European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors (ESMART)

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This study has been transitioned to CTIS with ID 2024-514791-40-00 check the CTIS register for the current data. Based on results from a comparative review (Paoletti 2013), we hypothesize that if the toxicity profile and the PK parameters observed...

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

Summary

ID

NL-OMON49633

Source
ToetsingOnline

Brief title
ESMART

Condition

- Leukaemias
- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
pediatric cancer

Research involving
Human

Sponsors and support

Primary sponsor: Institut Gustave Roussy
Source(s) of monetary or material Support: Ministerie van OC&W,Astra Zeneca,Bristol-Myers Squibb,Celgene Corporation,geringe bijdrage vanuit IGR;free drug van diverse farmaceuten;en eigen fondsen,Novartis

Intervention

Keyword: Children, Molecular abnormalities, Pediatric Cancer, Phase I/II

Outcome measures

Primary outcome

Trial End-points

1. The recommended phase II dose (RP2D) will be defined as the adult

recommended dose (adjusted for weight or BSA) if toxicity

and PK profiling are similar in children and in adults, or a higher dose,

providing it is below or equal to the maximum tolerated

dose (MTD).

2. The maximum tolerate dose (MTD) will be defined as the dose associated with

or closest to 25% of DLTs in cycle 1.

3. Dose Limiting Toxicities (DLT) will be defined using CTCAE v4.03.

4. Overall response rate (ORR); duration of response (DOR) will be defined as

the time period between the first documented

response (PR or CR) and the time of progression, according to RECIST v1.1, RANO

criteria for patients with HGG, INRC

criteria for patients with NB, etc.

5. Duration of response for patients free of progression at the cutoff date

will be censored at the last Imaging response scan date;

progression-free survival (PFS) will be defined as the time from treatment initiation until the date of first documented progression or death from any cause. Patients alive and free of progression at the cut-off date will be censored at the last assessment date.

6. Adverse events according to the NCI CTCAE V4.03 in all cycles of treatment.

7. PK parameters, including but not limited to plasma concentration time profiles, AUClast, AUCtau, Cmin, Cmax, Tmax, Clearance, Halflife time.

8. To explore relationship between the molecular profile of the tumor samples, circulating tumor DNA and tumor growth measured as modification of the sum of the diameters of the target lesions over time.

Secondary outcome

NA

Study description

Background summary

The first molecular profiling protocols have been launched in Europe (MOSCATO-01 (Geoerger 2014), MAPPYACTS, INFORM, iTHER, SM-PAEDS, etc.) determining multiple actionable alterations in pediatric recurrent cancers. Increasingly, stratified approaches are being implemented to enrich clinical trials of molecularly targted agents and possibly improve outcomes in specific populations i.e. a molecularly enriched/predictive biomarker-driven approach. The diversity and heterogeneity of the detected molecular alterations and the low number of pediatric patients mandate an adapted, innovative trial design for the attributed treatment options in order to satisfy the current unmet medical need. This basket trial is designed to cover the targeting of several survival pathways in oncogenesis that are currently not adequately employed for pediatric patients in Europe.

Study objective

This study has been transitioned to CTIS with ID 2024-514791-40-00 check the CTIS register for the current data.

Based on results from a comparative review (Paoletti 2013), we hypothesize that if the toxicity profile and the PK parameters observed in children treated at the adult RP2D are similar to those in adults; escalating to the MTD is not necessarily required, unless a dose-activity relationship has been documented in adults. Therefore, for each agent or combination of agents being investigated, there will be two co-primary objectives:
1. Phase I: To define or validate that the adult single agent RP2D of the selected drug or combination of drugs is safe in children/adolescents and equivalent to that seen in adults, in pediatric/adolescent patients with malignancies which are recurrent or refractory to standard therapy.
2. Phase II: To determine the preliminary activity (as measured by tumor response) of these agents in patients harboring specific molecular alterations or tumor types that may be associated with the mechanism of action of these drugs (i.e. molecularly enriched patient cohorts, where possible).

Secondary:
1. To characterize the toxicity profile of the agent(s) in pediatric/ adolescent patients.
2. To characterize single or multiple-dose PK of the agent(s).
3. To evaluate the progression free survival and incidence of longterm responders (>6 months).
4. To evaluate whether the response rate is higher in the enriched population as compared to the non-enriched population overall,
by targeted treatment and by arm.

Exploratory:
1. To explore, define and/or validate pharmacodynamic (Pd) biomarkers of target inhibition, where possible.
2. To explore relationships between measures of tumor expression of the molecular target(s), circulating tumor DNA and tumor growth.
3. To explore the expression of immunomarker (ARM J)

Study design

This is an international, multi-center, open-label, prospective, phase I/II dose-validation study with a RP2D confirmation part, which is open to being expanded to refine an efficacy assessment for each agent.
Each arm is driven separately with common procedures, quality control and reporting.
For all patients, an extensive molecular analysis of their tumor tissue performed prior to study entry will be requested that will serve to select the

most appropriate arm according to the algorithm provided below.
If no molecular alteration in the pathways selected for this trial are identified, patients may still be enrolled into this study and assigned to a particular treatment arm open for accrual, according to physician discretion, if a strong scientific rationale exists to support the notion that the patient may derive clinical benefit, and if the patient fulfills all other inclusion and no exclusion criteria.
The study is designed to be amended subsequently with new treatment arms in future for up to a maximum of 9 years.

Intervention

Arm A. Ribociclib + Topotecan and Temozolomide
ARM C. AZD1775 + Carboplatin
ARM D. Olaparib + Irinotecan
ARM I: Enasidenib
ARM J: Lirilumab + Nivolumab

Study burden and risks

NA

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)
Elderly (65 years and older)

Inclusion criteria

1. Patients must be diagnosed with a haematologic or solid tumor malignancy that has
progressed despite standard therapy, or for which no effective
standard therapy exists.
2. Age < 18 years at inclusion; patients 18 years and older may be
included after discussion with the sponsor if they have a pediatric
recurrent/refractory malignancy.
3. Patient must have had advanced molecular profiling (i.e. WES/WGS +/-
RNAseq) of their
recurrent or refractory tumor i.e. at the time of disease
progression/relapse; exceptionally patients with advanced
molecular profiling at diagnosis may be allowed.
4. Evaluable or measurable disease as defined by standard imaging
criteria for the patient*s tumor type (RECIST v1.1, RANO criteria
for patients with HGG, INRC criteria for patients with NB,
Leukemia criteria, etc.).
5. Performance status: Karnofsky performance status (for patients
>12 years of age) or Lansky Play score (for patients <=12 years of
age) >= 70%. Patients who are unable to walk because of paralysis
or stable neurological disability, but who are up in a wheelchair,
will be considered ambulatory for the purpose of assessing the
performance score.
6. Life expectancy >= 3 months
7. Adequate organ function:
Hematologic criteria (Leukemia patients are excluded from
hematological criteria):
- Peripheral absolute neutrophil count (ANC) >= 1000/µL
(unsupported)
- Platelet count >= 100,000/µL (unsupported)
- Hemoglobin >= 8.0 g/dL (transfusion is allowed)
Cardiac function:
- Shortening fraction (SF) >29% (>35% for children < 3 years)
and left ventricular ejection fraction (LVEF) >=50% at baseline, as
determined by echocardiography (mandatory only for patients

who have received cardiotoxic therapy).
- Absence of QTc prolongation (QTc > 450 msec on baseline ECG, using the Fridericia correction [QTcF formula]) or other clinically significant ventricular or atrial arrhythmia.
Renal and hepatic function:
- Serum creatinine <= 1.5 x upper limit of normal (ULN) for age
- Total bilirubin <= 1.5 x ULN
- Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT) <= 2.5 x ULN; aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase/SGOT <= 2.5 x ULN except in patients with documented tumor involvement of the liver who must have AST/SGOT and ALT/SGPT <= 5 x ULN.
8. Able to comply with scheduled follow-up and with management of toxicity.
9. Females of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to initiation of treatment. Sexually active women of childbearing potential must agree to use acceptable and appropriate contraception during the study and for at least 6 months after the last study treatment administration. Sexually active males patients must agree to use condom during the study and for at least 6 months (7 months for arm J) after the last study treatment administration. Acceptable contraception is listed in Appendix 12.
10. For all oral medications patients must be able to comfortably swallow capsules (except for those for which an oral solution is available); nasogastric or gastrostomy feeding tube administration is allowed only if indicated.
11. 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.
12. Patient affiliated to a social security regimen or beneficiary of the same according to local requirements.

Exclusion criteria

1. Patients with symptomatic central nervous system (CNS) metastases who are neurologically unstable or require increasing doses of corticosteroids or local CNS-directed therapy to control their CNS disease. Patients on stable doses of corticosteroids for at least 7 days prior to receiving study drug may be included.
2. 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).
3. Clinically significant, uncontrolled heart disease (including history

of any cardiac arrhythmias, e.g., ventricular, supraventricular, nodal arrhythmias, or conduction abnormality, unstable ischemia, congestive heart failure within 12 months of screening)
4. Active viral hepatitis or known human immunodeficiency virus (HIV) infection or any other uncontrolled infection.
5. Presence of any >= CTCAE grade 2 treatment-related toxicity with the exception of alopecia, ototoxicity or peripheral neuropathy.
6. Systemic anticancer therapy within 21 days of the first study dose or 5 times its half-life, whichever is less.
7. Previous myeloablative therapy with autologous hematopoietic stem cell rescue within 8 weeks of the first study drug dose
8. Allogeneic stem cell transplant within 3 months prior to the first study drug dose. Patients receiving any agent to treat or prevent graft-versus host disease (GVHD) post bone marrow transplant are not eligible for this trial.
9. Radiotherapy (non-palliative) within 21 days prior to the first dose of drug (or within 6 weeks for therapeutic doses of MIBG or craniospinal irradiation).
10. 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, but for these procedures, a 48 hour interval must be maintained before the first dose of the investigational drug is administered.
11. Currently taking medications with a known risk of prolonging the QT interval or inducing Torsades de Pointes (Refer to Appendix 8).
12. Currently taking medications that are mainly metabolized by CYP3A4/5, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or the drug transporters Pgp (MDR1), BCRP, OATP1B1, OATP1B3, OCT1 and OCT2 and have a low therapeutic index that cannot be discontinued at least 7 days or 5 x reported elimination half-life prior to start of treatment with any of the investigational drugs and for the duration of the study (Refer to Appendix 9).
13. Known hypersensitivity to any study drug or component of the formulation.
14. Pregnant or nursing (lactating) females.
15. Vaccinated with live, attenuated vaccines within 4 weeks of the first dose of study drug.

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):	14-05-2018
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AZD1775
Generic name:	AZD1775
Product type:	Medicine
Brand name:	Idhifa
Generic name:	Enasidenib
Product type:	Medicine
Brand name:	Kisqali
Generic name:	Ribociclib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Lynparza
Generic name:	Olaparib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Opdivo
Generic name:	Nivolumab

Ethics review

Approved WMO Date:	07-12-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-02-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-08-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	11-10-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-08-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Not approved Date:	25-01-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-02-2022
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	CTIS2024-514791-40-00
EudraCT	EUCTR2016-000133-40-NL
ClinicalTrials.gov	NCT02813135
CCMO	NL60586.078.17