Sarcomas and DDR-Inhibition; a neoadjuvant phase I combined modality study - SADDRIN-1

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This study has been transitioned to CTIS with ID 2024-514907-32-00 check the CTIS register for the current data. To assess the safety and tolerability profile, in the pre- and perioperative period (up to 30 days post-surgery), of combined modality...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Musculoskeletal and connective tissue neoplasms
Study type	Interventional

Summary

ID

NL-OMON56068

Source
ToetsingOnline

Brief title
SADDRIN-1

Condition

- Musculoskeletal and connective tissue neoplasms
- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
sarcomas, soft tissue sarcomas

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Astra Zeneca,AstraZeneca

Intervention

Keyword: DDR inhibitors, radiotherapy, sarcomas, soft tissue sarcomas

Outcome measures

Primary outcome

To study the safety and tolerability profile in the pre- and perioperative period (up to 30 days post-surgery), treating newly diagnosed, non-metastatic soft tissue sarcoma patients, by AZD1390-based CMT, with respect to systemic toxicities as well as to wound healing post-surgery and to establish a RP2D for further investigations.

Secondary outcome

n.a.

Study description

Background summary

Despite improvements in surgery and radiation for soft tissue sarcoma (STS) patients, local relapses remain an important event for these patients. Most STS subtypes are considered radioresistant and immune cold tumor due to a lack of T-cell infiltration. Investigations into radiosensitization mediated by combining systemic compounds with neoadjuvant radiotherapy may translate into an increased rate of pathological responses, increased T-cell infiltration, an increased rate of R0 resections, and thus fewer local relapses.

Radiotherapy is highly potent in inducing DNA damage. Normal cells are usually sufficiently able to repair this damage timely before the next fraction because of an intact DNA Damage Response (DDR) pathway. Frequently, tumor cells have (partial or complete) defects in the DDR pathways rendering them more sensitive to radiation than normal tissues. Inhibition of constituents of the DDR pathways may further widen the therapeutic window of fractionated radiotherapy, and combined with radiotherapy may result in increased tumor T-cell infiltration, creating an opportunity for immunotherapy. Clinical studies into radiosensitization of STS by combinations of radiotherapy and DDR inhibitors with or without immunotherapy are warranted. In this study the DDR candidate

inhibitor is new drug candidate AZD1390 targeting ATM (Ataxia Telangiectasia Mutated). The immunotherapy candidate of this study is durvalumab (MEDI4736) targeting PD-L1 (programmed death-ligand 1).

Study objective

This study has been transitioned to CTIS with ID 2024-514907-32-00 check the CTIS register for the current data.

To assess the safety and tolerability profile, in the pre- and perioperative period (up to 30 days post-surgery), of combined modality treatment (CMT) by administering AZD1390 with or without anti PD-L1 checkpoint inhibition and radiotherapy concurrently treating newly diagnosed, non-metastatic soft tissue sarcoma patients with AZD1390-based CMT, in the specific context of systemic toxicities, wound healing post-surgery and in defining the RP2D for the combinations to support further clinical evaluation.

Study design

A prospective phase 1 clinical study investigating AZD1390 + radiotherapy or AZD1390 + radiotherapy and durvalumab, where the dose of AZD1390 will be dose escalated, the dose of radiotherapy remains fixed at 25 x 2 Gy, and the dose of durvalumab remains fixed at 1,500 mg Q4W.

Intervention

Preoperative radiotherapy to a total dose of 25 x 2 Gy, in an overall treatment time of five weeks in combination with either dose-escalated AZD1390 or dose-escalated AZD1390 combined with a fixed dose of durvalumab followed by surgery. Both radiotherapy and surgery are not investigational interventions in this study; they are standard of care.

Study burden and risks

Patients will be exposed to both the local and systemic toxicities of the combinations of radiotherapy with either AZD1390 or AZD1390 plus durvalumab. Patients may experience wound complications after surgery. Patients may potentially benefit from higher control rates should AZD1390 exhibit radiosensitization properties and/or enhance the susceptibility of sarcomas to anti PD-L1 immunotherapy and may potentially benefit from higher control rates as a result of PD-L1 immunotherapy.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Histologically confirmed newly diagnosed intermediate to high grade soft tissue sarcoma localized to the extremities or trunk- and chest wall, for which the standard treatment is a combination of and RT and surgery (deep seated and/or > 5cm in largest tumor diameter and/or an anticipated close resection margin and/or grade II/III according to the FNCLCC definition);
• Patients staged by at least a CT scan of the chest (and a CT scan of the abdomen, if deemed indicated according to local practices, e.g. in case of a myxoid liposarcoma). Staging may also be performed by FDG-PET scanning and or total body MRI scans. This staging procedure should not reveal metastatic disease. If, however, a low metastatic burden is detected such that this does not preclude the application of both preoperative RT and definitive surgery, patients are allowed to participate;

• WHO Performance Status <= 2;
• Able and willing to undergo preoperative RT;
• Able and willing to undergo definitive surgery;
• Able and willing to comply with regular follow-up visits;
• Able and willing to swallow and retain oral medication;
• Age >= 18 years;
• Body weight >30kg;
• Must have a life expectancy of at least 12 weeks;
• Adequate organ function as defined in Table 4
• Signed written informed consent prior to any study specific procedures or sampling

Exclusion criteria

Pathological diagnosis
• Patients with any type soft tissue sarcoma located above the clavicles;
• Patients with recurrent sarcomas who underwent prior radiotherapy to the target lesion (if the primary sarcoma was managed by surgery only and no perioperative radiotherapy, patients are eligible);
• Ewing sarcoma and other PNET family tumors, rhabdomyosarcomas (both pediatric and adult), bone sarcomas;

Concurrent therapies
• Neoadjuvant chemotherapy to be scheduled between end of radiotherapy and definitive surgery is not allowed. (neoadjuvant chemotherapy before start of study radiotherapy is allowed);
• Intention to perform an isolated limb perfusion, instead of a tumor resection;
• Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug;

Medical History
• Prior malignancies; except another malignancy and disease-free for >= 5 years, or completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma;
• Prior surgical procedure within 28 days prior to the first dose of durvalumab, excluding minor surgical procedures e.g procedures only recuing local anesthesia.
• Past medical history of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease;
• History or presence of myopathy or raised CK >5 x ULN on 2 occasions at screening. CK should not be measured following strenuous exercise or in the presence of a plausible alternative cause of CK increase, which may confound interpretation of the results. If CK levels are significantly elevated at baseline (>5 x ULN) a confirmatory test should be carried out within 5 - 7

days. If the repeat test confirms a baseline CK >5 x ULN, treatment should not be started;
• History and/or presence of COVID-19: (a)Previous severe course of COVID-19 (ie, hospitalisation, extracorporeal membrane oxygenation, mechanically ventilated), (b) Clinical signs and symptoms consistent with COVID-19, eg, fever, dry cough, dyspnoea, sore throat, fatigue or confirmed current infection by appropriate laboratory test within the last 4 weeks prior to screening;

Cardiac function
• Cardiac dysfunction defined as: Myocardial infarction within six months of study entry, NYHA Class II/III/IV heart failure, unstable angina or unstable cardiac arrhythmias;
• Any of the following cardiac criteria:
* Mean resting corrected QT interval (QTcF) > 470 msec obtained from 3 electrocardiograms (ECGs) (QTc interval will be calculated using Fridericia*s formula);
* Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG, e.g., complete left bundle branch block, third degree heart block;
* Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years-of-age. Patients stable on concomitant medications known to prolong the QT interval may be allowed to participate in the study provided that their mean resting corrected QT interval (QTcF) is < 470 msec at baseline and after discussion with the Medical Monitor;

Concurrent and prior medication
• Concomitant treatment with medicines listed as *prohibited* or *excluded* (section 3.1.4);
• Treatment with moderate and strong inhibitors or inducers of CYP3A4 within 2 weeks before the first dose of study treatment (3 weeks for St John*s Wort);
• Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients;

Prior and concurrent clinical trials
• Participation in another clinical study with an investigational product during the last 3 months;
• Concurrent enrolment in another clinical study or, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study;

Other
• Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial;
• Judgment by the investigator that the patient should not participate in the

study if the patient is unlikely to comply with study procedures, restrictions and requirements;
• Female patients who are pregnant or breast feeding;
• Male or female patients of reproductive potential who are not willing to employ effective birth control during treatment;

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-07-2022
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AZD1390
Generic name:	AZD1390
Product type:	Medicine
Brand name:	IMFINZI
Generic name:	Durvalumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	07-12-2021

Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	29-12-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	11-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-09-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-10-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-07-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-07-2024
Application type:	Amendment
Review commission:	METC NedMec

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
EU-CTR	CTIS2024-514907-32-00
EudraCT	EUCTR2021-000042-17-NL
ClinicalTrials.gov	NCT05116254
CCMO	NL76411.031.21