# A Multicenter, Randomized, Open-Label Phase 3 Study to Investigate the Efficacy and Safety of Aldoxorubicin Compared to Investigator*s Choice in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcomas Who Either Relapsed or Were Refractory to Prior Non-Adjuvant Chemotherapy

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The primary objective of this study is to determine the efficacy of administration of aldoxorubicin compared to investigator*s choice of treatment in subjects with metastatic, locally advanced, or unresectable soft tissue sarcomas who have relapsed...

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| **Ethical review** | Approved WMO |
| **Status** | Will not start |
| **Health condition type** | Soft tissue neoplasms malignant and unspecified |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON40874

**Source**
ToetsingOnline

**Brief title**
ALDOXORUBICIN-P3-STS-01

### Condition

- Soft tissue neoplasms malignant and unspecified

**Synonym**
soft tissue tumors; soft tissue sarcoma

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** PRA Group BV
**Source(s) of monetary or material Support:** CytRx Corporation

## Intervention

**Keyword:** Aldoxorubicin, Refractory, Relapsed, Soft Tissue Sarcomas

## Outcome measures

### Primary outcome

The primary objective of this study is to determine the efficacy of administration of aldoxorubicin compared to investigator*s choice of treatment in subjects with metastatic, locally advanced, or unresectable soft tissue sarcomas who have relapsed or were refractory to prior non-adjuvant chemotherapy, as measured by progression-free survival (PFS).

### Secondary outcome

The secondary objectives of this study are to evaluate the efficacy of aldoxorubicin as measured by OS, safety of aldoxorubicin compared to investigator*s choice in this population assessed by the frequency and severity of adverse events (AEs), abnormal findings on physical examination, laboratory tests, vital signs, echocardiogram (ECHO) evaluations, electrocardiogram (ECG) results, and weight, as well as disease control rate, and tumor response.

The exploratory objectives are to determine the PK of aldoxorubicin,

doxorubicin, and doxorubicinol following IV administration of aldoxorubicin,

and to evaluate the exposure-response relationships between aldoxorubicin,

doxorubicin, and/or doxorubicinol and PFS, OS, and selected safety parameters,

and quality of life.

# Study description

### Background summary

Aldoxorubicin (INNO-206; DOXO-EMCH) is a novel prodrug that binds covalently to circulating albumin. The drug is accumulated in tumors and doxorubicin is released in the tumor by cleaving the acid labile linker (EMCH) in the low pH tumor environment. This carrier-linked prodrug has demonstrated enhanced antitumor activity with reduced toxicity in several murine models when compared with free doxorubicin.
Patients with metastatic, locally advanced, or unresectable soft tissue sarcomas who have failed prior chemotherapies have a poor prognosis with PFS of around 2-4.6 months and median OS of approximately 9-12 months. Several chemotherapy regimens have been explored as palliative therapy for subjects with these patients and include such agents as ifosfamide, gemcitabine, docetaxel, vinorelbine, dacarbazine, temozolomide, epirubicin, pazopanib and liposomal doxorubicin. However, these regimens can be quite toxic and have not significantly impacted either progression-free or OS in these individuals. Pazopanib, recently approved in the US and Europe, does appear to extend PFS in soft tissue sarcoma patients (except liposarcomas) who have relapsed after receiving prior chemotherapy compared to no treatment, but does not increase OS. Aldoxorubicin may improve upon the activity of doxorubicin without an increase in toxicity as has been demonstrated in animal studies.

### Study objective

The primary objective of this study is to determine the efficacy of administration of aldoxorubicin compared to investigator*s choice of treatment in subjects with metastatic, locally advanced, or unresectable soft tissue sarcomas who have relapsed or were refractory to prior non-adjuvant chemotherapy, as measured by progression-free survival (PFS).

and

The secondary objectives of this study are to evaluate the efficacy of

aldoxorubicin as measured by OS, safety of aldoxorubicin compared to investigator*s choice in this population assessed by the frequency and severity of adverse events (AEs), abnormal findings on physical examination, laboratory tests, vital signs, echocardiogram (ECHO) evaluations, electrocardiogram (ECG) results, and weight, as well as disease control rate, and tumor response.

and

The exploratory objectives are to determine the PK of aldoxorubicin, doxorubicin, and doxorubicinol following IV administration of aldoxorubicin, and to evaluate the exposure-response relationships between aldoxorubicin, doxorubicin, and/or doxorubicinol and PFS, OS, and selected safety parameters, and quality of life.

**Study design**

This is a phase 3 open-label study evaluating the efficacy and safety of aldoxorubicin administered at 350 mg/m2 (260 mg/m2 doxorubicin equivalent) intravenously on Day 1 every 21 days until tumor progression or unacceptable toxicity occurs compared to investigator*s choice of treatment among 5 different therapies. These therapies include: 1) dacarbazine administered at 1000 mg/m2 by intravenous infusion (IVI), over 90±15 minutes on Day 1 every 21 days until tumor progression or unacceptable toxicity occurs; 2) pazopanib, 800 mg orally each day until tumor progression or unacceptable toxicity occurs; 3) gemcitabine, 900 mg/m2 by IVI in less than 60 minutes on Days 1 and 8, plus docetaxel, 100 mg/m2 by IVI over 1 hour on Day 8 of a 21 day cycle until tumor progression or unacceptable toxicity occurs; 4) doxorubicin, 75 mg/m2 by IVI over 5 to 30 minutes every 21 days for a maximum cumulative dose of 550 mg/m2 or unacceptable toxicity occurs; or 5) ifosfamide 2.0 g/m2 administered over 2 to 4 hours on Days 1-4 of a 21 day cycle + mesna per standard site administration regimen until tumor progression or unacceptable toxicity occurs. The investigative site must pre-specify their choice of treatments for the comparator arm to be used at their site, and no more than 3 treatment regimens may be selected for the comparator arm at each site which must be selected prior to the study site initiation visit. Subjects will be randomized 1:1 to receive either aldoxorubicin or investigator*s choice of up to 3 control regimens pre-selected by the study site. Pretreatment with G-CSF is permitted according to ASCO Guidelines.

**Intervention**

site bezoeken, toediening van studie medicatie, het invullen van een patientendagboekje en tijdens de gehele onderzoeksperiode: lichamelijk onderzoek, Echo, ECG, CT-scan/MRI, vitale functies meten en bloed- en urinemonsters verstrekken

study visits, administration of study drugs, completion of patient diaries and for the entire duration of the study; physical examination, Echo, ECG, CT-scan/MRI, blood draw and collection of urine samples

**Study burden and risks**

Possible side effects of Aldoxorubicine, doxorubicine, doxorubicinol, dacarbazine, pazopanib (Votrient), gemcitabine, docetaxel, ifosfamide. Risks related to blood draw, ECG, Echo, infusion, CT-scans/MRI

## Contacts

**Public**
PRA Group BV

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NL
**Scientific**
PRA Group BV

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## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

**Age**
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1. Has provided written informed consent prior to any study related activities.
2. Age *15 years (US only), and 18-80 (rest of world (ROW)), male or female.
3. Histological confirmation of intermediate or high grade soft-tissue sarcoma. Tissue must be sent to a central pathology lab for review but will not preclude entry onto the study. Final assignment of tumor grade and histology will be based on the designation provided by the central pathology review.
4. An adequate tumor specimen obtained by either excisional biopsy, incisional biopsy or core needle biopsy must be sent to the central pathology lab for evaluation. The material must measure at least 0.8 × 0.1 cm in size or contain at least 50 tumor cells.
5. Locally advanced, unresectable, and/or metastatic soft-tissue sarcoma of intermediate or high grade with evidence of disease progression by either computed tomography (CT) or magnetic resonance imaging (MRI) scan, or clinical judgment on or after the last cancer therapy within 6 months prior to randomization.
6. Relapsed or refractory (lack of response) to *1 course of systemic therapy regimen(s), excluding adjuvant or neoadjuvant chemotherapy, and is incurable by either surgery or radiation.
7. Capable of providing informed consent and complying with trial procedures.
8. ECOG PS 0-2.
9. Life expectancy >12 weeks.
10. Measurable tumor lesions according to RECIST 1.1 criteria.[50]
11. Women must not be able to become pregnant (e.g., post-menopausal for at least 1 year, surgically sterile, or practicing adequate birth control methods) for the duration of the study. (Adequate contraception includes: oral contraception, implanted contraception, intrauterine device implanted for at least 3 months, or barrier method in conjunction with spermicide.)
12. Males and their female partner(s) of child-bearing potential must use 2 forms of effective contraception (see Inclusion 11 plus condom or vasectomy for males) from the last menstrual period of the female partner during the study treatment and agree to continue use for 6 months after the final dose of study treatment.
13. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
14. Accessibility to the site that optimizes the subject*s ability to keep all study-related appointments.

## Exclusion criteria

1. Prior exposure to >375 mg/m2 of doxorubicin or liposomal doxorubicin.
2. Palliative surgery and/or radiation treatment within 30 days prior to date of randomization.
3. Exposure to any investigational agent within 30 days of date of randomization.
4. Exposure to any systemic chemotherapy within 30 days of date of randomization.
5. An inadequate tumor specimen as defined by the central pathologist.
6. Current evidence/diagnosis of alveolar soft part sarcoma, extraskeletal myxoid chondrosarcoma, rhabdomyosarcoma, osteosarcoma, gastrointestinal stromal tumor (GIST),

dermatofibrosarcoma (unless transformed to fibrosarcoma), Ewing*s sarcoma, Kaposi*s sarcoma, mixed mesodermal tumor, clear cell sarcomas.
7. Evidence of central nervous system (CNS) metastasis who have not received prior definitive therapy for their lesions.
8. History of other malignancies except cured basal cell carcinoma, cutaneous squamous cell carcinoma, melanoma in situ, superficial bladder cancer or carcinoma in situ of the cervix unless documented free of cancer for *5 years.
9. Laboratory values: Screening serum creatinine >1.5 x upper limit of normal (ULN), alanine aminotransferase (ALT) >3×ULN or >5×ULN if liver metastases are present, total bilirubin >2×ULN, absolute neutrophil count (ANC) <1,500/mm3, platelet concentration <100,000/mm3, hemoglobin
<9 g/dL.
10. Clinically evident congestive heart failure (CHF) > class II of the New York Heart Association (NYHA) (Appendix D) guidelines.
11. Current, serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V (Appendix F).
12. Baseline QTc >470 msec and/or previous history of QT prolongation while taking other medications.
13. Concomitant use of medications associated with a high incidence of QT prolongation is not allowed (Appendix G).
14. History or signs of active coronary artery disease with or without angina pectoris within the last 6 months.
15. Serious myocardial dysfunction defined by ECHO as absolute left ventricular ejection fraction (LVEF) below the institution*s lower limit of predicted normal.
16. Known history of HIV infection.
17. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or
anti-fungals. The Medical Monitor should be contacted for any uncertainties.
18. Major surgery within 30 days prior to date of randomization.
19. Current or past substance abuse or any condition that might interfere with the subject*s participation in the study or in the evaluation of the study results.
20. Any condition that is unstable and could jeopardize the subject*s participation in the study.

# Study design

## Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |

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| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Will not start |
| Enrollment: | 4 |
| Type: | Anticipated |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Aldoxorubicin |
| Generic name: | - |
| Product type: | Medicine |
| Brand name: | Dacarbazine |
| Generic name: | - |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Doxetaxel |
| Generic name: | - |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Gemcitabine |
| Generic name: | - |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Votrient |
| Generic name: | - |
| Registration: | Yes - NL intended use |

# Ethics review

Approved WMO

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|---|---|
| Date: | 17-06-2014 |
| Application type: | First submission |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |
| Approved WMO Date: | 25-09-2014 |
| Application type: | First submission |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |
| Approved WMO Date: | 25-11-2014 |
| Application type: | Amendment |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |
| Approved WMO Date: | 05-12-2014 |
| Application type: | Amendment |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |
| Approved WMO Date: | 19-03-2015 |
| Application type: | Amendment |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |
| Approved WMO Date: | 23-09-2015 |
| Application type: | Amendment |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |
| Approved WMO Date: | 16-10-2015 |
| Application type: | Amendment |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |
| Approved WMO Date: | 27-10-2015 |
| Application type: | Amendment |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |

## 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 | EUCTR2013-004103-40-NL |
| ClinicalTrials.gov | NCT02049905 |
| CCMO | NL48870.058.14 |