A PROSPECTIVE, RANDOMIZED, OPEN-LABEL PHASE 2 STUDY TO EVALUATE THE SUPERIORITY OF INOTUZUMAB OZOGAMICIN MONOTHERAPY VERSUS ALLR3 FOR INDUCTION TREATMENT OF CHILDHOOD HIGH RISK FIRST RELAPSE B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKAEMIA

Published: 08-11-2022
Last updated: 14-09-2024

This study has been transitioned to CTIS with ID 2023-509810-13-00 check the CTIS register for the current data. Primary Objectives Efficacy: To demonstrate the superiority of InO monotherapy vs ALLR3 induction in paediatric participants between 1...

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

Summary

ID

NL-OMON53624

Source
ToetsingOnline

Brief title
InO Monotherapy vs ALLR3 as Induction Treatment of childhood ALL

Condition

- Leukaemias

Synonym
Relapsed Acute Lymphoblastic Leukemia and Relapsed Childhood leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: Pfizer Inc

Intervention

Keyword: ALLR3, CHILDHOOD LEUKEMIA, HIGH RISK ALL, HIGH RISK RELAPSED ALL, INOTUZUMAB

Outcome measures

Primary outcome

Primary:

Efficacy: To demonstrate the superiority of InO monotherapy vs ALLR3 induction

in paediatric participants between 1 and <18 years with HR first bone marrow

relapse CD22-positive BCP ALL

Endpoints: MRD-negative, CR/CRp/CRi (per investigator assessment) at the end of

induction therapy (MRD negativity is assessed by central lab and defined as

leukemic blasts <1x10-4 by RQ-PCR [with reflex to FC result if MRD is

non-evaluable by RQ-PCR]).

Estimands: The treatment effect in the targeted population of InO monotherapy

assessed by the MRD negative CR/CRp/CRi rate, based on investigator assessment

per modified NCCN criteria (Section 10.12 of the full protocol) vs ALLR3

induction from the date of randomization to EOT.

Secondary outcome

Secondary:

Key Secondary Efficacy: To evaluate the long-term efficacy of InO monotherapy vs ALLR3 regimen with respect to EFS

Endpoints: EFS, defined as the time from randomization until objective progression, relapse from CR/CRp/CRi, based on investigator assessment per response criteria, failure to achieve CR/CRp/CRi by the end of induction, MRD persistence prior to HSCT, second malignancy, or death due to any cause.

Key Secondary Estimand: EFS: treatment effect in the targeted population of InO monotherapy induction on EFS based on investigator assessment compared to the ALLR3 induction from randomization to the date of event.

Efficacy: To evaluate the long-term efficacy of InO monotherapy vs ALLR3 regimen with respect to:

• DOR

• HSCT rate

• CAR T-cell therapy rate

• OS

Endpoints: DOR, defined as time from date of first documented response (CR/CRp/CRi) to the date of first documented objective progression, relapse from CR/CRp/CRi as determined by investigator assessment per modified NCCN response criteria, MRD persistence prior to HSCT, or death due to any cause, whichever occurs first.

HSCT (and CAR T-cell therapy) rate, defined as the number and percentage of participants being transplanted and those receiving CAR T-cell therapy after

treatment with InO or ALLR3.

OS, defined as the time from the date of randomization to the date of death due

to any cause.

Estimands: Not Applicable

Safety: To evaluate the safety and tolerability of InO monotherapy vs ALLR3

induction

Enpoints: Incidence and severity of AEs graded per NCI CTCAE v4.03.

Estimands: Not Applicable

Pharmacokinetics

To evaluate the PK of InO

npoints:Cmax and Ctrough

Estimands: Not Applicable

Study description

Background summary

ALL is the most frequent malignant disease in childhood with an incidence of approximately 4 in 100,000 children per year. In the past 2 decades, significant improvement in outcome has been made in the treatment of childhood ALL, with current rates of EFS in first CR of 80% to 90% with the use of multidrug front-line protocols (Pui et al, 2004; Mitchell et al, 2010; Moricke et al, 2010). Although the prognosis for relapsed childhood ALL is substantially improved with intensive multidrug chemotherapy and allo HSCT, these therapies are also associated with major acute and long term toxicities, including early and late treatment related deaths. In addition, the low rate of MRD negativity especially for patients with early relapse (high risk) or late relapse with residual disease after reinduction chemotherapy (intermediate risk) indicates the continued unmet medical need and importance of developing

new induction therapies for this patient setting.

Study objective

This study has been transitioned to CTIS with ID 2023-509810-13-00 check the CTIS register for the current data.

Primary Objectives
Efficacy:
To demonstrate the superiority of InO monotherapy vs ALLR3 induction in paediatric participants between 1 and < 18 years with HR first bone marrow relapse CD22-positive BCP ALL

Secondary Objectives:
Key Secondary Efficacy: To evaluate the long-term efficacy of InO monotherapy vs ALLR3 regimen with respect to EFS
Efficacy: To evaluate the long-term efficacy of InO monotherapy vs ALLR3 regimen with respect to:
• DOR
• HSCT rate
• CAR T-cell therapy rate
• OS
Safety: To evaluate the safety and tolerability of InO monotherapy vs ALLR3 induction
Pharmacokinetics: To evaluate the PK of InO C

Study design

This prospective, randomized, multicenter, open-label, Phase 2 study is designed to evaluate the superiority of InO monotherapy vs ALLR3, after 1 cycle of induction treatment in paediatric participants (between 1 and <18 years) with HR first bone marrow relapse CD22-positive BCP ALL, and to evaluate the safety and tolerability, PK and long-term efficacy. Treatment with study intervention will end after induction therapy; follow-up for efficacy and safety will continue for up to 5 years from randomization. Refer to Section 1.2 of the protocol for the study design schema.
End of Treatment is defined as occurring upon recovery from 1 cycle of study therapy (Day 28 ± 2 days), or one day before initiation of new anticancer therapy, whichever occurs first.
Approximately 100 participants will be randomized (2:1) to receive 1 cycle of either InO monotherapy or ALLR3 (block 1) therapy during induction. Refer to Section 6 of the protocol for details.
After completion of induction therapy (ie, study therapy), it is anticipated that the majority of responding participants will proceed immediately to consolidation therapy. Non-responders are expected to proceed with salvage therapy at the investigator*s discretion.

Participants responding to induction therapy are expected to proceed to SOC consolidation therapy upon recovery of blood counts, but no sooner than 7 days after last dose of study intervention.
To standardize consolidation therapy for study participants, responders will be encouraged to enroll in the IntReALL BCP 2020 (I2020 trial) sponsored by Charite University, Berlin, Germany. All participants enrolled in the HR stratum of I2020 will receive SOC consolidation therapy, consisting of:
• 1 cycle of multi-agent chemotherapy (HC1; regimen includes dexamethasone, vincristine, asparaginase, methotrexate 1g/m2 and cyclophosphamide over 6 days). This consolidation cycle is intended to allow recovery of CD19+ cells prior to blinatumomab.
• followed by 1 cycle of blinatumomab, based on results from (Brown et al, 2021; Locatelli et al, 2021)
• followed by allogeneic HSCT, based on results from the FORUM randomized trial (Peters et al, 2021).
B1931036 responders who do not enroll in the I2020 trial should receive the same or similar SOC consolidation therapy.
All participants (responders and non-responders) will proceed to long-term follow-up for this study (Refer to Table 3). All subsequent anticancer therapy will be determined by the treating physician.

Intervention

Intervention Groups and Duration
Participants will be randomized (2:1) to receive 1 cycle of either InO monotherapy or ALLR3 (block 1) therapy during induction.

InO Monotherapy Arm
Participant in the InO arm will receive 1 course (3 doses) of InO intravenously for 1 cycle (28 days). Each InO dose will be infused over 60 minutes ± 15 minutes. On Day 1, a 2-hour medical observation period is required at the end of infusion. On Days 8 and 15, a 1-hour medical observation period is required. There must be a minimum of 6 days between InO doses.
• Day 1: 0.8 mg/m2
• Day 8 (±1 day) and Day 15 (±1 day): 0.5 mg/m2/dose

ALLR3 Therapy Arm
Control arm participants will receive the following study interventions:
Mitoxantrone 10 mg/m2 administered via IV infusion over 1 hour (± 15 min) on Days 1 and 2, unless the Day 2 dose is contraindicated due to toxicity.
Vincristine 1.5 mg/m2 (maximum single dose 2 mg) administered by slow IV push or as a 15 min infusion (± 5 min) on Days 3, 10, 17 and 24 (±1 day per dose). For participants weighing 10 kg or less, the starting dose of vincristine will be 0.05 mg/kg, administered once a week (on days noted above).
Dexamethasone 20 mg/m2/day administered orally (or IV) divided into two daily doses (maximum 40 mg/day) as two 5-day blocks (Days 1-5 and Days 15-19).

PEG-ASP 1000 units/m2 IV administered on Days 3 and 17 (± 1 day per dose).

Intrathecal Therapy
IT methotrexate alone or triple IT (methotrexate + cytarabine + prednisolone or hydrocortisone) is strongly recommended for all participants on Days 1, 8, and EOT based on the participant*s screening CNS status and investigator*s judgement.
Every effort should be made to administer the planned doses of all study intervention according to the SoA.

Study burden and risks

Benefit/Risk Assessment
More detailed information about the known and expected benefits and risks and reasonably expected AEs of InO may be found in the IB, which is the SRSD for this study. The SRSD for each agent in the ALLR3 therapy is UK SmPC (Accord Healthcare) for mitoxantrone, UK SmPC (Hospira) for vincristine, UK SmPC (Noridem 3.3 mg/ml) for dexamethasone, and EU SmPC (Oncaspar) for PEG-ASP. The SRSD for each agent in the IT therapy is the UK SmPC (Accord Healthcare 25mg/ml Solution for Injection) for methotrexate, UK SmPC (Accord Healthcare 20mg/ml) for cytarabine, Netherlands SmPC (Di-Adreson-F 25 mg) for prednisolone and Swiss SmPC (SoluCortef) for hydrocortisone.

Benefit Assessment
There remains an urgent unmet need to develop novel therapeutic strategies for paediatric patients facing relapse of HR ALL. Contemporary reinduction regimens have relied on further intensification of standard chemotherapeutic agents with higher doses and/or compacted drug schedules. However, these strategies fail to address one of the major challenges present in many HR ALL patients at relapse; intrinsic chemoresistance. Most current strategies have not only failed to improve remission rates, but have also reached tolerability limits, with toxic death rates ranging from 3% to 8% (Sun et al, 2016; von Stackelberg et al, 2016). As further dose intensification is not tolerable, new therapeutic approaches which incorporate novel agents into conventional therapeutic strategies are urgently needed to overcome chemoresistance and thus improve outcomes. InO monotherapy is expected to lead to higher MRD negative remission rates as a prerequisite for further effective consolidation and allogeneic HSCT, and thus for improved EFS. Furthermore, it is expected to lead to less toxicity with respect to aplasia and neutropenia, and consequently to less severe infections as the most frequent reason for treatment-related mortality, furthermore to less organ toxicity representing the broad spectrum of AEs caused by aggressive multiagent chemotherapy.

Overall Benefit/Risk Conclusion
Taking into account the measures taken to minimize risk to study participants, the potential risks identified in association with InO are justified by the anticipated benefits that may be afforded to participants under the age of 18

years with relapsed HR ALL.

Potential Risk of Clinical Significance

Inotuzumab Ozogamicin
• Hepatotoxicity, including SOS
• Myelosuppression/cytopenia
• Infections and hemorrhage
• QT prolongation
• Second Primary Malignancy
Potential risks are based on the SmPC, and the IB.
Mitigation Strategy:
• Monitor closely: TBILI, ALT, AST values and for S/S of SOS.
• Start defibrotide early, as clinically indicated.
• Monitor closely: CBC, diff/plt, S/S infection or bleeding.
• ECG monitoring as clinically indicated.
• Long-term, monitor for S/S of SPM.

Mitoxantrone (Control arm only)
• Cardiac dysfunction
• Myelosuppression
• Systemic infection
• Secondary AML and MDS
Potential risks are based on the SmPC.
Mitigation Strategy:
• Assess for cardiac S/S, PE, ECG, Echo.
• Monitor CBC with diff/plts and for S/S of infection or bleeding.
• Monitor AEs and laboratory results.
• Administer preventive antibiotic/antimycotic therapy.

Vincristine (Control arm only)
• Peripheral neuropathy
Potential risks are based on the SmPC.
Mitigation Strategy:
• Monitor for AEs.

Dexamethasone/Methylprednisolone (mainly relates to high doses for control arm only)
• Increased susceptibility to infections
• Growth suppression when used over a prolonged period of time
• Increased ICP
• Pancreatitis and/or increased blood glucose
• Hypothalamic-pituitary-adrenal suppression
• Renal, urinary, GI and/or hepatobiliary effects
• Psychiatric adverse reactions
• Cardiac and/or vascular effects
• Kaposi*s sarcoma

Potential risks are based on the SmPC.
Mitigation Strategy:
• Monitor CBC with diff/plt and observe for S/S of infection or bleeding.
• Monitor PE, AEs and lab results closely.
• Assess for cardiac S/S by history, PE, ECG and ECHO as clinically indicated.
• Administer preventive antibiotic/antimycotic therapy.

PEG-Asparaginase (Control arm only)
• CNS effects
• Pancreatitis
• Coagulopathy
• Myelosuppression/microbial infections of the mouth
Potential risks are based on the SmPC.
Mitigation Strategy:
• Monitor AEs and lab results; observe for S/S of infection or bleeding.
• Observe for signs of clotting or bleeding.

Methotrexate (Intrathecal)*
• Occasionally causes headaches, dizziness, tiredness, blurred vision, or loss of balance for a few hours.
• Up to 15% of children develop neurological changes e.g. fits, change in level of consciousness, abnormal movements or confusion.
• Very rarely, leukoencephalopathy, most common in children who have had CNS leukemia, and after radiotherapy.
Potential risks are based on the SmPC.
Mitigation Strategy:
• Monitor and provide supportive care as clinically indicated
*Triple IT therapy may also be used at the discretion of the Investigator.
Potential risks for each agent in the IT therapy are based on the SmPCs for each agent as documented in Section 2.3.

All Study Interventions
• Reproductive and developmental toxicity (assuming exposure during pregnancy and/or while breast feeding)
Mitigation Strategy: Follow protocol guidelines for contraception requirements. Mandatory contraception will be implemented in WOCBP and males (see Section 5.3.1).

Lumbar puncture and bone marrow aspirate/biopsy
• Pain, infection
• LP (spinal cord/nerve injury)
Based on standard medical practice.
Mitigation Strategy:
• Use of local/general anesthetic and sterile technique.
• Performed by qualified medical practitioners per local SOC.
*Triple IT therapy may also be used at the discretion of the Investigator.
Potential risks for each agent in the IT therapy are based on the SmPCs for

each agent as documented in Section 2.3.

Contacts

Public
Pfizer

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NL
Scientific
Pfizer

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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

Participants must meet the following key inclusion criteria to be eligible for enrollment into the study:
1. Male or female participants between 1 and <18 years of age.
2. Morphologically confirmed diagnosis of first relapse HR BCP ALL:
• CD22-positive ALL as defined by local institution.
• Bone marrow involvement of >= 5% leukemic blasts (>= M2 status).
3. Cardiac shortening fraction >= 30% by echocardiogram or ejection fraction >

50% by MUGA.

Exclusion criteria

Participants with any of the following key characteristics/conditions will be excluded:
1. Any history of prior or ongoing hepatic SOS or prior liver failure [defined as severe acute liver injury with encephalopathy and impaired synthetic function (INR of >=1.5)].
2. Prior allo-HSCT or CAR T-cell therapy.
3. Isolated extramedullary leukemia.
4. Philadelphia-chromosome positive ALL, ie. BCR-ABL/t(9;22) present.
5. Prior therapy with a calicheamicin-conjugated antibody (eg, InO or gemtuzumab ozogamicin).
6. Participants with active, uncontrolled bacterial, fungal, or viral infection.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	31-07-2023
Enrollment:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Besponsa
Generic name:	INOTUZUMAB OZOGAMICIN
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	DEXAMETHASONE PHOSPHATE
Generic name:	DEXAMETHASONE PHOSPHATE
Product type:	Medicine
Brand name:	MITOXANTRONE HYDROCHLORIDE
Generic name:	MITOXANTRONE HYDROCHLORIDE
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Pegaspargase
Generic name:	Pegaspargase
Product type:	Medicine
Brand name:	VINCRISTINE SULFATE
Generic name:	VINCRISTINE SULFATE

Ethics review

Approved WMO Date:	08-11-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-02-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	06-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	12-05-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-06-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-07-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-05-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-05-2024
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	CTIS2023-509810-13-00
EudraCT	EUCTR2022-000186-40-NL

Register	ID
CCMO	NL81874.041.22