International phase I/II expansion trial of the MEK inhibitor selumetinib in combination with dexamethasone for the treatment of relapsed/refractory RAS-pathway mutated paediatric and adult Acute Lymphoblastic Leukaemia

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Phase IPrimary Objective- To define the recommended phase II dose (RP2D) of selumetinib/dexamethasone combination in adult and paediatric patients with relapsed/refractory, RAS pathway mutant ALLSecondary Objectives- To evaluate safety and...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON55542

Source
ToetsingOnline

Brief title
SeluDex

Condition

- Leukaemias

Synonym
Acute Lymphoblastic Leukemia (ALL), Leukemia

Research involving

Human

Sponsors and support

Primary sponsor: University of Birmingham
Source(s) of monetary or material Support: Ministerie van OC&W,Astra Zeneca,Astra Zeneca en vergoeding per patient van de University of Birmingham

Intervention

Keyword: Acute Lymphoblastic leukaemia, Dexamethason, RAS-pathway, Selumetinib

Outcome measures

Primary outcome

Phase I

Primary endpoints:

- The selection of RP2D based on dual primary measures of dose limiting

toxicities (DLT) and PK (ΔAUC)

Phase II

Primary endpoints:

- Response rate

Secondary outcome

Secondary endpoints Phase 1:

- Toxicity evaluation; PK variables of selumetinib in combination with

dexamethasone; response to treatment

Secondary endpoints Phase 2:

- Toxicity evaluation; PK variables of selumetinib in combination with

dexamethasone; difference in PK of selumetinib as single agent and in

combination with dexamethasone

Phase I/II

Research (tertiary) endpoints

- Exploratory PD biomarker studies, if clinical responses are observed

Study description

Background summary

Acute lymphoblastic leukaemia (ALL) is the most common childhood cancer, with incidence in the UK of 2.8-6 per year per 100,000 population for children between 0-9 years, and incidence of 0.9-2.1 for the age group between 10-19 years. While the overall cure rate for newly diagnosed paediatric ALL is approaching 90%, children with relapsed ALL (rALL) are still facing a poor outlook, with reported event free survival rates of 30-50%, and rALL remains a frequent cause of death. In adults, the frequency of ALL is significantly lower, with a UK incidence of 0.5-1 per 100,000 population in the 20-40 year age group rising to 1-2 per 100,000 in the >70 age years population. ALL in adulthood has proven to be more challenging to treat compared to childhood ALL with the disease being more resistant to chemotherapy, and patients have a reduced treatment tolerance especially in the elderly population. Only 40-50% of patients less than 60 years old will survive 5 years, and overall survival in elderly patients is significantly worse. Overall survival for rALL in adult patients is less than 10% if treated with chemotherapy alone, and about 20% if patients can undergo an allogeneic haematopoietic stem cell transplantation (HSCT).

Advancements in knowledge about cancer biology have identified key pathways like the RAS/RAF/MEK/ERK signalling cascade. This pathway has a central role in transducing signals from the cell surface to intracellular targets, and has been shown to harbour activating somatic mutations in a large proportion of patients with newly diagnosed and relapsed ALL[3,9]. Patients with relapsed ALL carrying RAS-pathway activating mutations (KRAS, NRAS, FLT3 and PTPN11) comprised 38% of all relapsed patients[3], and they were associated with high risk features (lower incidence of favourable cytogenetics, ETV6-RUNX1, early relapse/relapse on treatment, CNS disease at relapse).

Selumetinib is a potent and selective allosteric MEK1/2 inhibitor which has been evaluated in Phase II/III clinical trials for a number of cancers,

including BRAF mutation-positive melanoma, metastatic uveal melanoma, pancreatic, colorectal, KRAS mutation-positive NSCLC. It has a favourable toxicity profile (common side effects: diarrhoea, nausea/vomiting, rash, swelling of face/extremities) and has demonstrated anti-tumour activity as a monotherapy. In some adult cancers like advanced non-small-cell lung cancer however, it has greater efficacy in combination, e.g. with docetaxel.

Follow up on the Irving data has shown very strong synergy between selumetinib and the synthetic glucocorticoid dexamethasone, both in vitro and in the orthotopic primagraft mouse model. Glucocorticosteroids (GC) such as dexamethasone, are pivotal agents in the treatment of all lymphoid malignancies due their ability to specifically induce apoptosis in developing lymphocytes, and induction of proapoptotic BIM is key to this affect. BIM is inactivated by ERK phosphorylation, and benchmark MEK inhibitors have demonstrated synergy with GC in ALL cell line models in vitro. Using mutant ALL cell lines and primagraft cells sensitive to selumetinib and highly resistant to GC (GI50>10 μM), the Irving group has demonstrated very strong synergy in vitro with these drugs, with a Combination Index of <0.1 and a corresponding enhancement of BIM induction, suggesting co-exposure may be highly effective for the treatment of RAS pathway activated ALL.

The in vitro synergy observed with selumetinib and dexamethasone has been confirmed in an orthotopic mouse model with three different RAS pathway mutant ALL primagrafts, including KRAS mutated relapsed primary-derived cells. Weight loss was observed in mice dosed with dexamethasone, resulting in a decrease in the ideal dose of 1 mg/kg twice per day (BD) to 0.25 mg/kg once per day (QD). There was no additional weight loss with the drug combination. Associated pharmacodynamic experiments confirmed the mechanism of action of both drugs, and the enhancement of BIM induction with the drug combination.

Preclinical evaluation of selumetinib has shown differential sensitivity in RAS pathway mutated primary ALL cells compared to wild type cells in vitro and this was mirrored in vivo using a xenograft model[3]. This is an orthotopic system in which NOD SCID gamma null mice are engrafted with primary-derived (primagraft) ALL cells which recapitulates the human disease.
Selumetinib-treated mice engrafted with RAS pathway mutated primagraft ALL cells showed significantly reduced levels of peripheral, spleen and CNS ALL compared to animals treated with vehicle control, and importantly no activity was seen with RAS wildtype primagraft cells.
In addition, animals engrafted with RAS-mutant cells and treated with vehicle control showed extensive CNS disease during postmortem examination, whereas in animals treated with selumetinib that was significantly reduced.
The pharmacodynamic analyses after selumetinib dosing in vivo showed an abrogation of the p-ERK signal indicating inhibition of ERK, and induction of apoptosis with an increased signal for BIM and cleaved PARP.

Study objective

Phase I
Primary Objective
- To define the recommended phase II dose (RP2D) of selumetinib/dexamethasone combination in adult and paediatric patients with relapsed/refractory, RAS pathway mutant ALL
Secondary Objectives
- To evaluate safety and tolerability, and analyse pharmacokinetics (PK)

Phase II
Primary Objective
- To assess the preliminary anti-leukemic activity of the combination in relapsed/refractory, RAS pathway-mutant ALL patients
Secondary Objectives
- To evaluate safety and tolerability, and analyse PK

Study design

An international, two-phase, two-group dose finding design, to include paediatric and adult patients: phase I for dose finding; phase II for dose expansion. Group P will enrol all patients under 18 years of age and Group A will enrol all patients who are 18 years or older.

Intervention

Patients will receive selumetinib on cycle 1 day 1, then continuously from cycle 1 day 4 onwards, combined with dexamethasone which will be administered as a pulsed dose on days 2-4, 8-11, 15-18 and 22-25 during cycle 1.The pulsed dose for dexamethasone will continue on days 1-4 during cycle two, then on days 1-5 for any subsequent cycles. Dose levels for each cohort will be determined throughout phase I using a statistical model, observation of dose limiting toxicities, and pharmacokinetic analysis. Phase II patients will be administered the recommended phase II dose determined from the phase I part of the trial using the same schedule.

Study burden and risks

ALL is the most common malignancy of childhood. Although the majority of children with newly diagnosed ALL will achieve a complete remission, approximately 20% will experience a relapse. The remission rates of relapsed ALL are less than the rates for newly diagnosed ALL, which demonstated the need for novel agents to improve outcomes for patients with relapsed disease. Current standard of care therapies for ALL include dexamethasone. The addition of a MEK inhibitor in patients with a RAS-pathway mutation could further boost clinical response through a mechanism of action that differs from the current

chemotherapy.
The safety profile of selumetinib in children and adults for different indicators seems mild and include rash, diarrhea, feeling sick or tired, swollen extremities and face. A complete overview of the adverse effects are found in the investigator brochure (IB).

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

Inclusion criteria

• Morphologically proven relapsed/refractory (M2 or M3 marrow; >=1st relapse for adults, >=2nd relapse in paediatric group - see Appendix 5) or progressive B cell precursor or T-Acute Lymphoblastic Leukaemia (ALL) with demonstrated RAS

pathway activating mutations (NRAS, KRAS, FLT3, PTPN11, cCBL, NF1, BRAF, IKZF2, IKZF3, IL7Rα or JAK1) identified during the trial screening process
• B cell precursor patients must either:
o Have received CAR -T cell therapy, or
o Be awaiting CAR -T cell therapy, or
o Be considered ineligible for CAR -T cell therapy
• Group P (paediatric): <18 years of age; Group A (adult): >=18 years of age
• Adequate renal function:
o Group A: Serum creatinine <1.5 x upper limit of normal (ULN)
o Group P as follows:
* <= 5 years: Serum creatinine <0.8 mg/dL or 70 µmol/L
* > 5 years but <= 10 years: Serum creatinine <1 mg/dL or 88 µmol/L
* > 10 years but <= 15 years: Serum creatinine <1.2 mg/dL or 106 µmol/L
* > 15 years: Serum creatinine <1.5 mg/dL or 132 µmol/L
• Patient is able to swallow selumetinib capsules whole
• Performance status (PS): Group A - Eastern Cooperative Oncology Group (ECOG) <=2 (Appendix 6); Group P - Lansky play scale >=60% (Appendix 7) or Karnofsky scale >=60% (Appendix 8)
• Women of childbearing potential (see section 7.9.1 for definition) must have a negative pregnancy test
• Patients who are women of childbearing potential and male patients with partners who are women of child bearing potential must agree to use appropriate contraception (see section 7.9.1 for definition) whilst on trial.
• Written informed consent
• Absence of any psychological, familial, sociological or geographical factors potentially hampering compliance with the trial protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
• Patients who relapse or progress after HSCT need to be at least at day +100, with no signs of Graft versus Host Disease and off immunosuppressive therapy for at least one week.
• Patients who relapse or progress after CAR T cell therapy should be at least 4 weeks after infusion of CAR T cells.
• Patients must have a body surface area (BSA) >= 0.55 m2.

Exclusion criteria

• ALL without presence of RAS-pathway activating mutations
• Mature B-cell leukaemia and Philadelphia positive ALL
• Prior exposure to MEK, RAS or RAF inhibitors
• Any unresolved toxicity >= CTCAE Grade 2 from previous anti-cancer therapy, except for alopecia
• Cardiac conditions as follows:
Group A and P
o Prior or current cardiomyopathy including but not limited to the following:

* Known hypertrophic cardiomyopathy
* Known arrhythmogenic right ventricular cardiomyopathy
o Even if full recovery has occurred, previous moderate or severe impairment of left ventricular systolic function (LVEF <45% on ECHO in Group A; SF <29% in Group P but excluding transient impairments due to e.g. anaemia/sepsis or results not thought to represent a true reflection of cardiac function)
o Severe valvular heart disease
o Severe congential heart disease
o Uncontrolled hypertension:
* Group A: BP >=150/95 mmHg despite medical therapy
* Group P: BP >=95th percentile for age, height and gender (please refer to Blood Pressure by Age and Height Percentiles tables in Appendices 8 and 9)
Group A
o Baseline (LVEF) below the lower limit of normal (LLN) or <55% measured by ECHO
o Acute coronary syndrome within 6 months prior to trial registration
o Uncontrolled Angina - Canadian Cardiovascular Society grade II-IV despite medical therapy (Appendix 11)
o Symptomatic heart failure New York Heart Association (NYHA) Class II-IV, prior or current cardiomyopathy, or severe valvular heart disease (Appendix 12)
o Atrial fibrillation with a ventricular rate >100 bpm on Electrocardiogram (ECG) at rest
o QTcF >450ms in male patients or >=460ms in female patients, or other factors that increase the risk of QT prolongation
Group P
o Baseline SF <29%
o Atrial fibrillation with a ventricular rate >130 bpm on Electrocardiogram (ECG) at rest
o QTcF >450ms in patients <12 years or >=460ms in patients >=12 but <18 years
• Ophthalmological conditions as follows:
o Current or past history of retinal pigment epithelial detachment (RPED)/central serous retinopathy (CSR) or retinal vein occlusion
o Intraocular pressure (IOP) > 21 mmHg or uncontrolled glaucoma (irrespective of IOP)
• Pregnant and breast feeding females
• Known severe hypersensitivity to selumetinib, dexamethasone or combination medications or any excipient of these medicinal products, or history of allergic reactions attributed to compounds of similar chemical or biologic composition to selumetinib
• Have received or are receiving an IMP or other systemic anti-cancer treatment (not including dexamethasone, prednisolone or hydroxycarbamide) within 4 weeks (6 weeks for nitrosoureas, mitomycin, and suramin) prior to trial registration, or within a period during which the IMP or systemic anticancer treatment has not been cleared from the body (e.g. a period of 5 *half-lives*), whichever is the most appropriate and as judged by the investigator
• Have had recent major surgery within a minimum 4 weeks prior to trial registration, with the exception of surgical placement of vascular access

• Have received radiation therapy within 4 weeks prior to trial registration, or limited field of radiation for palliation within 7 days of the first dose of trial treatment
• Laboratory values as listed below (SI units):
o Serum bilirubin >1.5 x ULN (unless due to Gilbert*s syndrome)
• Have evidence of any other significant clinical disorder or laboratory finding that, as judged by the investigator, makes it undesirable for the patient to participate in the trial.
• Have any evidence of a severe or uncontrolled systemic disease (e.g. unstable or uncompensated respiratory, cardiac, hepatic, or renal disease, active infection (including hepatitis B, hepatitis C, HIV), active bleeding diatheses, or renal transplant)
• Have refractory nausea and vomiting, chronic gastrointestinal diseases (e.g., inflammatory bowel disease), or significant bowel resection that would adversely affect the absorption/bioavailability of the orally administered trial medication
• Any other active malignancy which, in the opinion of the investigator would limit the ability of the patient to complete the study

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-01-2021
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Selumetinib
Generic name:	Selumetinib

Ethics review

Approved WMO Date:	08-10-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	13-05-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	24-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-03-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-06-2021
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	17-08-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-10-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-10-2021
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
EudraCT	EUCTR2016-003904-29-NL
ISRCTN	ISRCTN92323261
CCMO	NL64779.041.19