# A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Doxorubicin plus Olaratumab versus Doxorubicin plus Placebo in Patients with Advanced or Metastatic Soft Tissue Sarcoma

Published: 26-08-2015
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The primary objective is to compare doxorubicin plus olaratumab versus doxorubicin plus placebo with respect to OS in patients with advanced or metastatic soft tissue sarcoma (STS) or advanced or metastatic leiomyosarcoma (LMS), not amenable to...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Soft tissue neoplasms malignant and unspecified |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON47908

**Source**
ToetsingOnline

**Brief title**
I5B-MC-JGDJ (ANNOUNCE)

### Condition

- Soft tissue neoplasms malignant and unspecified

**Synonym**
Advanced or Metastatic Soft Tissue Sarcoma / Soft Tissue Sarcoma

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Eli Lilly
**Source(s) of monetary or material Support:** tbd

## Intervention

**Keyword:** Antibody Olaratumab, Doxorubicin, PDGFR&alfa, Soft Tissue Sarcoma

## Outcome measures

### Primary outcome

Efficacy: Overall survival (time from randomization to death) is the primary

per-patient measure for efficacy.

### Secondary outcome

Efficacy:

Radiographic assessments will be performed according to Response Evaluation

Criteria in Solid Tumors (Response Evaluation Criteria in Solid Tumors

[RECIST], Version 1.1) criteria, will be performed every 6 weeks (±7 days)

until radiographic documentation of PD.

The following additional efficacy measures will be determined for each patient,

with planned statistical analyses specified in Section 12 of the Protocol. *

Progression-free survival (PFS)

Objective Response Rate (ORR)

Disease Control Rate (DCR)

Time to first worsening of the mBPI-sf (Brief Pain Inventory Short Form

Modified) *worst pain* score

Duration of disease control (DDC)

Time to any progression (censoring for death without progression)

Time to any new metastases (censoring for death and for other type of PD)

New-metastases-free survival (nMFS)

Time to any progression based solely on increased sum of target lesions

Time to first worsening of the QLQ-C30 scale scores (for example, Global Health Status / Quality of Life score, Physical Functioning score, and Role Functioning score)

Time to first worsening of ECOG performance status

Second PFS (PFS2) after end of study treatment while on subsequent anticancer therapy

Safety:

Safety will be evaluated based on reported adverse events (AEs), physical examinations, vital signs, laboratory tests, electrocardiograms (ECGs), and results from echocardiograms (ECHOs) or multigated acquisition (MUGA) scans. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRATM) and graded using the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0. Clinical laboratory toxicity will be graded using NCI-CTCAE criteria, Version 4.0.

Patient-Reported Outcomes (PROs):

Pain will be assessed with the Brief Pain Inventory Short Form Modified [mBPI-sf], HRQoL will be assessed with The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 version 3.0

[EORTC QLQ-C30] and health state will be assessed with the EuroQol 5-Dimension 5-Level [EQ-5D-5L]. Patients will complete the instruments on Day 1 of every cycle and at the 30-day short-term follow-up visit. A full due diligence will be taken to collect PRO measures during long-term follow-up (every 6 weeks [±7 days] until PD, thereafter every 2 months [±7 days] for the first 2 years, then every 6 months [±14 days] until the patient*s death or overall study completion).

Immunogenicity:

Blood samples will be collected to determine olaratumab antibodies in serum at baseline, during the study, and in the event of an olaratumab/placebo infusion-related reaction (IRR) serum will be collected as soon as possible after the onset, at the resolution, and 30 days (±3 days) after the IRR.

Pharmacokinetics:

Blood samples will be collected to assess the serum concentrations of olaratumab and the plasma concentration of doxorubicin. Serum concentrations of olaratumab will be assayed using a validated enzyme-linked immunosorbent assay (ELISA) method. Doxorubicin concentrations in plasma will be analyzed using a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) assay.

Biomarkers:

Samples will be collected and analyses will be performed on biomarkers relevant to pathways associated with STS, the mechanism of action of olaratumab or

doxorubicin, and/or cancer-related conditions, and may also be used for related

research methods. The evaluation of the samples may involve analysis of DNA,

RNA, and/or proteins.

# Study description

### Background summary

Olaratumab is a recombinant human immunoglobulin G subclass 1 (IgG1)-type monoclonal antibody that binds to platelet-derived growth factor receptor (PDGFR)α.

Previously reported data support the molecule being advanced in human trials, including the Sponsor*s Phase 1b/2 trial, titled *A Phase 1b/2 Randomized Phase 2 Study Evaluating the Efficacy of Doxorubicin With or Without a Human Anti-PDGFRα Monoclonal Antibody (IMC-3G3) in the Treatment of Advanced Soft Tissue Sarcoma.* (studyI5B-MC-JGDG)
The primary analysis of this trial (based on 103 PFS events observed as of the 15 August 2014 cutoff date) showed a statistically significant improvement in PFS over doxorubicin alone. The median PFS was 28.6 weeks for the investigational arm and 18.0 weeks for the control arm. At the time of the primary analysis, an interim analysis of OS (based on 83 events) showed an improvement (HR=0.44; p = 0.0005) with a median of
64.0 weeks on the control arm compared to 108.7 weeks for the combination.

The proposed study, Study I5B-MC-JGDJ (JGDJ), is a Phase 3 trial to assess the efficacy and safety of olaratumab in combination with doxorubicin for the treatment of advanced or metastatic STS that is not amenable to treatment with surgical resection or radiotherapy with
curative intent. Study JGDJ has been designed to confirm the results of Study JGDG. The study design has been discussed with global regulatory agencies, including the Committee for Medicinal Products for Human Use (CHMP).

### Study objective

The primary objective is to compare doxorubicin plus olaratumab versus doxorubicin plus placebo with respect to OS in patients with advanced or metastatic soft tissue sarcoma (STS) or advanced or metastatic leiomyosarcoma (LMS), not amenable to treatment with surgery or radiotherapy with curative intent.

The secondary objectives of the study are to compare doxorubicin plus

olaratumab versus doxorubicin plus placebo
with respect to progression-free survival, objective response rate, disease control rate, patient-reported outcomes (Pain, Health-related Quality of Life, and health status), duration of disease control, safety and tolerability, and pharmacokinetics (PK) and immunogenicity.

**Study design**

Study I5B-MC-JGDJ is a global, multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 trial that will compare the efficacy and safety in patients with advanced or metastatic STS treated with doxorubicin (75 mg/m2 on Day 1) plus olaratumab (loading dose of 20 mg/kg on Days 1 and 8 in Cycle 1, followed by 15 mg/kg on Days 1 and 8 in subsequent cycles) versus doxorubicin (75 mg/m2 on Day 1) plus placebo (on Days 1 and 8) in a 21-day cycle.

The study will enroll 460 patients in 1:1 randomization (230 patients in the investigational arm
and 230 patients in the control arm). Enrollment will be conducted so that approximately
200 patients with LMS and 260 patients with other (non-LMS) histology will be randomized.

Eligible patients will be randomized 1:1 into the 2 treatment options and stratified as follows:
• Number of prior systemic therapies for advanced/metastatic disease (0 versus >=1)
Note: Any therapy administered in the adjuvant/neoadjuvant setting will not be considered as a prior line of therapy here.
• Histological tumor type (leiomyosarcoma versus liposarcoma versus pleomorphic versus other STS types)
• Eastern Cooperative Oncology Group performance status (ECOG PS) (0 versus 1)
• Region (North America versus Europe versus Rest of World [ROW])
• Patients will receive combination treatment for 8 cycles followed by monotherapy olaratumab or placebo until evidence of progressive disease (PD), unacceptable toxicity, death, or other withdrawal criteria are met. No crossover will be permitted.

**Intervention**

Eligible patients will be randomized 1:1 into 1 of 2 treatment options (olaratumab plus
doxorubicin or placebo plus doxorubicin).

Patients assigned to the investigational arm will receive 2 loading doses of olaratumab at 20 mg/kg on Days 1 and 8 in Cycle 1 followed by doxorubicin 75

mg/m2 IV on Day 1 of a 21-day cycle, then 15 mg/kg IV on Days 1 and 8 followed by doxorubicin 75 mg/m2 IV on Day 1 of a 21-day cycle in all subsequent cycles. Patients assigned to the control arm will receive placebo (equivalent volume) IV on Days 1 and 8 followed by doxorubicin 75 mg/m2 IV on Day 1 of a 21-day cycle.

Patients will receive combination treatment for 8 cycles, followed by monotherapy olaratumab or placebo until evidence of progressive disease (PD), unacceptable toxicity, death, or other withdrawal criteria are met. No crossover will be permitted.

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

**Study burden and risks**

The Investigational Product and other medication required by Protocol and the study procedures are associated with certain risks and discomforts, as described in the patient information leaflet. The combination of experimental medicine (olaratumab), chemotherapy and study procedures may be associated with additional risks or discomforts that at this point are not fully known.

Olaratumab in combination with doxorubicin has been administered to 455 patients. Safety data from 257 patients of the study JGDJ are not included, since the study was blinded as of 19 October 2018 and the analysis of the data is ongoing. Patients treated with olaratumab may experience the side effects listed for olaratumab given alone.

Given the fact that this specific group of patients has, on average, a limited life expectancy, current treatment options are limited and this therapy is aimed at establishing the potential use in this specific group of patients, this study would be justified.

# Contacts

**Public**
Eli Lilly

Island House, 11 Eastgate Business Park, Little Island,
Cork T45KD39

IE
**Scientific**
Eli Lilly

Island House, 11 Eastgate Business Park, Little Island,
Cork T45KD39
IE

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

Patients are eligible to be included in the study only if they meet all of the following criteria:
[1] The patient signed an ICF and authorization for release of health information for research prior to any study-specific procedures being performed.
[2] The patient is aged >= 18 years at study entry.
[3] The patient has histologically confirmed diagnosis of locally advanced unresectable or metastatic STS not amenable to curative treatment with surgery or radiotherapy. Patients with a diagnosis of Grade 1 liposarcoma are eligible if there is histological or radiographic evidence of evolution to more aggressive disease. Patients with Kaposi*s sarcoma and gastrointestinal stromal tumors (GIST) will be excluded. Note: Evidence of disease progression is required for patients that are not newly diagnosed.
[4] The patient has measurable or nonmeasurable but evaluable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1, Eisenhauer et al. 2009; refer to Attachment 6 of the Protocol). Tumors within a previously irradiated field will be designated
as *nontarget* lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiotherapy.
[5] The patient has a performance status 0-1 on the Eastern Cooperative Oncology Group (ECOG) scale (refer to Attachment 4 of the Protocol).
[6] The patient has not received any previous treatment with anthracyclines.
[7] The patient may have had any number of prior systemic cytotoxic therapies for

advanced/metastatic disease and are considered appropriate candidates for anthracycline therapy. All previous anticancer treatments must be completed >= 3 weeks (21 days) prior to first dose of study drug.
[8] The patient has resolution of adverse events and of all clinically significant toxic effects of prior locoregional therapy, surgery, radiotherapy, or systemic anticancer therapy to <= Grade 1, by National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0.
[9] Availability of tumor tissue is mandatory for study eligibility. The patient must have consented to provide archived formalin-fixed paraffin embedded (FFPE) tumor tissue or be subject to a pre-treatment re-biopsy of primary or metastatic tumor tissue for future central pathology review and translational research (if archived tissue is unavailable) (refer to Section 10.4.2.3 of the Protocol regarding tissue collection parameters).
[10] The patient has adequate hematologic, organ, and coagulation function within 2 weeks (14 days) prior to randomization:
• Absolute neutrophil count (ANC) >=1.5 x 109/L. Granulocyte colony-stimulating factor (G-CSF) cannot be administered within 2 weeks (14 days) prior to randomization.
• Platelet count >=100 x 109/L
• Hemoglobin >=9.0 g/dL. No transfusions are allowed within 2 weeks (14 days) prior to randomization.
• The creatinine clearance is >=45 mL/min (refer to Attachment 5 for the Cockcroft-Gault formula)
Proteinuria <=1000 mg in 24 hours (if routine urinalysis indicates >=2+ proteinuria)
• Total bilirubin below upper limit of normal (ULN) (except for patients with Gilbert*s Syndrome, who must have a total bilirubin <3 mg/dL)
• Alanine aminotransferase/aspartate aminotransferase (AST/ALT) <= 3.0 × ULN; if the liver has tumor involvement, AST and ALT <=5.0 × ULN are acceptable.
• The patient has an adequate coagulation function as defined by International Normalized Ratio (INR) or prothrombin time (PT) <=1.5 x ULN, and partial thromboplastin time (PTT or aPTT) <=1.5 x ULN if not receiving anticoagulation therapy. For patients receiving anticoagulants, exceptions to these coagulation parameters are allowed if they are within the intended or expected range for their
therapeutic use. Patients must have no history of active bleeding (defined as within 14 days of first dose of study drug) or pathological condition that carries a high risk of bleeding (for example, tumor involving major vessels or known esophageal varices).
[11] The patient has left ventricular ejection fraction (LVEF) >=50% assessed within 28 days prior to randomization.
[12] Females of child-bearing potential must have a negative serum pregnancy test within 7 days prior to randomization.
(a) Exceptions: Females not of child-bearing potential due to surgical sterilization (at least 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by medical history or menopause.
A *postmenopausal woman* is a woman meeting either of the following criteria:
• spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications during the amenorrhea that induced the amenorrhea (for example, oral contraceptives,

hormones, gonadotropin releasing hormone, antiestrogens, selective estrogen receptor modulators (SERMs), or chemotherapy
• spontaneous amenorrhea for 6 to 12 months and a follicle-stimulating hormone (FSH) level >40 mIU/mL
[13] Females of child-bearing potential and males and must agree to use highly effective contraceptive precautions during the trial and up to 6 months following the last dose of study drug. A highly effective method of birth control is defined as one that results in a low failure rate (that is, <1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices (IUDs), sexual abstinence, or a vasectomized partner.
[14] The patient has, in the opinion of the investigator, a life expectancy of at least 3 months.

## Exclusion criteria

Patients will be excluded from the study if they meet any of the following criteria:
[15] The patient is diagnosed with GIST or Kaposi sarcoma.
[16] The patient has active central nervous system (CNS) or leptomeningeal metastasis (brain metastasis) at the time of randomization. Patients with a history of a CNS metastasis previously treated with curative intent (for example, stereotactic radiation or surgery) that have not progressed on follow-up imaging, have been asymptomatic for at least 60 days and are not receiving systemic corticosteroids and or/anticonvulsants, are eligible. Patients with signs or symptoms of neurological compromise should have appropriate radiographic imaging performed before randomization to rule out brain metastasis.
[17] The patient has received prior treatment with doxorubicin, epirubicin, idarubicin, and/or other anthracyclines or anthracenediones; the patient has received prior treatment with olaratumab or has participated in a prior olaratumab trial.
[18] The patient had prior radiotherapy of the mediastinal/pericardial area or whole pelvis radiation.
[19] The patient has history of another primary cancer, with the exception of a) curatively treated non-melanomatous skin cancer, b) curatively treated cervical carcinoma in situ, c) other primary non-hematologic malignancies or solid tumor treated with curative intent, no known active disease and no treatment administered during the last 3 years prior to randomization.
[20] The patient has electively planned or will require major surgery during the course of the study.
[21] The patient has uncontrolled intercurrent illness including, but not limited to, an ongoing/active infection requiring parenteral antibiotics, symptomatic congestive heart failure (CHF), left ventricular dysfunction (LVEF < 50%), severe myocardial insufficiency, cardiac arrhythmia, cardiomyopathy, or a psychiatric illness/social situation that would limit compliance with study requirements.
[22] The patient has unstable angina pectoris, angioplasty, cardiac stenting, or myocardial infarction within 6 months of randomization.
[23] DELETED

[24] The patient has a QTcB interval of >450 msec for males and >470 msec for females on screening electrocardiogram (ECG) utilizing Bazett*s correction (refer to formula in Table JGDJ.8 of the Protocol).
[25] Females who are pregnant or breastfeeding
[26] The patient has a known allergy to any of the treatment components including a history of allergic reactions attributed to compounds of chemical or biological composition similar to olaratumab.
[27] The patient is enrolled in, or discontinued study treatment from another trial involving an investigational agent or use of non-approved drug or device within 28 days of being randomized in this trial, or concurrent enrollment in any other type of medical research judged scientifically or medically incompatible with this trial. Patients participating in surveys or observational studies are eligible to participate in this study.
[28] DELETED.
[29] The patient has a known investigator-assessed active fungal, bacterial, or viral infection including
human immunodeficiency virus (HIV) or viral (A, B, or C) hepatitis (screening is not required).

# Study design

## Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 31-12-2015 |
| Enrollment: | 15 |
| Type: | Actual |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Olaratumab |
| Generic name: | Olaratumab |

## Ethics review

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|---|---|
| Approved WMO Date: | 26-08-2015 |
| Application type: | First submission |
| Review commission: | METC Isala Klinieken (Zwolle) |
| Approved WMO Date: | 13-11-2015 |
| Application type: | First submission |
| Review commission: | METC Isala Klinieken (Zwolle) |
| Approved WMO Date: | 04-12-2015 |
| Application type: | Amendment |
| Review commission: | METC Isala Klinieken (Zwolle) |
| Approved WMO Date: | 12-01-2016 |
| Application type: | Amendment |
| Review commission: | METC Isala Klinieken (Zwolle) |
| Approved WMO Date: | 06-04-2016 |
| Application type: | Amendment |
| Review commission: | METC Isala Klinieken (Zwolle) |
| Approved WMO Date: | 22-04-2016 |
| Application type: | Amendment |
| Review commission: | METC Isala Klinieken (Zwolle) |
| Approved WMO Date: | 19-07-2016 |
| Application type: | Amendment |
| Review commission: | METC Isala Klinieken (Zwolle) |

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| Approved WMO Date: | 24-10-2016 |
| Application type: | Amendment |
| Review commission: | METC Isala Klinieken (Zwolle) |
| Approved WMO Date: | 02-02-2017 |
| Application type: | Amendment |
| Review commission: | METC Isala Klinieken (Zwolle) |
| Approved WMO Date: | 17-02-2017 |
| Application type: | Amendment |
| Review commission: | METC Isala Klinieken (Zwolle) |
| Approved WMO Date: | 18-04-2017 |
| Application type: | Amendment |
| Review commission: | METC Isala Klinieken (Zwolle) |
| Approved WMO Date: | 04-08-2017 |
| Application type: | Amendment |
| Review commission: | METC Isala Klinieken (Zwolle) |
| Approved WMO Date: | 04-09-2017 |
| Application type: | Amendment |
| Review commission: | METC Isala Klinieken (Zwolle) |
| Approved WMO Date: | 18-06-2018 |
| Application type: | Amendment |
| Review commission: | METC Isala Klinieken (Zwolle) |
| Approved WMO Date: | 06-07-2018 |
| Application type: | Amendment |
| Review commission: | METC Isala Klinieken (Zwolle) |
| Approved WMO Date: | 19-10-2018 |
| Application type: | Amendment |
| Review commission: | METC Isala Klinieken (Zwolle) |
| Approved WMO | |

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|---|---|
| Date: | 15-11-2018 |
| Application type: | Amendment |
| Review commission: | METC Isala Klinieken (Zwolle) |
| Approved WMO Date: | 11-02-2019 |
| Application type: | Amendment |
| Review commission: | METC Isala Klinieken (Zwolle) |
| Approved WMO Date: | 21-03-2019 |
| Application type: | Amendment |
| Review commission: | METC Isala Klinieken (Zwolle) |
| Approved WMO Date: | 02-04-2019 |
| Application type: | Amendment |
| Review commission: | METC Isala Klinieken (Zwolle) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2015□000134□30-NL |
| CCMO | NL54366.075.15 |

# Study results

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| Date completed: | 08-02-2019 |

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|---|---|
| Results posted: | 12-10-2020 |
| Actual enrolment: | 16 |

**First publication**
04-03-2019