International proof of concept therapeutic Stratification trial of Molecular Anomalies in Relapsed or Refractory HEMatological malignancies in children. Sub-Protocol D: Trametinib + Dexamethasone + Cyclophosphamide and Cytarabine in pediatric patients with relapsed or refractory hematological malignancies

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This study has been transitioned to CTIS with ID 2022-501869-41-00 check the CTIS register for the current data. PrimaryPhase I: To assess the safety and tolerability of the investigational agents and define the MTD/RP2D(s)Phase II: To evaluate the...

Ethical review	Approved WMO
Status	Pending
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON53652

Source
ToetsingOnline

Brief title
HEM-iSMART sub-protocol D

Condition

- Leukaemias

Synonym
leukemia (r/r ALL/LBL); alterations in RAS pathway

Research involving
Human

Sponsors and support

Primary sponsor: Prinses Máxima Centrum voor Kinderoncologie
Source(s) of monetary or material Support: Fight Kids Cancer,Novartis

Intervention

Keyword: RAS pathway activating mutations, relapsed or refractory hematological malignancies in children, Trametinib

Outcome measures

Primary outcome

The MTD (is defined as the highest dose level tested at which 0/6 or 1/6

patients experiences DLT during course 1 with at least 2 patients experiencing

DLT at the next higher dose. If the highest specified dose level (in general

dose level 2) in this study is reached with 0/6 or 1/6 patients experiencing

DLT during course 1 - i.e., the MTD has not been reached - this dose level will

be referred to as the highest tested dose (HTD), and this dose will be taken

forward as the RP2D. PK profiling may also be considered for the definition of

RP2D. Toxicities will be graded according to the NCI CTCAE V5.0.

Best overall Response Rate (ORR):

* For patients with leukemia: CR and MRD response after 1 cycle of treatment.

This includes determination of CR, CRp, CRi and MRD negativity rate in patients

suffering from overt morphological relapse of T-ALL at time of enrolment (morphological disease (M2/M3)), and the MRD negativity rate in those that entered with high-MRD levels but in morphological CR. These results will together be presented as a composite endpoint Overall Response rate (ORR). MRD negativity will be defined as <=1x10-4 as generated by multi-parameter flow cytometry.

* For patients with lymphoma: Response in LBL patients is defined as CR, PR, minor response (MR) as defined in International pediatric NHL response criteria (see protocol). In case of bone-marrow involvement MRD will be taken into account.

Secondary outcome

- To estimate the OS, EFS, CIR from C1D1 until death, first event, relapse; rate of transition to HSCT is calculated by the number of patients who receive stem cell infusion divided by the total number of patients enrolled.
- PK parameters, include plasma concentration time profiles, AUClast, AUCtau, Cmin, Cmax, Tmax, clearance, half-life time.
- QoL will be assessed at baseline and after cycle 1 and at the end of treatment using the PedsQL* Cancer Module

Study description

Background summary

Despite improvements of survival for pediatric patients beeing diagnosed with acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL), still a

significant proportion of patients relapse or do not respond to conventional chemotherapies; for those, the outcome remains dismal despite the recent incorporation of new agents. Successful drug development of immunotherapeutic approaches has improved the outcome in relapsed/refractory (r/r) B-ALL patients. However, this same success has not been seen in r/r T-ALL/T-LBL. Consequently, there is a clear unmet need to improve the outcome of r/r T-ALL/T-LBL patients. The incorporation of molecular tehniques, and our increased knowledge in tumor biology, open the door to individual approach based on genetic alterations. Here we describe sub-protocol D: - Ras pathway alterations play a pivotal role in a variety of malignant diseases leading to malignant transformation, inducing proliferation and therapeutic resistance. The RAS/RAF/MEK/ERK or the MAPK/ERK pathway is a critical signal transduction cascade implicated in normal growth and the uncontrolled proliferation of many human cancers. - In hematological conditions, low-level subclonal mutations of MAPK-pathway genes including KRAS, NRAS, PTPN11, NF1 and FLT3 are found in > 40% % of primary acute lymphoblastic leukemia (ALL) samples, including clonal mutations in around 25. In the relapsed setting up to 37.9 % of ALL samples show RAS pathway mutations, with complex gains and losses of particular mutations and subclones compared to primary disease. RAS pathway mutations correlate with inferior prognosis, central nervous system (CNS) positivity as well as reduced remission rates and - in regards to KRAS mutations - reduced overall survival (OS). - In T-cell (T)-ALL up to 12% of relapsed samples show RAS hotspot mutations, mainly affecting NRAS and KRAS. All of the patients suffering from RAS-mutated T-ALL in a cohort of 67 patients died, which indicates treatment resistance. RAS-mutations are frequently found in early T-cell precursor (ETP)-ALL and HOXA+ subtypes of T-ALL. Importantly, in T-ALL, RAS mutations occur in a predominantly mutually exclusive fashion with other IL-7Ra and downstream signaling components such as JAK, AKT and PTEN mutations. - There is evidence that trametinib can enhance the activity of dexamethasone in pediatric patients with leukemia. Combination studies with other targeted agents or conventional chemotherapeutics in adults and children conducted today show the feasibility of using trametinib in conjunction with other agents in a clinical setting. - Trametinib has been prospectively studied in first-in-child clinical trials. The recommended phase II dose (RP2D) is already identified, 0.025 mg/kg daily for pts >= 6y and 0.032 mg/kg for pts < 6y once a day. For trametinib most frequent toxicities are diarrhea, skin disorders, pyrexia and anemia. - Since T-ALL and T-lymphoblastic lymphoma (LBL) are highly proliferative diseases and given the fact that trametinib can be combined with chemotherapy, patients in this study will receive low doses cyclophosphamide and cytarabine.The safety and feasibility of combining these two agents with conventional chemotherapy has been demonstrated in pediatric studies.

Study objective

This study has been transitioned to CTIS with ID 2022-501869-41-00 check the CTIS register for the current data.

Primary
Phase I: To assess the safety and tolerability of the investigational agents and define the MTD/RP2D(s)
Phase II: To evaluate the activity of new drugs in T-ALL/T-LBL patients harboring specific alterations linked to mechanism of action of these drugs.

Secondary
To evaluate long term OS, EFS, incidence of relapse (CIR) and rate of transition to hematopoietic stem cell transplantation (HSCT).
PK of the targeted agents and quality of life (QoL).

Study design

i) Dose-finding part (Phase I): Rolling-6 design. Escalation occurs when <=2 DLTs are observed per dose-level

ii) Activity part (Phase II): Simon's two-stage design. We assume a null hypothesis of an overall response rate of <=10% (H0) based on historical data from patients regardless the underlining molecular alteration; the alternative hypothesis (H1) is of 40% for each sub-protocol. At least 1 responder out of 6 must be observed in order to go to the next phase. The drug will be considered promising when >= 4 responders out of 16 evaluable patients are seen at the RP2D. The sample size is calculated setting the alpha level to 7% and the power to 90%.

Planned recruitment period: 72 months
Follow-up period: 12 months after the last patient last visit for each sub-protocol
Planned study duration: 90 months

Intervention

In dose level 1, cycle 1 trametinib is taken orally once a day for 28 days, day 1-5 dexamethasone is given (orally or by IV infusion), on day 3 an IV infusion of cyclophosphamide and on day 5-8 and day 12-15 an IV infusion of cytarabine. In cycle 2 and beyond of the same dose level, the same schedule is followed only the IV infusion of cyclophosphamide is given on day 1 and the IV infusion of cytarabine on days 3-6 and day 10-13.

In dose level -1, a lower amount of dexamethasone is given and only 1 IV infusion of cytarabine on days 5-8. In cycle 2, cytarabine is given on days 3-6.

Study burden and risks

Ethical considerations:

This trial involves children and young adults with ALL and LBL for which no other curative options exist. Targeted therapies may improve the outcome for patients whose tumor present selected molecular alterations. The safety and efficacy evaluations are aligned with standard of care to avoid additional burden to patients. All proposed individual drugs have been already investigated in children and demonstrated to be safe. The study follows the good clinical practice and adheres to international requirements to conduct interventional studies in minors.

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

Patients must have any of the conditions (Group A to E) depicted below for being eligible for the trial. Patients need to fulfill all inclusion and exclusion criteria depicted in sections 5.1 and 5.2. T-ALL and T-LBL Cohort: Group A: T-ALL in first or greater relapse/refractory to at least one prior regimen defined as: - >= 5% blasts in the marrow after first line induction and consolidaton blocks or any re-induction therapy for 1st or subsequent relapse(s)/refractoriness OR - Be in complete morphological remission (< 5% blasts in the marrow) but having o MRD >=1 x 10-3 after first line induction and consolidaton blocks, or o >=1 x 10-4 after any re-induction therapy for 1st or subsequent relapse(s)/refractoriness. Group B: T-LBL (histology proven or diagnosed applying flow cytometry and/or cytomorphology of bone marrow (bone marrow blast count >= 5% but < 25 %), peripheral blood and effusions) in first or greater relapse/refractoriness to at least one prior induction regimen defined as: - Evidence of measurable disease by radiological criteria after first line induction and consolidaton blocks or any re-induction therapy for 1st or subsequent relapse(s)/refractoriness AND/OR - >= 5% blasts in the marrow after first line induction and consolidaton blocks or any re-induction therapy for 1st or subsequent relapse(s)/refractoriness OR - Be in complete morphological remission (< 5% blasts in the marrow and no extra-medullary disease) but having MRD >= 1 x 10-3 after first line induction and consolidaton blocks or >=1 x 10-4 after any re-induction therapy for 1st or subsequent relapse(s)/refractoriness. Group C: - Patients with either T-ALL or T-LBL who are in complete morphological remission (< 5% blasts in the marrow and no extra-medullary disease) but who have experienced a molecular reappearance defined as *reconversion after minimal residual disease (MRD) negativity* to reproducible MRD positivity (>=1 x 10-4). MRD positivity MUST be confirmed in two different samples in the bone marrow two weeks apart before the enrolment of these patients into the trial or by two independent methods (f.ex. PCR and flow-cytometry) at one measurement. BCP-ALL and B-LL Cohort: These patients can ONLY be enrolled into the dose finding phase (Phase I) of the sub-protocols at the moment. Group D: BCP-ALL in second or greater relapse or refractory to 2 prior regimens defined as: - >= 5% blasts in the marrow after any re-induction therapy for 2nd or subsequent relapse(s)/refractoriness OR - Be in complete morphological remission (< 5% blasts in the marrow) but having MRD >= 1 x 10-4 after any re-induction therapy for 2nd or subsequent relapse(s)/refractoriness NOTE: Patients with BCP-ALL MUST have received and failed hematopoietic stem cell transplantation (HSCT) and/or CAR-T therapy. Exceptions to this are: absence of a suitable donor, failure of manufacturing CAR-T, impossibility to access a CAR-T-program, patients not candidates to CAR-T-therapy due to clinical reasons. These patients need to be discussed with the sponsor on a single case basis. Group E: B-LBL (histology proven or diagnosed applying flow cytometry and/or cytomorphology of bone marrow (bone marrow blast count >= 5% but < 25 %), peripheral blood and effusions) in first or greater relapse/refractory to at least one prior induction regimen

defined as: - Evidence of measurable disease by radiological criteria after first line induction and consolidaton blocks or any re-induction therapy for 1st or subsequent relapse(s)/refractoriness AND/OR - >= 5% blasts in the marrow after first line induction and consolidaton blocks or any re-induction therapy for 1st or subsequent relapse(s)/refractoriness OR - Be in complete morphological remission (< 5% blasts in the marrow and no extra-medullary disease) but having MRD >= 1 x 10-3 after first line induction and consolidaton blocks or >=1 x 10-4 after any re-induction therapy for 1st or subsequent relapse(s)/refractoriness Patients with isolated extramedullary disease (IEM) are not eligible. IEM is defined as biopsy proven extramedullary disease after documented CR following initial therapy. Standardized response criteria for IEM are lacking which impairs analysis of the primary endpoint. In addition these patients might need to undergo local therapy (radiation and/or surgery) which is standardized exclusively for isolated CNS and testicular relapse and might confound outcome analysis if it is based on physician*s choice in particular for *other* IEM [57]. Patients with combined extramedullary and bone marrow disease fulfilling the above mentionned conditions group A-E with MRD >= 10-3 are eligible since standardized bone marrow assessment is available. These patients will undergo centralized review of bone marrow and of IEM response. 1. Children between 1 year (>= 12 months) and 18 years of age at the time of first diagnosis and less than 21 years at the time of inclusion and able to swallow tablets. Patients under 6 years old must weigh at least 26 kg at the time of enrollment. Patients over 6 years old must weigh at least 33 kg at the time of enrollment. 2. Performance status: Karnofsky performance status (for patients >12 years of age) or Lansky Play score (for patients <=12 years of age) >= 50% (Appendix I). 3. Written informed consent from parents/legal representative, patient, and age-appropriate assent before any study specific screening procedures are conducted, according to local, regional or national guidelines. 4. Patients must have had molecular profiling and flow-cytometric analysis of their recurrent or refractory disease at a time-point before the first inclusion into this trial (see section 9.1 of this protocol for detailed description of the molecular diagnostics required). Drug response profiling and methylation is highly recommended but not mandatory. Patients with molecular profiling at first diagnosis lacking molecular diagnostics at relapse or refractory disease may be allowed to be included after discussion with the sponsor. 5. Patients whose tumor present RAS pathway activating mutations including but not limited to KRAS, NRAS, HRAS, FLT3, PTPN11, MAP2K1, MP2K1 hotspot mutations, cCBL; NF1 del, as detected by molecular profiling. 6. Adequate organ function: -RENAL AND HEPATIC FUNCTION (Assessed within 48 hours prior to C1D1) : o Serum creatinine <= 1.5 x upper limit of normal (ULN) for age or calculated creatinine clearance as per the Schwartz formula or radioisotope glomerular filtration rate >= 60 mL/min/1.73 m2. o Direct bilirubin <= 2 x ULN (<= 3.0 × ULN for patients with Gilbert*s syndrome). o Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT) <= 5 x ULN; aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase/SGOT <= 5 x ULN. Note: Patients with hepatic disfunction related to the underling disease can be eligible even if they do not fulfill the aforementioned values for hepatic

transaminases. In these cases, patients need to be discussed with the sponsor to confirm the eligibility. -CARDIAC FUNCTION: o Shortening fraction (SF) >29% (>35% for children < 3 years) and/or left ventricular ejection fraction (LVEF) >=50% at baseline, as determined by echocardiography or MUGA. o Absence of QTcF prolongation (QTc prolongation is defined as >450 msec on baseline ECG, using the Fridericia correction), or other clinically significant ventricular or atrial arrhythmia.

Exclusion criteria

1. Pregnancy or positive pregnancy test (urine or serum) in females of childbearing potential. Pregnancy test must be performed within 7 days prior to C1D1. 2. Sexually active participants not willing to use highly effective contraceptive method (pearl index <1) as defined in CTFG HMA 2020 (Appendix II) during trial participation and until 6 months after end of antileukemic therapy. 3. Breast feeding. 4. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter drug absorption of oral drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome) in case of oral IMPs. 5. Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to the study drugs, or drugs chemically related to study treatment or excipients that contraindicate their participation, including conventional chemotherapeutics (i.e. cytarabine and cyclophosphamide, intrathecal agents) and corticoids. 6. Known active viral hepatitis or known human immunodeficiency virus (HIV) infection or any other uncontrolled infection. 7. Severe concomitant disease that does not allow treatment according to the protocol at the investigator*s discretion. 8. Subjects unwilling or unable to comply with the study procedures. 9. Previous treatment with trametinib. 10. Current use of a prohibited medication or herbal preparation or requires any of these medications during the study. See Section 7 and Appendix III for details. Drugs inducing QTc changes (prolongation of the QT interval or inducing Torsade de Points) are not permitted. 11. Unresolved toxicity greater than NCI CTCAE v 5.0 >= grade 2 from previous anti-cancer therapy, including major surgery, except those that in the opinion of the investigator are not clinically relevant given the known safety/toxicity profile of the study treatment (e.g., alopecia and/or peripheral neuropathy related to platinum or vinca alkaloid based chemotherapy) (Common Terminology Criteria for Adverse Events (CTCAE) (cancer.gov). 12. Active acute graft versus host disease (GvHD) of any grade or chronic GvHD of grade 2 or higher. Patients receiving any agent to treat or prevent GvHD post bone marrow transplant are not eligible for this trial. 13. Received immunosuppression post allogenic HSCT within one moth of study entry. 14. History or current evidence of retina vein occlusion (RVO) or central serous retinopathy are excluded. 15. Wash-out periods of prior medication: a. CHEMOTHERAPY: At least 7 days must have elapsed since the completion of cytotoxic therapy, with the exception of hydroxyurea, 6-mercaptopurine, oral methotrexate and steroids which are permitted up until

48 hours prior to initiating protocol therapy. Patients may have received intrathecal therapy (IT) at any time prior to study entry. b. RADIOTHERAPY: Radiotherapy (non-palliative) within 21 days prior to the first dose of drug. Palliative radiation in past 21 days is allowed. c. HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT): i. Autologous HSCT within 2 months prior to the first study drug dose. ii. Allogeneic HSCT within 3 months prior to the first study drug dose. d. IMMUNOTHERAPY: At least 42 days must have elapsed after the completion of any type of immunotherapy other than monoclonal antibodies (e.g. Inotuzumab) e. MONOCLONAL ANTIBODIES AND INVESTIGATIONAL DRUGS: At least 21 days or 5 times the half-life (whichever is shorter) from prior treatment with monoclonal antibodies or any investigational drug under investigation must have elapsed before the first study drug. f. SURGERY: Major surgery within 21 days of the first dose. Gastrostomy, ventriculo-peritoneal shunt, endoscopic ventriculostomy, tumor biopsy and insertion of central venous access devices are not considered major surgery.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-07-2023
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Mekinist
Generic name:	trametinib (tablets)

Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	02-03-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	11-05-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	02-07-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-08-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-08-2023
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	CTIS2022-501869-41-00
EudraCT	EUCTR2021-003398-79-NL
ClinicalTrials.gov	NCT05658640
CCMO	NL82569.041.22