A phase 1B of crizotinib either in combination or as single agent in pediatric patients with ALK, ROS1 or MET positive malignancies;Study ITCC 053

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This study has been transitioned to CTIS with ID 2023-504880-18-00 check the CTIS register for the current data. Primary• To determine the RP2D of crizotinib in combination with temsirolimus • To determine the safety and preliminary activity of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON54812

Source
ToetsingOnline

Brief title
CRISP

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
cancer, malignancies

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,Pfizer,Pfizer en diverse andere bronnen binnen de afdeling kinderoncologie

Intervention

Keyword: Anaplastic Large cell Lymphoma, Children, crizotinib, Neuroblastoma

Outcome measures

Primary outcome

Dose Limiting Toxicities (DLT) during the first cycle of crizotinib, in

combination with temsirolimus. For stratum 2; overall response rate for

stratum 1b and 3.

Secondary outcome

• Stratum 2 only: Overall response rate defined as the number of patients

achieving complete and partial responses by disease after 2 courses (8 weeks).

• Best overall response rate defined as best reported overall lesions response

at different evaluation time points from the start of study treatment until

disease progressionthe

Plasma concentration time profiles, PK parameters, including but not limited to

AUClast, AUCtau, Cmin, Cmax, Tmax, ,acc for crizotinib, temsirolimus .

• Progression-free survival (PFS)

• Overall survival

Biomarker endpoints

• Archival tumour sample and/or fresh frozen and/or embedded tumour sample

taken prior to enrolment will be analysed to show ALK, MET, ROS1 aberration

using next generation sequencing (NGS), FISH, immunohistochemistry (IHC).

• When available paired samples before and after 2 cycles of treatment will be analysed to show inhibition of ALK and the PI3K/AKT pathways.

• When available paired bone marrow sample In patients with neuroblastoma enrolled at the Royal Marsden Hospital before and after 2 cycles of treatment will be stored for neuroblastic cells isolation and target inhibition studies

• PRP samples before and 4 hours after the start of drug(s) administration at the beginning of cycle 1 and 2 will be analysed for target inhibition in PRP as surrogate tissue

• Tumor cf-DNA will be analysed before, during and after treatment in order to assess pre-treatment, in-treatment and post-treatment tumor genome alterations and to compare those to the aberrations found in the primary tumor samples.

• For ALCL sequential blood samples will be assessed for minimal disseminated disease by using NPM-ALK PCR as a marker for minimal residual disease and ALK antibodies concentrations

Study description

Background summary

Crizotinib is a ALK, MET and ROS1 inhibitor that has proven to be effective and is registered for ALK positive non-small cell lung carcinoma in adults. In children, various tumors harbour ALK/MET/ROS1 aberrations, and children with these tumours may potentially benefit from treatment with crizotinib. Crizotinib as single-agent in the pediatric phase I dose-escalation study showed favorable results in terms of toxicity, but variable results in terms of efficacy, despite dose-escalation to much higher dosages than used in adults. Very promising results were obtained in a small cohort of patients with ALCL, although not all patients responded. Especially in patients with neuroblastoma and ALK point-mutations responses were less promising than was anticipated, but

preclinical in-vitro and in-vivo studies have suggested that this may be overcome with the combined use of crizotinib with a TORC 1/2 inhibitor. In this study we therefore aim to evaluate combination therapy for different strata. For stratum 1 we will tried to combine crizotinib with vinblastine, based one earlier studies showing efficacy of vinblastine in the group of relapsed, ALK positive ALCL patients. This combination showed considerable toxicity. In collaboration with the pharmaceutical company, that has to meet requirements by the FDA, this group of patients will be treated with crizotinib monotherapy according to stratum 1b.For stratum 2 a combination of crizotinib with temsirolimus will be given to patients with relapsed, ALK positive neuroblastoma and rhabdomyosarcoma. Children who have other ALK- ROS or MET positive tumors and who have no other treatment options, will be enrolled in a separate stratum with crizotinib only (stratum 3).

Study objective

This study has been transitioned to CTIS with ID 2023-504880-18-00 check the CTIS register for the current data.

Primary

• To determine the RP2D of crizotinib in combination with temsirolimus
• To determine the safety and preliminary activity of single-agent crizotinib in ALK, MET or ROS1 positive tumors

Secondary

• To study the preliminary activity of crizotinib in combination with temsirolimus for relapsed or refractory ALK positive rhabdomyosarcoma or neuroblastoma (stratum 2)
• To study pharmacokinetics of single-agent crizotinib, and crizotinib in combination with r temsirolimus, and the potential drug-drug interactions between crizotinib and temsirolimus
• To assess best overall respons and overall survival
• To assess the duration of response, time to progression and progression free survival

Biomarker objectives
• To confirm target gene aberrations at enrollment in a central laboratory
• To study target activation at baseline
• To study target inhibition of ALK, AKT and mTOR pathway in all patients using Platelets-Rich-Plasma (PRP) as surrogate tissue and tumor tissue when available.
• To show pharmacodynamic effects of crizotinib alone or in combination with temsirolimus on ALK and PI3K/AKT pathways
• To study mechanisms of primary or acquired resistance in patients with resistant or progressive disease
• To study minimal disseminated disease and ALK antibody titers in patients

with ALCL as a possible predictive marker

Study design

For stratum 2, this is an open label, non-randomized, two part, phase 1b dose-finding study, with a dose escalation part followed by an expansion cohort. For stratum 1b and 3 it is an open label, non-randomized phase 1b/II study as an explorative cohort.

Intervention

In stratum 1, all patient will receive crizotinib twice daily (max 24 months)
In stratum 2, all patients will receive crizotinib twice daily in combination with temsirolimus once weekly (max 8 month). Crizotinib will be dose escalated according to the Escalation Method with Overdose Control (EWOC).

In stratum 3, all patients will receive crizotinib only (max 12 months).

Study burden and risks

All patients need to undergo a biopsy to obtain tumor material at the start of the study when feasible and with acceptable risk. This will be standard of care for most patients and will usually be done under anesthesia. Biopsies will be repeated if possible at the end of cycle 2, or at the end of study, whichever comes first for PD assessment. Radiological evaluation will be conducted every 2 months, consisting of either MRI/CT and/or MIBG; and may include bone marrow aspirate and biopsy evaluation, depending on the entity of the tumor and its localisation. PK assessment will be conducted at day 15 of cycle 1. Study visits will be weekly (including blood draw and physical examination) during the first 2 months of the study. From month 3 till month 12 (or end of study), study visits will be done every other week. Patients still on study after 12 months will be scheduled monthly until 24 month. Risk associated with this study are mainly the anticipated side-effects of crizotinib in combination with temsirolimus . Crizotinib has been shown to be relatively safe in children in a phase I study, but the number of treated patients is still limited. It also has not been combined before with temsirolimus. Due to the potential interaction between these drugs temsirolimus will be administered at 50% of the recommended dose. Mainly liver toxicity and bone marrow depression is anticipated. Considering the potential benefit of crizotinib especially in ALCL and IMT, we think that the potential benefits of treatment study outweigh the potential toxicity in these patients. In relapsed neuroblastoma and rhabdomyosarcoma new treatment modalities are urgently required given the poor outcome, which justifies enrolment in this study if informed consent is obtained.

Contacts

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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)

Inclusion criteria

Inclusion criteria
1b en 2:Histologically or cytologically confirmed diagnosis of relapsed/refractory ALCL, including first relapse, NBL or RMS
3: Histologically confirmed diagnosis of other solid tumor or lymphomas other than ALCL that is relapsed or refractory to standard therapy, or patients with newly diagnosed IMT for whom surgery may not be feasible for close proximity to vital structures, without prior tumor-shrinkage and no other feasible options are available as per local standard of care.when stratum 1b is completed, ALCL patients will be eligible to enroll into stratum 3

• Age at enrolment >=1 year of age and <= 21 years
• Lansky play score > 60%; or Karnofsky performance status > 60%.

Target gene aberration as defined as:
o stratum 1b: The t(2;5) translocation or rearrangement t(1;2), t(2;3), inv(2), t(2;22). proven by ALK- immunohistochemistry, FISH or NGS
stratum 2: A point mutation in the kinase domain of ALK, An amplification of the ALK gene,rearrangement in >15% of the tumor cells or An amplification of the MET-gene,MET mutation, TFE3 rearrangement,
stratum 3:
o A point mutation in the kinase domain of ALK, or MET mutation
o An amplification of the ALK or MET gene,
o A ROS1 or TFE3 rearrangement in > 15% of the tumor cells

• Life expectancy >= 12 weeks

• Disease involvement :
o stratum 1b Measurable disease defined as at least one nodule with a longest diameter greater than 1.5 cm (pediatric NHL response criteria)
stratum 2: For dose escalation measurable and non-measurable disease is allowed; For dose expansion measurable disease is mandated, except for neuroblastomas where MIBG or FDG avidity is sufficient
stratum 3:Measurable disease according to RECIST 1.1
Or, measurable disease as defined as at least one nodule with a longest diameter greater than 1.5 cm

• Any previous systemic anticancer therapy must have been completed at least 2 weeks prior to initiation of study medication
• No prior therapy directly targeting ALK or ROS1 or MET
• No treatment with any other investigational drug within the past 2 weeks or major surgery
Male and female patients of child-bearing potential must agree to use an effective method for males and a highly effective method for females

Exclusion criteria

• Other serious illnesses or medical conditions, • Current uncontrolled infection, • History of allergic reactions to the compounds or their solvents, • Patients with untreated CNS metastases and/or primary CNS tumors and/or meningeal, lymphoma involvement, defined as CNS3 status (patients with CNS2 are eligible), • Concurrent use of drugs or foods that are known potent CYP3A4 inducers or inhibitors CYP3A4 substrates with narrow therapeutic indices as well as medication with known QT*prolongation, •• Any of the following within the 3 months prior to starting study treatment: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, congestive

heart failure or cerebrovascular accident including transient ischemic attack.
• Use of live vaccines within 30 days of first dosing
* Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the, absorption of crizotinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea,, or malabsorption syndrome), • Not able to comply with scheduled follow*up and with management of toxicity., • A cardiac shortening fraction < 29%, • Ongoing cardiac dysrhythmias of NCI CTCAE Grade >=2, uncontrolled atrial fibrillation of any, grade, or QTcF interval >470 msec., • History of extensive disseminated/bilateral or known presence of grade 3 or 4 interstitial, fibrosis or interstitial lung disease, including a history of pneumonitis, hypersensitivity, pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and, pulmonary fibrosis, but not history of prior radiation pneumonitis., • No evidence of active graft*vs*host disease (GVHD) and at least 3 months post* allogeneic, HSCT. Must not receive GVHD prophylaxis., • For patients with childbearing potential, a negative test for pregnancy and agreement to use, effective contraceptive measures is required before entry on study.,• Spinal cord compression unless treated with the patient attaining good pain control and stable or recovered neurologic function.
• Prior malignancy (other than current malignancy): patients will not be eligible if they have evidence of active malignancy (other than non-melanoma skin cancer or localized cervical cancer, or localized and presumed cured prostate cancer) within the last 3 years.
• Carcinomatous meningitis or leptomeningeal disease
Plus for stratum 2:, • Patients with neuroblastoma and bone marrow disease only, are excluded.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruiting

Start date (anticipated):	22-05-2018
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Torisel
Generic name:	Temsirolimus
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Xalkori
Generic name:	Crizotinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	31-05-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-11-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-05-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	31-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-09-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-06-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-11-2021
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-12-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-12-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	CTIS2023-504880-18-00
EudraCT	EUCTR2015-005437-53-NL
CCMO	NL55691.078.16