2)	
Disease control rate (CR+PR+SD)	174 (67.4)	190 (75.7)	0.7	0.0595
95% CI for disease control rate[c]	(61.7, 73.2)	(70.4, 81.0)	(0.5, 1.0)	

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; ITT = intent-to-treat; IWRS = interactive web response system; N = number of randomized patients; n = number of patients in category; RECIST = Response Evaluation Criteria in Solid Tumors.

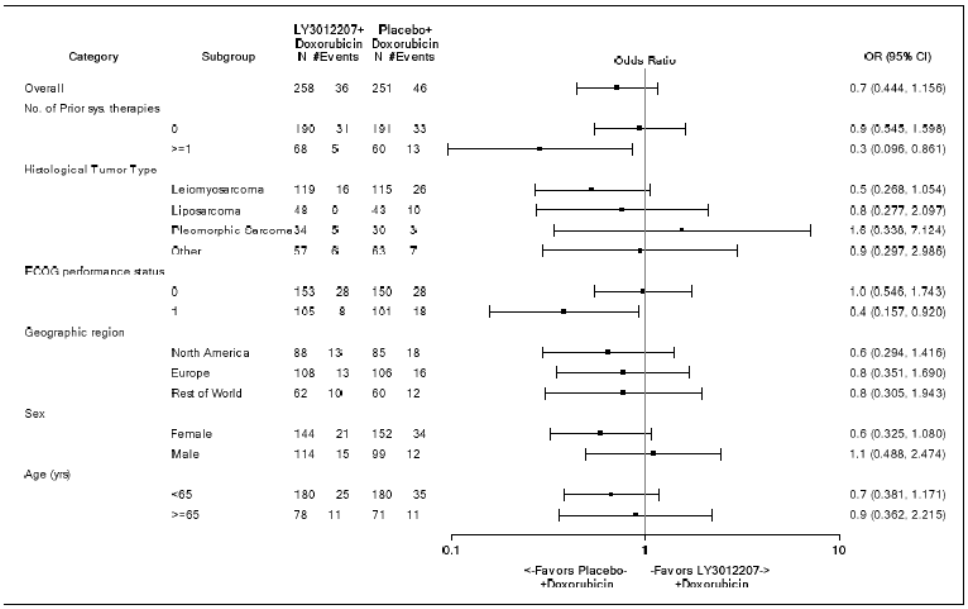
Note: Response criteria used was RECIST version 1.1.

a Stratified by the following strata: ECOG PS at baseline (IWRS), number of prior systemic therapies (IWRS), histological tumor type (IWRS).

b p-value was calculated by exact Cochran-Mantel-Haenszel test stratified by the randomization strata: ECOG PS at baseline (IWRS); number of prior systemic therapies (IWRS); histological tumor type (IWRS). Where a p-value was not calculable, the computations were not done because there were less than 2 non-missing levels in the data.

c Confidence intervals are based on the normal approximation.

The estimates of ORR in most prespecified subgroups favoured the control arm. Results strongly favoured the control arm for patients with ⩾1 prior systemic therapy (odds ratio [OR] 0.3) and an ECOG PS of 1 (OR 0.4).



Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; OR = odds ratio; sys = systemic.

Note: Hazard ratio and 95% CI (Wald) were estimated using stratified logistic regression model for overall and unstratified logistic regression models for subgroups.

Figure 11 Forest plot of unstratified subgroup analysis of response in the ANNOUNCE ITT population.

Secondary Endpoint - ORR and DCR LMS Population

ORR was numerically favoured in the control arm and DCR was statistically significantly favoured in the control arm in the LMS population.

Table 12 Objective Response Rate ANNOUNCE LMS Population

	Investigational Arm N = 119 n (%)	Control Arm N = 115 n (%)	Stratified Odds Ratio (95% CI)[a]	p-value[b]
Best Overall Response, n %				
Complete response (CR)	1 (0.8)	0 (0)		
Partial response (PR)	15 (12.6)	26 (22.6)		
Stable disease (SD)	59 (49.6)	69 (60.0)		
Progressive disease (PD)	40 (33.6)	17 (14.8)		
Not evaluable	4 (3.4)	3 (2.6)		
Objective response rate (CR+PR)	16 (13.4)	26 (22.6)	0.5	0.0890
95% CI for response rate[c]	7.3, 19.6	15.0, 30.3	0.3, 1.1	
Disease control rate (CR+PR+SD)	75 (63.0)	95 (82.6)	0.4	0.0011
95% CI for disease control rate[c]	54.4, 71.7	75.7, 89.5	0.2, 0.7	

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; IWRS = interactive web response system; LMS = leiomyosarcoma; N = number of randomized patients; n = number of patients in category; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Response criteria used was RECIST version 1.1.

a Stratified by the following strata: ECOG PS at baseline (IWRS), number of prior systemic therapies (IWRS).

b p-value was calculated by exact Cochran-Mantel-Haenszel test stratified by the randomization strata: ECOG PS at baseline (IWRS); number of prior systemic therapies (IWRS). Where a p-value was not calculable, the computations were not done because there were less than 2 non-missing levels in the data.

c Confidence intervals are based on the normal approximation.

Secondary Endpoint - Maximum Reduction in Tumor Size

Baseline tumour assessments were available for 244 of the 258 patients in the investigational arm and 236 of 251 patients in the control arm. Maximum change in tumour size was defined as the ratio of best postbaseline tumour size over that of baseline. The maximum reduction from baseline in the sum of target lesions (recorded in millimeters and based on investigator assessment) is presented per patient in a waterfall plot for the investigational arm and for the control arm in the following figures. In these plots, patients demonstrating a reduction in tumour size are shown on the left.

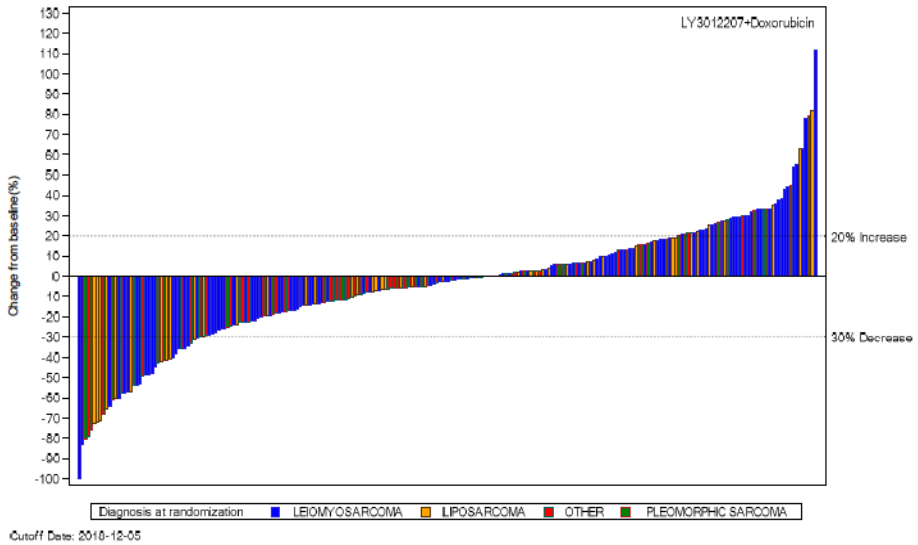


Figure 12 Waterfall plot for percent change in tumour size in the investigational arm based on investigator assessment in ANNOUNCE ITT population.

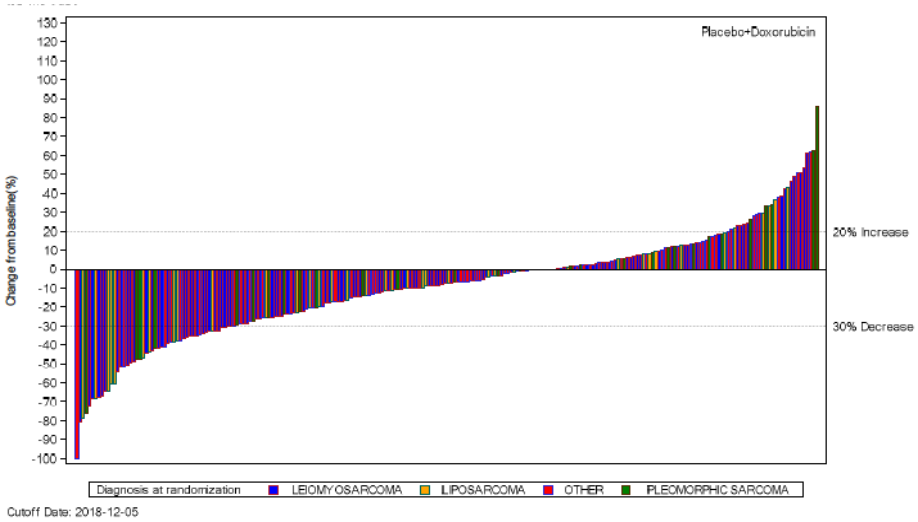


Figure 13 Waterfall plot for percent change in tumour size in the control arm based on investigator assessment in ANNOUNCE ITT population.

For the subset of patients with LMS, baseline tumour assessments were available for 117 of the 119 patients in the investigational arm and 110 of 115 patients in the control arm.

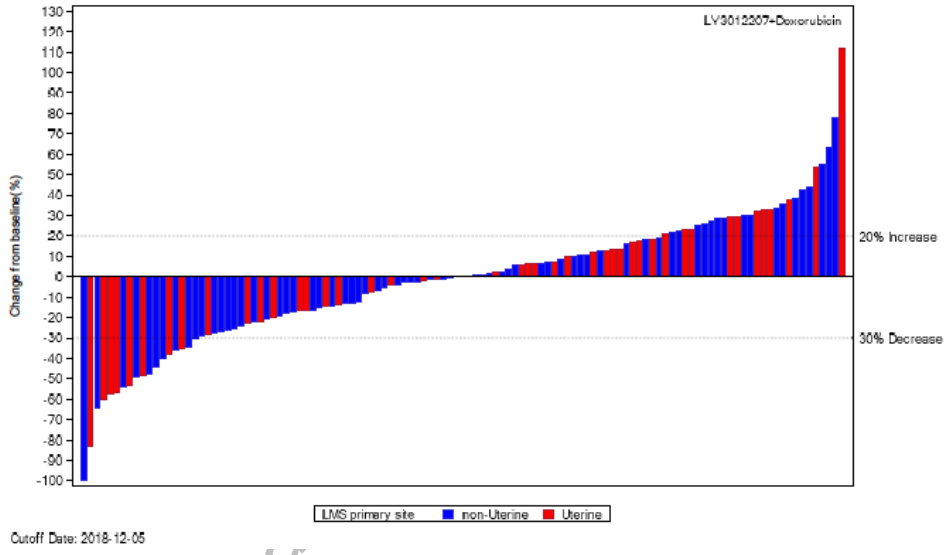


Figure 14 Waterfall plot for percent change in tumour size in the investigational arm based on investigator assessment ANNOUNCE LMS population.

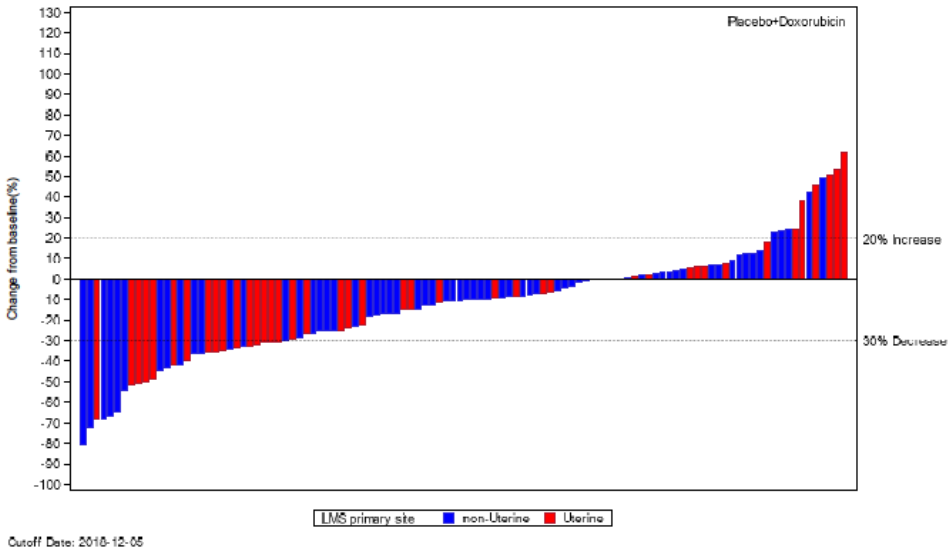


Figure 15 Waterfall plot for percent change in tumour size in the control arm based on investigator assessment in ANNOUNCE LMS population

Secondary Endpoint - Progression-Free Survival 2

Progression-free survival-2 was defined as the time from the randomization date to the date of disease progression on next-line treatment, or death due to any cause, whichever occurred first. In the ITT population, the analysis of PFS2 showed no difference between the investigational and control arms (18.6 and 17.9 months, respectively).

Secondary Endpoint - Time to Any Progression

In the ITT population, there was no difference in median time to any progression between the investigational and control arms (5.6 and 6.9 months, respectively).

Secondary Endpoint - Time to Any New Metastasis

In the ITT population, there was no difference in median time to any new metastasis between the investigational and control arms (16.4 and 20.4 months, respectively).

Secondary Endpoint - New Metastasis-free Survival

In the ITT population, there was no difference in median time to new metastasis-free survival between the investigational and control arms (15.2 and 16.7 months, respectively).

Secondary Endpoint - Time to Any Progression based on Increased Sum of Target Lesions

In the ITT population, there was no difference in median time to any progression based on increased sum of target lesions between the investigational and control arms (8.3 and 9.0 months, respectively).

Secondary Endpoint - Summary of Time to First Worsening of ECOG Performance Status

In the ITT population, there was no difference in median time to first worsening of ECOG performance status between the investigational and control arms (10.6 months and 9.9 months, respectively).

Exploratory Analysis of PDGFR Expression in Tumour Tissue

- PDGFR-α Expression

Tumour tissue was available for analysis from 462 patients with non-missing results in the ITT population of ANNOUNCE.

PDGFR-α expression by immunohistochemistry was well balanced between the arms, with 58.3% and 57.3% of the evaluable samples positive for expression in the investigational and control arms, respectively.

There was no significant association of PDGFR-α status and response to olaratumab in terms of OS or PFS. Consistent with literature reports that PDGFR-α expression may be a poor prognostic indicator in some soft tissue sarcomas[2], PDGFR-α negative cases showed better OS than PDGFR-α positive cases, regardless of treatment arm.

- PDGFR-β Expression

Tumour tissue was available for analysis from 464 patients with non-missing results in the ITT population of ANNOUNCE (hereafter, the translational research population).

PDGFR-β expression by immunohistochemistry was well balanced between the arms, with 71.2% and 68.1% of the evaluable samples positive for expression in the investigational and control arms, respectively. There was no significant association of PDGFR-β status and response to olaratumab in terms of OS or PFS in the translational research population.

- PDGFR-α Expression in LMS Subset

The impact of PDGFR-α status was examined in evaluable patients in the subset of patients with LMS.

Overall survival was longer in LMS patients that were PDGFR-α negative than in those that were PDGFR-α positive in both treatment arms (investigational arm, p=0.02; control arm, p=0.0006). Similarly, PFS of LMS patients that were PDGFR-α negative in the control arm was longer than those that were PDGFR-α positive (investigational arm, p=0.0065; control arm, p<0.0001).

Patient-Reported Outcomes

Between patients in the investigational and control arms respectively, there were no statistically significant differences on time to first worsening of the QLQ-C30 Global Health Status/QoL score (restricted mean difference -0.78 months [95% CI:-1.98, 0.42]; p=0.204).

Between patients in the investigational and control arms respectively, there were no statistically significant differences (restricted mean difference -0.19 months [95% CI: -1.88, 1.49]; p=0.821) in time to first worsening of the mBPI-sf "worst pain" score.

Between patients in the investigational and control arms respectively, there were no statistically significant differences (restricted mean difference 0.79 months [95% CI: -0.18, 1.76]; p=0.109). Fewer than 20% of patients increased analgesic use from baseline in either study arm, with the exception of Cycle 1, where 14.7% of patients in the investigational arm and 20.7% of patients in the control arm increased analgesic levels.

There were no clinically meaningful changes during treatment from baseline utility score as measured by the EQ-5D-5L for either patients in the investigational arm or patients in the control arm (mean difference from baseline was less than ±0.05 at all time points with at least 20 evaluable patients).

Pharmacokinetics

Olaratumab serum concentrations observed were within the expected range. PK analysis results were consistent with prior analysis of data from previous clinical studies.

[2] Blandford MC, Barr FG, Lynch JC, Randall RL, Qualman SJ, Keller C. Rhabdomyosarcomas utilize developmental, myogenic growth factors for disease advantage: a report from the children's oncology group. *Pediatr Blood Cancer*. 2006;46(3):329-338.

Immunogenicity Results

Immunogenicity samples were requested for all patients at multiple time points throughout the study.

From these analyses, 250 patients in the investigational arm and 238 patients in the control arm were found to be evaluable for the presence or absence of antidrug antibodies (ADA). The incidence of treatment-emergent ADAs (TE-ADA) was 3.2% in the investigational arm and 8.8% in the control arm. Treatment-emergent ADA titers ranged from 1:10 to 1:320. Neutralizing antibodies were detected in all of the patients with TE-ADA, aside from 1 patient in the investigational arm who had inconclusive testing (either the last test value was inconclusive or 2 or more sequential tests were inconclusive). The limited sample size of patients precludes definitive conclusions on the effect of immunogenicity on efficacy; however, the observed outcomes in patients with TE-ADAs did not suggest any effect of immunogenicity on efficacy.

Due to low number of TE-ADA positive patients from ANNOUNCE, it is unlikely to contribute sufficient information to the current understanding of the impact of immunogenicity on olaratumab PK. Therefore, the effect of immunogenicity on PK of olaratumab was not evaluated for ANNOUNCE.

2.3. Data on safety

Patient exposure

The safety population included all randomized patients who received at least one dose of study drug. Of the 509 randomized patients in the ITT population, 506 received at least 1 dose of any study treatment, including 257 patients in the investigational arm and 249 patients in the control arm.

Table 13 Exposure to Olaratumab or Placebo ANNOUNCE Safety Population

	Investigational Arm N = 257	Control Arm N = 249
Number of patients who received olaratumab or placebo[a]	257	249
Duration of treatment (weeks)		
Mean (SD)	28.13 (27.48)	32.40 (29.05)
Median duration (weeks)	19.00	26.00
Range (weeks)	3.00-160.71	3.00-156.29
Cycles received per patient[b], n		
Mean (SD)	9.07 (9.00)	10.45 (9.54)
Median	6.00	8.00
Range	1.00-53.00	1.00-51.00
Cumulative dose per body weight (mg/kg)[c]		
Mean (SD)	262.49 (261.34)	308.69 (282.75)
Median	185.87	249.82
Range	3.32-1626.29	20.00-1480.20

Abbreviations: N = number of treated patients; n = number of patients in the specified category; SD = standard deviation.

a Number of patients who received at least 1 dose of olaratumab or placebo either partial or complete.

b Patient is considered to have received a treatment cycle after receiving at least 1 dose of olaratumab or placebo either partial or complete.

c One patient in the investigational arm had infusion interrupted immediately after the administration started and the site did not enter the actual dose, so this patient is excluded from this analysis.

Table 14 Exposure to Doxorubicin ANNOUNCE Safety Population

	Investigational Arm N = 257	Control Arm N = 249
Number of patients who received doxorubicin[a]	255	249
Duration of doxorubicin treatment (weeks)		
Mean (SD)	16.40 (8.49)	18.04 (8.21)
Median duration (weeks)	18.00	23.00
Range (weeks)	3.00 - 29.14	3.00 - 31.29
Cycles received per patient[b], n		
Mean (SD)	5.23 (2.66)	5.74 (2.58)
Median	6.00	7.00
Range	1.00-8.00	1.00-8.00
Cumulative dose per BSA (mg/m^2)		
Mean (SD)	375.35 (191.62)	415.62 (187.51)
Median	409.15	482.79
Range	72.33 - 627.12	73.83 - 633.96

Abbreviation: BSA = body surface area; N = number of treated patients; n = number of patients in the specified category; SD = standard deviation.
a Number of patients who received at least 1 dose of doxorubicin either partial or complete.
b Patient is considered to have received a treatment cycle after receiving at least 1 dose of doxorubicin either partial or complete.

Starting with cycle 1, dexrazoxane (in a 10:1 ratio to the doxorubicin dose) to mitigate cardiotoxicity during treatment with doxorubicin was allowed at the investigator's discretion and was recommended for all patients who received 5 or more cycles of doxorubicin. Exposure to dexrazoxane was balanced between the two treatments arms.

Table 15 Exposure to Dexrazoxane ANNOUNCE Safety Population

	Investigational Arm N = 257	Control Arm N = 249
Number of patients who received dexrazoxane[a]	162	162
Duration of therapy (weeks)		
Mean (SD)	12.72 (6.49)	13.17 (6.34)
Median duration (weeks)	12.00	12.00
Range (weeks)	3.00-37.00	3.00-28.00
Cycles received per patient[b]		
Mean (SD)	3.91 (1.97)	4.10 (2.00)
Median	4.00	4.00
Range	1.00-8.00	1.00-8.00
Patients who received ≥1 cycle, n (%)	162 (63.0)	162 (65.1)
Patients who received ≥2 cycles, n (%)	144 (56.0)	146 (58.6)
Patients who received ≥3 cycles, n (%)	122 (47.5)	123 (49.4)
Patients who received ≥4 cycles, n (%)	97 (37.7)	109 (43.8)
Patients who received ≥5 cycles, n (%)	40 (15.6)	47 (18.9)
Patients who received ≥6 cycles, n (%)	33 (12.8)	37 (14.9)
Patients who received ≥7 cycles, n (%)	21 (8.2)	22 (8.8)
Patients who received ≥8 cycles, n (%)	15 (5.8)	18 (7.2)
Number of patients who started dexrazoxane by:		
Cycle 1	64 (39.5)	42 (25.9)
Cycle 2	2 (1.2)	3 (1.9)
Cycle 3	8 (4.9)	22 (13.6)
Cycle 4	9 (5.6)	5 (3.1)
Cycle 5	72 (44.4)	82 (50.6)
Cumulative Dose per BSA (mg/m^2)		
Mean (SD)	2776.35 (1415.97)	2923.51 (1457.69)
Median	2802.78	2985.47
Range	452.96-6183.76	451.71-6870.81

Abbreviation: BSA = body surface area; N = number of treated patients; n = number of patients in the specified category; SD = standard deviation.
a Number of patients who received at least 1 dose of dexrazoxane either partial or complete.
b Patient is considered to have received a treatment cycle after receiving at least 1 dose of dexarazoxane either partial or complete.

Adverse events

Nausea, neutropenia and fatigue were the most frequently reported treatment-emergent adverse events (TEAEs), each occurring in more than half of patients in both treatment arms. The rate of

known doxorubicin-related toxicities namely haematological toxicities (neutropenia, thrombocytopenia, anaemia and febrile neutropenia) and gastrointestinal toxicities (nausea, vomiting and diarrhoea) was balanced between the treatment arms. In addition, the rate of (consolidated) musculoskeletal pain was similar between the 2 treatment arms.

Table 16 Overview of TEAEs ANNOUNCE population

Adverse Event Category[a]	Investigational Arm N = 257 n (%)	Control Arm N = 249 n (%)
Patients with ≥1 TEAE	252 (98.1)	247 (99.2)
Related to any study treatment[b]	238 (92.6)	233 (93.6)
Patients with ≥1 TEAE CTCAE Grade ≥3	195 (75.9)	182 (73.1)
Related to any study treatment[b]	171 (66.5)	157 (63.1)
Patients with ≥1 SAE	100 (38.9)	87 (34.9)
Related to any study treatment[b]	70 (27.2)	64 (25.7)
Patients who discontinued study treatment due to TEAE	11 (4.3)	11 (4.4)
Related to any study treatment[b]	6 (2.3)	6 (2.4)
Patients who discontinued study treatment due to SAE	9 (3.5)	6 (2.4)
Related to any study treatment[b]	4 (1.6)	4 (1.6)
Patients who died due to TEAE on study treatment[c]	5 (1.9)	2 (0.8)
Related to any study treatment[b]	2 (0.8)	0 (0.0)
Patients who died due to TEAE on therapy or within 30 days of last dose of study drug[c]	5 (1.9)	3 (1.2)
Related to any study treatment[b]	2 (0.8)	0 (0.0)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in safety population; n = number of subjects in the specified category; TEAE = treatment-emergent adverse event; SAE = serious adverse event.

Note: MedDRA Version 21.1.

a Patients may be counted in more than 1 category.

b Includes events that were considered related to study treatment as judged by the investigator.

c Deaths are also included as serious adverse events and discontinuations due to adverse events.

Table 17 Summary of overall TEAEs and consolidated TEAE categories (any grade) occurring in ≥5% of patients by the investigational arm ANNOUNCE Safety Population

	Investigational Arm N = 257 n (%)	Control Arm N = 249 n (%)
Preferred Term *Consolidated TEAE Category*	**Any Grade**	**Any Grade**
Patients with any AE		
Nausea	153 (59.5)	166 (66.7)
Neutropenia	142 (55.3)	144 (57.8)
Fatigue	139 (54.1)	147 (59.0)
Alopecia	112 (43.6)	124 (49.8)
Anemia	110 (42.8)	113 (45.4)
Musculoskeletal pain	92 (35.8)	85 (34.1)
Mucositis	89 (34.6)	101 (40.6)
Leukopenia	81 (31.5)	78 (31.3)
Constipation	79 (30.7)	87 (34.9)
Diarrhea	74 (28.8)	75 (30.1)
Decreased appetite	71 (27.6)	92 (36.9)
Vomiting	63 (24.5)	69 (27.7)
Thrombocytopenia	58 (22.6)	62 (24.9)
Pyrexia	48 (18.7)	46 (18.5)
Dyspnea	46 (17.9)	36 (14.5)
Dysgeusia	45 (17.5)	51 (20.5)
Abdominal pain	45 (17.5)	53 (21.3)
Febrile neutropenia	45 (17.5)	41 (16.5)
Cough	43 (16.7)	61 (24.5)
Headache	43 (16.7)	42 (16.9)
Edema peripheral	34 (13.2)	23 (9.2)
Dyspepsia	28 (10.9)	29 (11.6)
Dizziness	27 (10.5)	34 (13.7)
Lymphopenia	19 (7.4)	17 (6.8)
Neuropathy	17 (6.6)	24 (9.6)
Hypertension	16 (6.2)	20 (8.0)
Rash	16 (6.2)	23 (9.2)
Hypokalemia	14 (5.4)	12 (4.8)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of treated patients; n = number of patients with given event; TEAE = treatment-emergent adverse events.

Adverse Event of Special Interest: Infusion-related Reactions

In the investigational arm, the rate of immediate hypersensitivity reactions was 11.7% for all grade events and 2.3% for Grade ⩾3 events, consistent with previous safety profile of olaratumab. Of these, 2.4% were anaphylactic reactions, usually occurring at the first olaratumab infusion. Immediate non-anaphylactic reactions were reported in 9.3% patients and were Grade 1/2 in severity.

Adverse Event of Special Interest: Cardiac Arrhythmias

The incidence of the AESI of cardiac arrhythmias was higher in the investigational arm than in the control arm (12.8% vs. 9.6%). Most of these reactions were Grade 1 and did not lead to treatment discontinuations or dose modifications. Grade ⩾3 events also occurred more frequently in the investigational arm (2.7% vs.0.8%).

Adverse Event of Special Interest: Cardiac Dysfunction

The incidence of all grades of events in the cardiac dysfunction AESI category of was slightly higher in the investigational arm compared with the control arm (18.3% vs. 13.7%, respectively); the majority of events were non-serious Grade 1 and 2 events. The incidence of Grade ⩾3 events was similar in both arms (investigational arm, 2.3%; control arm, 2.4%). These findings were in context of higher cumulative doxorubicin drug exposure in the control arm compared to the investigational arm. When events of edema and peripheral edema not associated with an AE suggestive of cardiac dysfunction or a significant decrease in left ventricular function were excluded, the true incidence of events in the cardiac dysfunction category 9.3% in the investigational arm and 6.8% in the control arm).

Deaths

The majority of the deaths were due to disease progression of the underlying malignancy. These events were reasonably expected in this trial population.

Serious Adverse Events

The rate of SAEs was comparable between the treatment arms. Febrile neutropenia was the most frequent SAE in both arms and the only SAE that occurred at frequency of ⩾5% in patients in the investigational arm [investigational arm, 33 patients (12.8%); control arm, 33 patients (13.3%)]. There were 3 serious IRRs (consolidated term) reported in investigational arm and 1 in the control arm.

Laboratory findings

There were no clinically relevant findings on ECGs, in incidence of treatment-emergent abnormal laboratory values, or in incidence of abnormal vital signs between treatment arms. Slightly more patients treated with olaratumab required hospitalization for AEs during the course of the study (14.8% in the investigational arm vs. 11.2% in the control arm). The number of transfusions required as supportive care was similar between treatment arms. The use of granulocyte and erythroid colony stimulating factors, glucocorticosteroids, antihistamines, and anti-emetic medications was also similar between treatment arms.

Immunological events

The observed rate of treatment-emergent antidrug antibodies (TE-ADAs) in olaratumab-treated patients was 8 out of 250 immunogenicity evaluable patients (3.2%). Neutralizing antibodies were observed in all patients with TE- ADAs, aside from one patient on the investigational arm who had inconclusive testing. Based on these very small numbers a definitive conclusion could not be made, but it did not appear that TE-ADAs lead to any apparent impact on olaratumab serum exposure, efficacy, overall safety, or IRRs.

Discontinuation due to adverse events

The number of patients who discontinued treatment for adverse events was similar between the treatment arms (n=11, 4.3% for investigational arm and n=11, 4.4% for control arm).

2.4. Differences between phase II JGDG and phase III ANNOUNCE studies

While the reasons for the discrepancy between the observed efficacy results for study JGDG and ANNOUNCE are not clear, the table below summarises the known differences in the design of the two trials.

Table 188 Differences between phase II JGDG and phase III ANNOUNCE studies

Category		Phase 2	ANNOUNCE
Study type		Open label	Double-blinded, placebo-controlled
Region		US only	Multinational[a]
Premedication: Antihistamine and steroids		Not required	Required[b]
Dexrazoxane		Allowed starting cycle 5	Allowed starting cycle 1 Recommended after cycle 5
First-cycle olaratumab dose		15 mg/kg	Loading dose: 20 mg/kg
Olaratumab monotherapy		Olaratumab monotherapy allowed after progression for patients on doxorubicin-alone arm	No olaratumab monotherapy allowed on protocol for patients on doxorubicin-alone arm
Patient-related outcomes		Did not include patient-reported outcomes	Included patient-reported outcomes
Statistical analysis	Primary endpoint	Single: PFS	Two primary: OS in ITT population and/or in leiomyosarcoma population
	Stratification	• Tumor expression of PDGFRα • Lines of prior treatment • ECOG PS • Histology (leiomyosarcoma, synovial sarcoma, other)	• Lines of prior treatment • ECOG PS • Histology (leiomyosarcoma, liposarcoma, undifferentiated pleomorphic sarcoma, other) • Region (North America, Europe, other)
	Sample size	N=130	Target N=460
Biomarker analyses		Association of tumor expression (by IHC) of PDGFRα and related markers with PFS and OS	Association of tumor and stromal expression (by IHC) of PDGFRα and related markers with PFS and OS

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; IHC = immunohistochemistry; ITT = intent to treat; N = number of patients; OS = overall survival; PDGFRα = platelet-derived growth factor receptor alpha; PFS = progression-free survival.

a US, Argentina, Australia, Austria, Belgium, Brazil, Canada, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Japan, South Korea, Mexico, Netherlands, Poland, Russia, Spain, Sweden, Switzerland, Taiwan and UK.

b Premedication was required starting with ANNOUNCE protocol amendment (b), approved in January 2016.

Heterogeneity of soft tissue sarcoma

STS is a heterogeneous group of tumours that includes over 50 tumour subtypes that can be located anywhere in the body[3,4]. This potential heterogeneity is not explicitly controlled for and may be unbalanced between the JGDG (Phase 2) and ANNOUNCE (Phase 3) trials; however, both stratified randomisation by histological tumour type (phase 2: LMS vs. synovial sarcoma vs. other STS types; phase 3: LMS versus LPS versus undifferentiated pleomorphic sarcoma versus other STS types).

Possible variation in the histologic grade

In the phase 2 JGDG study, 36% of patients had an "unknown/unreported" histologic grade; this was 20% in phase 3. There could have been more high-grade histologies in phase 2, potentially impacting the control arm overall survival (OS) rates. Similarly, in the phase 2 study 100% of patients had metastatic disease, compared to the phase 3 study, in which 83% of patients had metastatic disease.

Additionally, the potential impact of a therapeutic agent with preliminary evidence of a marked OS benefit in STS may have led investigators in the phase 3 trial to enrol patients with lower tumour volume, more indolent disease that could improve outcomes in both phase 3 treatment arms compared to the phase 2 trial.

Histology

As is normal, control of histology randomisation was done within each trial, not across trials, leading to further heterogeneity. In this instance, histologies were well balanced between arms; however, there is discrepancy between the trials; in the phase 3 study, the investigational arm included 10% more LMS patients and approximately 50% fewer UPS patients than in the phase 2 trial. Additional comparisons of histology between study JGDG and ANNOUNCE show that the results of study JGDG may have been driven more by a strong influential subset of patients than an overall predominant effect in the full study population.

[3] Sharma *et al.*: Efficacy and safety of pharmacological interventions in second- or later-line treatment of patients with advanced soft tissue sarcoma: a systematic review. *BMC Cancer* 2013 13:385.
[4] D'Angelo *et al.*: Sarcoma immunotherapy: past approaches and future directions. Sarcoma. 2014;2014:391967.

Study design

Study JGDG was open-label and allowed patients in the control arm to receive olaratumab monotherapy after doxorubicin treatment. In contrast, study JGDJ (ANNOUNCE) was a double-blind, placebo controlled study and did not allow for control arm patients to receive olaratumab monotherapy. While, theoretically, the use of olaratumab in the study JGDG control arm could have reduced the OS of the control arm as a whole, additional analyses do not support this hypothesis. Patients in the study JGDG control arm receiving olaratumab had similar OS to those not receiving olaratumab.

3. Benefit-risk balance

Favourable effects

ANNOUNCE (I5B-MC-JGDJ) was a randomized, double-blind, placebo-controlled, phase 3 trial of olaratumab plus doxorubicin versus placebo plus doxorubicin in patients with locally advanced or metastatic soft tissue sarcoma. It was designed to confirm the OS benefit previously shown in the smaller phase 1b/2 study JGDG. The latter showed an unexpected survival gain in patients with advanced/metastatic STS recruited in the United States. Even though the primary endpoint of that study (PFS) did not reveal a clear delay in the tumour progression for the experimental arm, the longer survival associated with the olaratumab combination treatment supported the granting of a conditional marketing authorisation. The ANNOUNCE (JGDJ) study was then requested as a specific obligation to confirm the efficacy and safety of olaratumab in same population for whom Lartruvo is currently indicated.

Overall, 509 adult patients with advanced or metastatic soft tissue sarcoma not amenable to treatment with surgery or radiotherapy with curative intent (of those 234 were leiomiosarcoma, LMS) were randomized 1:1, stratified by number of prior systemic therapies for advanced/metastatic disease, histological tumour type, and ECOG PS, to the investigational arm (n=258; LMS n=119) with olaratumab plus doxorubicin or the control arm (n=251; LMS n=114) with placebo plus doxorubicin. Doxorubicin was administered for a maximum of 8 cycles every 3 weeks, along with olaratumab/placebo which was continued after 8 cycles until PD, unacceptable toxicity, death, or other withdrawal criteria. Compared to the currently recommended posology of olaratumab (15 mg/kg on days 1 and 8 of each 3 week cycle), a loading cycle of 20 mg/kg on day 1 and day 8 of cycle 1 was used, to minimize the number of patients exposed to sub-therapeutic olaratumab serum levels without an increased risk of toxicity, based on PK and matched case-control analysis by exposure quartiles results. Baseline patient and disease characteristics appeared overall well balanced.

The primary endpoint for this study was OS in the ITT population and in the LMS population. In the ITT population, the median OS was 20.37 months in the investigational arm and 19.75 months in the control arm (HR=1.047 [95% CI: 0.841, 1.303]; p=0.69), and the OS KM curves are completely overlapping, indicating that adding Lartruvo to doxorubicin had no favourable effect on OS. Further OS analyses showed that in most subgroups HR estimates ranged from 0.9 to 1.1, consistent with the overall OS results. No difference was seen in OS in the LMS population either.

There was a significant difference in PFS in the ITT population based on investigator assessment, but in favour of the control arm. The median PFS was 5.42 months in the investigational arm and 6.77 months in the control arm (HR=1.231 [95% CI: 1.009, 1.502]; p=0.042). No significant difference in PFS between the treatment arms in the LMS population was found.

No statistically significant difference in ORR or DCR in the ITT population was observed between the investigational arm and control arms, and both rates favoured the control arm. In the LMS population,

ORR was in favour of the control arm (no statistical significance) and DCR was statistically significant in favour of the control arm.

No difference was observed in any of the other secondary endpoints analysed in the ITT population. The analyses of ANNOUNCE study showed that PDGFR-α status did not have any predictive role of the response to olaratumab in terms of OS or PFS, and that PDGFR-α was a poor prognostic factor, consistently with literature data. With regard to PDGFR-β, no significant association was found between PDGFR-β status and response to olaratumab in terms of OS or PFS. PDGFR-β did not seem to have a clear prognostic role in STS either.

Unfavourable effects

The results of the ANNOUNCE study confirmed the safety profile seen in the previous phase II study.

The rate of TEAE was overall similar in both treatment arms (98.1% vs 99.2%). Nausea, neutropenia and fatigue were the most frequently reported TEAEs. The rate of haematological toxicities (neutropenia, thrombocytopenia, anaemia and febrile neutropenia) and gastrointestinal toxicities (nausea, vomiting and diarrhoea) was balanced between the treatment arms. In addition, the rate of (consolidated) musculoskeletal pain was similar between the 2 treatment arms.

Infusion related reactions, cardiac arrhythmia and cardiac dysfunction are considered events of special interest for olaratumab. The rate of potential immediate (i.e. occurring on the day of infusion) hypersensitivity reactions was higher in the investigational arm for all grade events (11.7% vs. 7.2%) and Grade ≥3 events (2.3% vs 0.8%) but no fatal events were reported. Overall, 6 patients in the investigational vs none in the control arm developed an anaphylactic reaction. All anaphylactic reactions occurred during the first olaratumab infusion. Immediate non-anaphylactic reactions were reported in 9.3% patients and were grade 1/2 in severity.

Cardiac arrhythmia events were more commonly reported in the investigational arm (any grade 12.8% vs 9.6%; grade >=3 2.7% vs 0.8%).

The incidence for all grades of events in the cardiac dysfunction AESI category was 18.3% in the investigational arm and 13.7% in the control arm, the majority being events of peripheral oedema (13.2 vs 9.2%) and oedema (1.2% vs 0%). When excluding the event of oedema not associated with an AE suggestive of cardiac dysfunction or a significant decrease in left ventricular function, the true incidence of cardiac dysfunction was 9.3% in the investigational arm and 6.8% in the control arm. However, this remains higher in the investigational arm.

Few more SAE (38.9% vs 34.9%) occurred in the investigational arm than in the control arm. Febrile neutropenia was the most frequently SAE occurring with similar frequency in both arms (12.8% vs 13.3%). No data on AE adjusted by exposure are available. There are also no data regarding the toxicity observed in subjects in the investigational arm when treated with olaratumab maintenance.

Frequency of patients with TEAE leading to treatment discontinuation was similar in both arms (4.3% vs 4.4%).

A total of 170 (66.1%) vs 158 (63.5%) of patients died in the investigational vs control arm, respectively, mostly attributed to study disease (63.4% vs 61%). Deaths due to adverse events were overall similar in both arms (7[2.7%] vs 6 [2.4%]). Death due to AEs on therapy or within 30 days from the last dose of study drug were 5 (1.9%) vs 3 (1.2%) (investigational arm: pulmonary embolism in 2 subjects, acute respiratory failure, aspiration and pneumonia in one patient each; control arm: cerebrovascular accident, ischemic stroke and sepsis, each in one patient). Of those, 2 TEAE leading to deaths were considered related to study treatment in the investigational arm (pneumonia and aspiration) vs none in the control arm.

Safety analysis by age category (<65 vs >=65 years) showed higher toxicity in older subjects, although this occurred equally in both arms.

The different exposure to doxorubicin between investigational arm and the control group was noted. According to the protocol, doxorubicin 75 mg/m^2 was to be administered (after olaratumab or placebo) on day 1 of cycles 1 to 8 (of 3 weeks each). However, the median duration of doxorubicin treatment was 18 weeks and 23 weeks for the investigational and control groups, respectively. The median of the number of cycles received were higher in the control arm (6 vs 7) and the median of cumulative dose per body surface area (mg/m^2) was also higher for the control group (409 vs 483). These data seem to suggest a different tolerability to doxorubicin depending on the group, which appears to be different from that observed in the previous phase II trial, where the exposure to doxorubicin was higher for patients in the investigational group as compared to the control group (7 vs 4).

Benefit-risk assessment and discussion

In summary, no benefit of adding Lartruvo to doxorubicin in patients with advanced STS was observed in the ANNOUNCE study.

The sample size, conduct of the study, endpoints, statistical methods or randomisation do not seem to explain the discrepancy between ANNOUNCE and the phase II JGDG. The patient disposition of the ANNOUNCE trial does not indicate major differences between arms in reasons for treatment discontinuation. The baseline characteristics appear to be evenly balanced, both in histology and disease at randomization.

All the sensitivity analyses carried out in the ANNOUNCE study, both in the ITT population an in the LMS group, point in the same direction (no favourable effect of olaratumab). The Kaplan-Meier curves for OS are overlapping. The subgroup analyses do not reveal any subgroup of interest where there could be some benefit. Even the post-discontinuation therapy is balanced. The only significant difference found in PFS was in the ITT population, but in favour of the control arm. Neither the exploratory analysis of PDGFR-α expression nor the immunogenicity appear to explain the absence of benefit.

No new safety concerns arose from the ANNOUNCE study.

It seems no single reason can explain the discrepancy in results between phase II JGDG and phase III ANNOUNCE studies. ANNOUNCE as the confirmatory trial was specifically designed to show differences in OS. The strength of the evidence from the phase III ANNOUNCE study is necessarily higher due to higher patient numbers and the blinded design with no cross-over. The heterogeneity could also play a role in the two studies. STS is a disease which encompasses a wide range of different tumour histologies, some of them with different prognosis and specific treatments. It is plausible that a different rate of several histologies between the two studies could have had an impact in the dissimilar efficacy observed.

Overall, the results of the ANNOUNCE study are mature and robust to draw the conclusion that the study showed lack of therapeutic efficacy associated with olaratumab treatment in the authorised indication. Even though no new safety concerns arose from the ANNOUNCE study, any safety concerns associated with olaratumab render the benefit-risk balance of Lartruvo negative in view of the lack of therapeutic efficacy observed in the study. Consequently, as the ANNOUNCE study was imposed as a specific obligation to confirm the efficacy and safety of olaratumab in the authorised indication, the conditional marketing authorisation for Lartruvo should be revoked.

In order to ensure continued supply of Lartruvo to patients who are currently on treatment and who appear, in the opinion of the treating physician, to be benefiting from olaratumab treatment, the MAH proposed that the marketing authorisation is maintained temporarily with amendments to the product

information to reflect that treatment would be reserved for this group of patients. This is however not an option in view of the clear conclusion that the benefit-risk balance is negative. CHMP noted that there are *lex specialis* provisions in the European Union legislation (Article 117(3) of Directive 2001/83/EC) regarding the continuing supply after revocation of the marketing authorisation, should this be considered appropriate by the competent authorities.

4. Grounds for Opinion

Whereas

- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Lartruvo.
- The Committee reviewed the results of the ANNOUNCE (JGDJ) study, which was conducted to fulfil the specific obligation with a view to confirming a favourable benefit-risk balance for the conditional marketing authorisation for Lartruvo, pursuant to Article 14-a of Regulation (EC) No 726/2004.
- The Committee noted that no benefit was observed from adding Lartruvo to doxorubicin in the treatment of patients with advanced soft tissue sarcoma, when compared to doxorubicin alone.
- The Committee, as a consequence, concluded that Lartruvo lacks therapeutic efficacy and that the benefit-risk of Lartruvo is not favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommends the revocation of the marketing authorisation for Lartruvo.