Inotuzumab Ozogamicin for pediatric CD22-positive relapsed/refractory ALL

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Nonclinical pharmacodynamic studies indicate that InO can be an effective therapeutic agent against B-lymphoid malignancies and support its clinical evaluation as a targeted therapeutic option for B-cell NHL and ALL. Inotuzumab ozogamicin (InO) is a…

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON27023

Bron
Nationaal Trial Register

Verkorte titel
ITCC-059

Aandoening

pediatric CD22-positive relapsed / refractory Acute Lymphoblastic Leukemia

Ondersteuning

Primaire sponsor: ErasmusMC, Rotterdam
Overige ondersteuning: o.a. Pfizer

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

In stratum 1A: Dose-limiting toxicities (DLTs) during the first course of therapy.

In phase 2 cohort: Overall Response Rate, measured as best response during InO treatment

Stratum 2: Safety and tolerability

Stratum 1B and 1B-ASP: Dose-limiting toxicities (DLTs) during the first cycle of InO when added to a modified UKALL-R3 re-induction chemotherapy regimen without or with ASP.

Stratum 3: ORR: % of pats with CR, CRi, CRp, measured as best response to InO treatment

Toelichting onderzoek

Achtergrond van het onderzoek

Inotuzumab Ozogamicin for pediatric CD22-positive relapsed/refractory ALL

Doel van het onderzoek

Nonclinical pharmacodynamic studies indicate that InO can be an effective therapeutic agent against B-lymphoid malignancies and support its clinical evaluation as a targeted therapeutic option for B-cell NHL and ALL. Inotuzumab ozogamicin (InO) is a humanized IgG4 antibody that binds with high affinity to CD22. CD22 is found on B-cell ALL and lymphoma cell lines. Upon binding to CD22 on target tumor cells, the antibody-antigen complex is rapidly internalized and subsequently leads to calicheamicin activation. Activation of calicheamicin causes DNA damage which often results in apoptosis and cell death. Based on promising preclinical results, InO was subsequently studied in phase I-III trials as single-agent as well as in combination with rituximab ± conventional chemotherapy in adult patients with relapsed/refractory B-NHL, and as a single agent for patients with B-cell ALL. Given the activity of InO in adult ALL and the medical need in pediatric relapsed/refractory ALL, development of InO in pediatric ALL seems highly warranted.

Onderzoeksopzet

Different timelines apply for the different cohorts. Patient inclusions of stratum 1A and phase 2 cohort are closed (collection of FUP information still ongoing). Last patient inclusion stratum1b/1b-ASP planned for Q2-2022. Last patient inclusion for stratum 3 is planned for Q1-2023. Collection of FUP info is 3 years.

Onderzoeksproduct en/of interventie

A course of therapy is defined as 3 doses of InO administered weekly on days 1, 8 and 15.

Course 1 will last 22 days (with delays allowed up to 42 days, depending on response and recovery from toxicity), and all subsequent courses will last 28 days, again with delays up to 42 days.

In addition to InO they will receive Anti-emetics and Methylprednisolone on day 1,8 and 15 and intrathecal MTX at day 1.

Patients will receive up to 6 cycles of treatment. Disease evaluation will take place after each course.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

Age

Patients must be ≥ 1 and < 18 years of age at the time of enrollment.

• The first 3 BCP-ALL patients on dose level 1 must be aged 6 years to less than 18 years.

• Then at least 2 additional patients must be enrolled from age 1 year to less than 6 years at the same dose level.

• After this requirement is met, subsequent dose levels may enroll patients aged 1 year to less than 18 years.

• In case 2 younger patients are not yet recruited, patients aged 6 to less than 18 years may continue to be enrolled at dose level 1 until a maximum of 6 patients are enrolled.

Stratum 1A and 1B: Diagnosis

Patients must have either second or greater relapsed or refractory BCP-ALL, or refractory disease as defined below, and must meet the following criteria:

• Patients must have M2 or M3 marrow status (≥ 5% blasts by morphology)

• The malignant clone needs to be CD22 surface antigen positive (in either the bone marrow or peripheral blood) by institutional standards as determined by the local immunophenotyping laboratory.

• The first 6 patients must have M3 marrow status (≥ 25% blasts by morphology).

• Refractory is defined as newly diagnosed patients who are induction failures after at least 2 previous regimens without attainment of remission, or patients with refractory first relapse after 1 previous reinduction regimen without attainment of remission.

Phase 2 Cohort: Diagnosis

Patients must have either second or greater relapsed or refractory BCP-ALL, or refractory disease as defined below, and must meet the following criteria:

• Patients must have M2 or M3 marrow status (≥ 5% blasts by morphology)

• The malignant clone needs to be CD22 surface antigen positive (in either the bone marrow or peripheral blood) by institutional standards as determined by the local immunophenotyping laboratory.

• The first 6 patients must have M3 marrow status (≥ 25% blasts by morphology).

• Refractory is defined as newly diagnosed patients who are induction failures after at least 2 previous regimens without attainment of remission, or patients with refractory first relapse after 1 previous reinduction regimen without attainment of remission.

Stratum 2: Diagnosis

Patients must have second or greater relapsed or refractory CD22-positive B-cell malignancy including but not limited to diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL), Burkitt lymphoma, Burkitt leukemia or B-cell precursor lymphoblastic lymphoma:

• There must be histologic verification of disease at original diagnosis or subsequent relapse.

• Patient must have evaluable or measurable disease documented by radiographic criteria or bone marrow disease present at study entry.

• The malignant cells need to be CD22 surface antigen positive (in either biopsy material, the bone marrow or peripheral blood) by institutional standards as determined by the local immunophenotyping laboratory.

Stratum 3: Diagnosis

Patients must have 1st BM or combined relapsed of VHR CD22-positive BCP-ALL defined as:

• any relapse <18 months from initial diagnosis and/or

• cytogenetic-high risk characteristics: KTM2A/AF4, E2A/TCF3-PBX1, t(1;19) or E2A/TCF3-HLF t(17;19), hypodiploidy (less than 40 chromosomes), TP53 mutation and/or deletion.

• excluding patients transplanted in 1st CR.

• M2 or M3 marrow status (≥ 5% blasts by morphology)

• CD22 surface antigen positive (in either the BM or PB)

• Evidence of prior fusion gene abnormalities is acceptable

• cytogenetic-high risk characteristics determined by chromosome banding analysis (CBA), FISH, PCR and/or Next Generation Sequencing

Performance Level and Life Expectancy

• Karnofsky > 60% for patients > 16 years of age and Lansky > 60% for patients ≤ 16 years of age. (See Appendix I for Performance Scales).

• Patient must have a life expectancy of at least 6 weeks.

Prior Therapy

Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy defined as resolution of all such non-hematologic toxicities to ≤ Grade 2 per the CTCAE 4.03 prior to entering this study, with the exception of the authorized laboratory abnormalities as defined in the inclusion/exclusion criteria.

• Chemotherapy:

At least 7 days must have elapsed since the completion of cytotoxic therapy, with the exception of hydroxyurea, 6-mercaptopurine and steroids which are permitted up until 48 hours prior to initiating protocol therapy. Patients may have received intrathecal therapy at any time prior to study entry. Patients who relapse while receiving maintenance chemotherapy will not be required to have a waiting period before enrollment onto this study.

• Radiotherapy:

At least 28 days must have elapsed since any prior radiation therapy.

• Hematopoietic Stem Cell Transplant:

At least 180 days must have elapsed since previous allo-HSCT. Patient must have no evidence of active graft vs. host disease. Patient must not be receiving GVHD prophylaxis or treatment.

• Hematopoietic growth factors:

At least 7 days must have elapsed since the completion of therapy with GCSF or other growth factors at the time of enrollment. At least 14 days must have elapsed since the completion of therapy with pegfilgrastim (Neulasta®).

• Immunotherapy:

At least 42 days must have elapsed after the completion of any type of immunotherapy, e.g. tumor vaccines or chimeric antigen receptor T cell (CART) therapy. Patients may not have received prior CD22-targeted therapy (immunotoxin or CART therapy).

• Monoclonal antibodies:

At least 3 half-lives of the antibody must have elapsed after the last dose of a monoclonal antibody (ie: Rituximab = 66 days, Epratuzumab = 69 days), with the exclusion of blinatumomab. Patients must have been off blinatumomab infusion for at least 14 days and all drug-related toxicity must have resolved to grade 2 or lower as outlined in the inclusion and exclusion criteria.

• Investigational drugs:

At least 7 days or 5 drug half-lives (whichever is longer) must have elapsed since prior treatment with any experimental drug (with the exception of monoclonal antibodies) under investigation. No residual toxicities should be observed following previous treatment. An experimental drug is defined as any drug that is not approved and licensed for sale by the FDA for institutions in the United States, by the EMA for institutions in Europe, by Health Canada for institutions in Canada and by The Therapeutic Goods Administration for institutions in Australia.

• Prior calicheamicin exposure:

Patient has not received prior treatment with a calicheamicin-conjugated antibody (e.g. gemtuzumab ozogamicin).

Renal and Hepatic Function

• Patient’s serum creatinine must be ≤ 1.5 x institutional upper limit of normal (ULN) according to age. If the serum creatinine is greater than 1.5 times normal, the patient must have a radioisotope GFR ≥ 70mL/min/1.73m2.

• Patient’s AST and ALT must be ≤ 2.5 x institutional ULN.

• Patient’s total bilirubin must be ≤ 1.5 x institutional ULN unless the patient has documented Gilbert syndrome, and AST and ALT are □□2.5 x ULN.

Cardiac Function

• Patient must have a shortening fraction ≥ 30% by echocardiogram or an ejection fraction >

50% by MUGA.

Reproductive Function

• Female patients of childbearing potential must have a negative urine or serum pregnancy test confirmed prior to enrollment.

• Female patients with infants must agree not to breastfeed their infants while on this study.

• Male and female patients of child-bearing potential must agree to use an effective method of contraception approved by the investigator during the study and for 90 days after the last dose of InO.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

Isolated extramedullary relapse

Patients with isolated extramedullary disease are excluded (not applicable to lymphoma patients except for isolated CNS-relapse)

VOD/SOS

Patients with any history of prior or ongoing VOD/SOS per the modified Seattle criteria are excluded, as specified in appendix 3, or prior liver-failure [defined as severe acute liver injury with encephalopathy and impaired synthetic function (INR of ≥1.5)].

Infection

Patients will be excluded if they have a systemic fungal, bacterial, viral or other infection that is exhibiting ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics or other treatment. The patient may not have:

• A requirement for vasopressors;

• Positive blood culture within 48 hours of study enrollment;

• Fever above 38.2 within 48 hours of study enrollment with clinical signs of infection. Fever that is determined to be due to tumor burden is allowed if patients have documented

negative blood cultures for at least 48 hours prior to enrollment and no concurrent signs or symptoms of active infection or hemodynamic instability.

• A positive fungal culture within 30 days of study enrollment.

• Active fungal, viral, bacterial, or protozoal infection requiring IV or oral treatment. Chronic prophylaxis therapy to prevent infections is allowed.

Other anti-cancer therapy

Patients will be excluded if there is a plan to administer non-protocol anti-cancer therapy including but not limited to chemotherapy, radiation therapy, or immunotherapy during the study period.

Allergic reaction

Patients with prior Grade 3/4 allergic reaction to a monoclonal antibody are excluded.

Concurrent disease

Patients will be excluded if they have significant concurrent disease, illness, psychiatric disorder or social issue that would compromise patient safety or compliance with protocol therapy, interfere with consent, study participation, follow up, or interpretation of study results.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	01-07-2016
Aantal proefpersonen:	156
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nee

Ethische beoordeling

Positief advies

Datum:	31-03-2016
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL5629
NTR-old	NTR5736
Ander register	Sponsor : ITCC-059 // 2016-000227-71

Resultaten