FaR-RMS - An overarching study for children and adults with Frontline and Relapsed RhabdoMyoSarcoma

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This study has been transitioned to CTIS with ID 2024-510579-40-00 check the CTIS register for the current data. PRIMARY OBJECTIVES*Phase 1 Dose Finding Studies:-To determine the recommended phase II dose (RP2D) of new systemic therapy regimens. *...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Soft tissue neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52510

Source
ToetsingOnline

Brief title
FaR-RMS

Condition

- Soft tissue neoplasms malignant and unspecified

Synonym
malignant neoplasm derived from striated skeletal muscle tissue, Rhabdomyosarcoma

Research involving
Human

Sponsors and support

Primary sponsor: Universitiy of Birmingham
Source(s) of monetary or material Support: Ministerie van OC&W,Bayer,Cancer Research UK

Intervention

Keyword: cancer, childhood, Pediatric soft-tissue sarcoma, Rhabdomyosarcoma

Outcome measures

Primary outcome

Phase 1b: Recommended Phase II Dose (RP2D)

Upfront chemo VHR (CT1A): Event-free survival

Upfront chemo HR (CT1B): Event-free survival

Maintenance chemo (CT2): Event-free survival

Radiotherapy (RT1A and RT1B):Local Failure Free Survival (LFFS)

Radiotherapy (RT1C): Local Failure Free Survival (LFFS)

Radiotherapy (RT2): Event-free Survival

Relapse (CT3): Event-free survival

Secondary outcome

Phase 1b: MTD, Toxicity, DLT, Response

Upfront chemo VHR (CT1A): OS, Toxicity, Response

Upfront chemo HR (CT1B): OS, Toxicity, Response

Maintenance chemo (CT2): OS, Toxicity

Radiotherapy (RT1A and RT1B): EFS, OS, Acute post-OK complications, Acute post-RT complications, wound complications, late complications, Loco-regional failure-free survival (LRFFS), HRQoL

Radiotherapy (RT1C): EFS, OS, Acute post-RT complications, LRFFS, late complications

Radiotherapy (RT2): OS, Acute post-RT complications, LRFFS, HRQoL

Relapse (CT3): OS, Toxicity, Best Response, Response, Duration of Response,

Duration of Best Respone, Objective Response, HRQoL, acceptablility,

palatability, PK, PD, biomarkers

All patients: EFS, OS

PET sub-study: PET responses, EFS, OS, LFFS

Study description

Background summary

Rhabdomyosarcoma (RMS) is a rare sarcoma, with 59% of cases presenting in children and the rest occurring in adulthood, where the prognosis is poorer. Although relatively rare, RMS is the commonest of the paediatric soft tissue sarcomas, affecting about 15-20 children (0-18 years) per year in The Netherlands. RMS arises in many different sites within the body and comprises two major histological sub-groups: alveolar (ARMS) and embryonal (ERMS). Because of its chemo-responsiveness, neoadjuvant chemotherapy is used in the majority of patients with a response rate (RR) of around 80-85%. However, despite its chemo-sensitivity, multimodality treatment including radiotherapy or surgery or both radiotherapy and surgery is needed to achieve long term local control and cure in the vast majority of cases. Patients with metastatic disease can achieve remission with intensive chemotherapy and local therapy in 75% of cases but the vast majority relapse, often at distant sites, resulting in a 3 year event-free survival (EFS) of only 27%. Unfortunately, at the time of relapse, RMS is generally very refractory to treatment and has a 5 year overall survival (OS) of less than 20%.

Chemotherapy is an integral component of multi-modality therapy for RMS. Incremental improvements in outcome have been achieved over the last three decades within clinical trials that have investigated stepwise modifications in the intensity and combinations of these drugs. In low and SR disease, this has proved very successful, with a current 3 year EFS rates of 95% and 77% respectively. However, the greatest treatment challenges are in HR, VHR and metastatic disease, as well as at relapse, where progress with currently available agents has been inadequate; EFS remains below 70%, 45%, and 30% respectively and novel approaches are needed.

Despite the significant improvements in outcomes for patients in the last 20 years, local control remains the principal challenge in localised RMS. Radiotherapy is a key component of local therapy for RMS. It is proposed that the effectiveness of radiotherapy in local control could be improved by modifying the dose and/or the timing of radiotherapy. Within FaR-RMS both

strategies will be investigated.
There are conflicting data as to whether radiotherapy to metastatic sites truly influences outcomes for RMS. To date, the standard of care for metastatic RMS has been systematic irradiation of all metastatic sites whenever feasible. FaR-RMS aims to investigate whether radiotherapy to metastatic sites improves survival for patients with unfavourable metastatic RMS and evaluate the effects on HRQoL of this treatment.

Since more than 90% of events in RMS appear > 12 months after diagnosis, i.e. off-therapy, new approaches with longer low-dose treatments, so-called maintenance or metronomic chemotherapy, have been developed. The optimal duration of maintenance therapy for patients in the highest risk disease is still unknown. The duration of maintenance therapy will be evaluated in FaR-RMS, with a 12 vs 24 months maintenance randomisation for VHR RMS, and a 6 vs 12 months maintenance randomization for HR RMS.

Study objective

This study has been transitioned to CTIS with ID 2024-510579-40-00 check the CTIS register for the current data.

PRIMARY OBJECTIVES
*Phase 1 Dose Finding Studies:
-To determine the recommended phase II dose (RP2D) of new systemic therapy regimens.
*Frontline chemotherapy questions:
-To compare systemic therapy regimens for patients with VHR disease at diagnosis (CT1A).
-To compare new systemic therapy regimens with standard chemotherapy for patients with HR disease at diagnosis (CT1B).
*Radiotherapy questions:
-To determine whether pre-operative or standard post-operative radiotherapy is better for patients with resectable disease (RT1A) .
-To determine whether dose escalation of radiotherapy improves the outcome in patients with a higher local failure risk (RT1B/C).
-To determine whether radiotherapy treatment of all sites of disease, including metastatic sites, when compared to radiotherapy treatment to the primary site and involved regional lymph nodes alone, improves the outcome for patients with unfavourable metastatic disease (RT2).
*Maintenance Chemotherapy Question:
-To determine whether the addition of a further 12 cycles of vinorelbine and cyclophosphamide (VnC) to standard 12 cycles of maintenance chemotherapy (i.e. 24 cycles total) improves the outcome for patients with VHR disease at diagnosis (CT2A).
-To determine whether the addition of a further 6 cycles of VnC (intravenous (i.v) vinorelbine, oral cyclophosphamide) to the standard 6 cycles (i.e. 12 cycles total) improves the outcome for patients with localised HR disease at

diagnosis (CT2B).
*Relapsed RMS Question:
-To determine whether new systemic therapy regimens improve event free survival in relapsed RMS compared to standard therapy (VIrT) (CT3).

MAIN OVERARCHING SECONDARY OBJECTIVES
-To validate whether the use of fusion status (PAX3/PAX7-FOXO1) in place of histopathological diagnosis improves risk stratification.
-To determine whether assessment of fusion status is necessary in tumours classified as Embryonal RMS (ERMS) by histopathology.
-To determine whether immunohistochemistry (IHC) assessment for protein expression driven by the fusion protein is an accurate surrogate for fusion status.
-To determine whether FDG PET- CT response assessment following induction chemotherapy is a prognostic biomarker for local failure and/ or survival.

SECONDARY OBJECTIVES (CT3)
- To determine the tolerability of the regimens
- To evaluate the anti-tumour activity and effect on overall survival of VIRR when compared to standard therapy
- To evaluate the effect on quality of life of VIRR when compared to standard therapy
- To evaluate the acceptability and palatability of regorafenib formulations
- To examine the pharmacokinetics of regorafenib

Study design

FaR-RMS is an over-arching study for patients with newly diagnosed and relapsed RMS including multi-arm, multi-stage questions with three principal aims. These are to evaluate:
-systemic therapy through the introduction of new agent regimens in the most advanced disease states: Very High Risk (VHR), High Risk (HR) and Relapse
-the duration of maintenance therapy
-radiotherapy to improve local control in VHR, HR and Standard Risk (SR) patients and to treat metastatic disease
In addition the study will evaluate:
-risk stratification through the use of PAX-FOXO1 fusion gene status instead of histological subtyping
-the use of FDG PET-CT response assessment as a prognostic biomarker for outcome following induction chemotherapy

FaR-RMS is intended to be a rolling programme of research with new treatment arms being introduced dependant on emerging data and innovation, provided it is within the pre-defined research remit of the trial. A maximum of three new arms will be added to each of the frontline (VHR and HR) and relapse randomisations; and a maximum of four new arms to the Phase 1b component

Intervention

Phase 1b study:
-VHR: Treatment with IrIVA or other new systemic therapy regimens added later on in dose finding study setting (with a maximum of 4 new arms).
Induction chemotherapy:
-VHR: Randomised treatment with IVADo, IrIVA and other new systemic treatment regimens added later on (with a maximum of 3 new arms).
-HR: Randomises treatment with IVA, IrIVA and other new systemic treatment regimens added later on (with a maximum of 3 new arms).
Maintenance chemotherapy:
-VHR: Randomised treatment with 12 or 24 cycles maintenance chemotherapy.
-HR: Randomised treatment with 6 or 12 cycles maintenance chemotherapy.
Radiotherapy:
-All patients with localized disease, resectable tumor: Randomised treatment with pre-surgery or post surgery RT.
-All patients with local, resectable, high local-failure risk: Randomised treatment with 41,4 Gy or 50,4 Gy RT.
-All patients with not-resectable, incomplete response, high local-failure risk: Randomised treatment with 50,4 Gy or 59,4 Gy RT.
-All patients with *unfavourable* metastatic disease: Randomised RT treatment all metastatic sites or primary tumor and loco-regional nodes only.
Relapsed RMS induction chemotherapy:
-Randomised treatment with VIrT, VIrRego or other systemic therapy regimens (with a maximum of 3 new arms).

Study burden and risks

Patients participating in this study receive an intensive multimodal treatment, with three or more cytotoxic drugs. They also receive this treatment or similar treatment if the do not participate in the study. The intensive treatment is necessary for the treatment of their rhabdomyosarcoma.

Some patients (HR, VHR, relapsed) receive extra or other drugs, added to the current standard chemo backbone. This is justified because the overall survival in these groups is poor. Safety and toxicity will be strictly monitored.

Some patients (HR and VHR) are randomized and receive 6 (HR) or 12 (VHR) additional maintenance courses after induction treatment. Extension of maintenance therapy may contribute to the improvement of overall-survival. Toxicity and burden will be monitored.

Patients with a high local failure risk are randomized and receive an higher dose radiotherapy on the primary tumor. This is justified because this could contribute to a better local treatment result and survival. Acute toxicity, late complications and quality of life (early and late) will be registered and

monitored.
These patients/parents are asked to complete a questionnaire four times.

Contacts

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Scientific
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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)
Children (2-11 years)
Babies and toddlers (28 days-23 months)
Newborns

Inclusion criteria

Mandatory at first point of study entry:
1. Histologically confirmed diagnosis of RMS (except pleomorphic RMS)
2. Written informed consent from the patient and/or the parent/legal guardian

Comprehensive inclusion criteria for each specific randomization or registration are described in the protocol.

Exclusion criteria

For study entry:
None.

Comprehensive exclusion criteria for each specific randomization or registration are described in the protocol.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-11-2020
Enrollment:	140
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cosmegen
Generic name:	Dactinomycin
Product type:	Medicine

Brand name:	Doxorubicin
Generic name:	Doxorubicin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Ifosfamide
Generic name:	Ifosfamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Irinotecan
Generic name:	Irinotecan
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Vincristine
Generic name:	Vincristine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	30-04-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	15-07-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	10-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	25-07-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-05-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-07-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-04-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-05-2024
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	CTIS2024-510579-40-00
EudraCT	EUCTR2018-000515-24-NL

Register	ID
ISRCTN	ISRCTN45535982
CCMO	NL71366.041.19