A Phase 1, Dose Escalation, and Cohort Expansion Study Evaluating NX-5948, a Bruton*s Tyrosine Kinase (BTK) Degrader, in Adults with Relapsed/Refractory B-cell Malignancies

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This study has been transitioned to CTIS with ID 2023-510541-25-00 check the CTIS register for the current data. This study*s phase 1a primary objectives are:• To evaluate the safety and tolerability of BTK degrader NX-5948, when taken orally, in...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Interventional

Summary

ID

NL-OMON54003

Source
ToetsingOnline

Brief title
NX-5948-301

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
B-cell lymphomas, blood cancer

Research involving
Human

Sponsors and support

Primary sponsor: Nurix Therapeutics, Inc
Source(s) of monetary or material Support: Industry

Intervention

Keyword: B-cell malignancies, Bruton□s Tyrosine Kinase (BTK), BTK Degrader, Lymphoma

Outcome measures

Primary outcome

This study*s phase 1a primary outcome parameters are:

• Incidence of treatment-emergent adverse events (TEAEs); Grade 3, 4, 5 TEAEs; serious adverse events (SAE); TEAEs leading to study drug discontinuation; deaths due to TEAEs, and all deaths

• Changes from baseline in safety parameters

• Incidence of dose limiting toxicities (DLTs)

This study*s phase 1b primary outcome parameters are:

• ORR

• Incidence of TEAEs; Grade 3, 4, 5 TEAEs; SAEs; TEAEs leading to discontinuation; deaths due to TEAEs; all deaths; and changes in safety parameters

Secondary outcome

This study*s phase 1a secondary outcome parameters are:

• NX-5948 PK parameters in plasma (maximum concentration [Cmax], time at which Cmax is observed [Tmax], half-life, area under the concentration time curve up to the last measurable concentration [AUC0-last], area under the concentration

time curve to the end of a dosing period [AUC0-tau], minimum concentration [Cmin], accumulation ratio).

• Changes from baseline of BTK levels in B cells

• Overall response rate (ORR)

• Complete response (CR) rate

For patients with CLL, CR/complete response with incomplete recovery (CRi)

• Time to first response

• Duration of response (DOR)

• Progression-free survival (PFS)

• Time to next therapy

This study*s phase 1b secondary outcome parameters are:

• NX-5948 PK parameters (Cmax, Tmax, half-life, AUC0-last, AUC0-tau, Cmin, accumulation ratio, Cerebrospinal Fluid (CSF): plasma concentration ratio) in plasma and CNS (for patients with CNS disease only)

• Changes from baseline of BTK levels in B cells

• CR rate

For patients with CLL, CR/ complete response with incomplete recovery.

• Time to first response

• DOR

• PFS

• Time to next therapy

Study description

Background summary

Non-Hodgkin*s lymphoma (NHL) accounts for 3% of both cancer diagnoses and deaths worldwide. There are approximately 509,000 new cases of NHL worldwide and 248,700 deaths (Thanda 2021) B-cell NHL accounts for 85% of all NHL cases. In the UK, the incidence of NHL is approximately 12 per 100,000 and the mortality is 3 per 100,000 (Thanda 2021). Patients with R/R NHL have extremely poor prognosis, especially after two prior therapies. Even when approved therapies exist, the median Overall Survival (OS) is low:
• 12.4 months median OS for polatuzumb vedotin with bendamustine and rituximab in DLBCL (Sehn 2019).
• 20.3 months median OS for idelalisib in FL (Gopal 2014).
• 19.0 months median OS for lenalidomide in MCL (Goy 2013).
Thus, there remains a high unmet medical need to develop novel and efficacious agents for patients with relapsed and refractory B-cell malignancies.

Lymphoid neoplasms of mature B-cells are classified in part based upon a comparison of the immunophenotype and genotype of the tumor cells to normal stages of B-cell development as well as other characteristic immunophenotypic and genetic features.
These tumors can be derived from any stage of mature B-cell development, including naive B-cells, germinal center B-cells, post-germinal center memory B-cells, or plasma cells. The most common B-cell neoplasms derive from cells that have experienced a germinal center reaction, which is initiated when antigen stimulated B-cells migrate into the germinal centers (or follicles) of secondary lymphoid organs (e.g., lymph nodes, spleen, and mucosa associated lymphoid tissues). Germinal center B-cells proliferate and undergo two events that permit the diversification of immunoglobulin genes, somatic hypermutation and heavy chain class switching. Most tumors of mature B-cells, including plasma cell neoplasms, show evidence of somatic hypermutation, and it is thought that "mistakes" that occur during somatic hypermutation and class switching are responsible for many of the acquired mutations that lead to B-cell transformation. The latest World Health Organization classification, updated in 2016, identifies more than 40 major B-cell malignancy subtypes with distinct genetic, morphologic, and clinical features.
BTK is a key component of the B-cell receptor (BCR) signaling pathway and has been clinically validated as a target in the treatment of B-cell malignancies. BTK inhibition has been shown to be safe and effective for several B-cell malignancies, but acquired resistance to currently approved agents leads to poor outcomes and has been difficult to overcome. BTK degradation may provide a promising mechanism of overcoming such resistance.
BCR signaling is indispensable for the adhesion, survival, and growth of human B-cells. Chronic activation of the BTK-mediated BCR signaling is a hallmark of many B-cell lymphoid malignancies making it an attractive therapeutic target.

Therapies targeting BTK are approved for the treatment of various B-cell lymphomas, including MCL, CLL, SLL, WM, and MZL. These BTKi*s bind covalently to cysteine 481 (C481) of the BTK protein and profoundly impair BCR signaling, however, acquired mutations of C481 are associated with clinical resistance to these agents and subsequent relapse. There are several noncovalent BTKi that do not require binding to C481, which are currently being investigated in clinical trials as potential therapies for patients with relapsed/refractory disease. However, other mutations have been shown to decrease the in vitro activity of these non-covalently bound BTKi suggesting that mutations may ultimately limit the effectiveness of these compounds as well.
Small molecule-induced protein degradation of BTK offers a unique approach to overcome such resistant mutations. NX-5948 is a chimeric targeting molecule that induces the degradation of BTK in cells through recruitment of cereblon, an adaptor protein of the E3 ubiquitin ligase complex, and promotes the formation of a ternary complex of CRBN, NX-5948, and BTK. Within this complex, ubiquitin is transferred to BTK directing it for degradation by the proteasome. Nurix has generated data demonstrating that NX-5948 degrades both wild type (DC50 of 1.81 nM in primary human B-cells) and ibrutinib-resistant forms of the BTK protein in a lymphoma cell line, representing a potential approach to targeting both wild-type and mutant pathways. In addition, NX-5948 demonstrates potent tumor growth inhibition across orally delivered doses in BTK-dependent mouse xenograft tumor models expressing either wild type or ibrutinib-resistant C481S BTK mutant protein. This therapeutic modality (i.e., targeted degradation) may also be beneficial in BTK-driven malignancies bearing non-C481 mutations arising in patients treated with non-covalent second-generation BTKi.

Study objective

This study has been transitioned to CTIS with ID 2023-510541-25-00 check the CTIS register for the current data.

This study*s phase 1a primary objectives are:
• To evaluate the safety and tolerability of BTK degrader NX-5948, when taken orally, in adult patients with R/R B cell malignancies
• To establish the Maximum Tolerated Dose (MTD) and/or recommended Phase 1b dose (s) of NX 5948 in adult patients with R/R B-cell malignancies.

This study*s phase 1a secondary objectives are:
• To characterize the PK profile of NX-5948
• To characterize the PD profile of NX-5948
• To assess preliminary anti-tumor activity of NX-5948

This study*s phase 1b primary objectives are:
• To evaluate the anti-tumor activity of NX 5948 in least 2 DLs in patients with CLL/SLL selected for Phase 1b safety expansion.
• To evaluate the anti-tumor activity of NX-5948 in patients with NHLs (MCL, MZL, DLBCL/HGBL, FL, PCNSL/SCNSL) or WM based on the DLs selected for Phase 1b

safety expansion.
• To further characterize and compare the safety and tolerability of at least 2 DLs of NX-5948 in patients with CLL/SLL based on the dose(s) selected in Phase 1a for Phase 1b safety expansion.
• To further characterize the safety and tolerability of NX-5948 in patients with NHLs (MCL, MZL, DLBCL/HGBL, FL, PCNSL/SCNSL) or WM based on the DLs selected in Phase 1a for Phase 1b safety expansion.
To establish the optimal dose for patients with CLL/SLL based on safety, tolerability, anti-tumor activity, and PK/PD profile for further evaluation of dose expansion arms.

This study*s phase 1b secondary objectives are:
• To further characterize the PK profile of at least 2 DLs of NX-5948
• To further characterize the PD profile of at least 2 DLs of NX-5948
• To further assess anti-tumor activity of NX-5948 in at least 2 DLs selected for Phase 1b safety expansion.

Study design

This is a first-in-human, open-label, multicenter, Phase 1a/1b study evaluating the safety, tolerability, and anti-tumor activity of NX-5948 in adult patients with relapsed/refractory B-cell malignancies. The study will be divided into 2 parts: dose escalation (Phase 1a) followed by safety expansion (Phase 1b).

Intervention

phase1a:
Subjects in this phase who meet all inclusion criteria and do not meet any of the exclusion criteria are assigned to 1 dose of the dose escalation period. The subjects are given one or more capsules to match a dose of 50, 100, 200, 300, 450, 600, 800 or 1000 mg/day. A higher dose can be decided. Each dose escalation cohort will include 3-6 patients and may enroll a maximum of 12 backfill subjects per previously clear dose level.
The study drug is a capsule taken with water in the morning. Fasting is required for 2 hours both before and after taking the capsules.
The night before the intensive PK visits (Cycle 1 Day 1 and Cycle 2 Day 1), the subject must be fasted, for at least 8 hours before study drug intake, up until 2 hours after study drug intake.

phase 1b:
In the second part of the study (the expansion), different groups of subjects receive the selected dose from the dose escalation part (1a) with a maximum of 20 subjects per arm.

Study burden and risks

Nonclinical data available for NX-5948 support possible toxicities, including reversible subcutaneous hemorrhage, mucosal effects, and decreased red cell mass (anemia/cytopenia). The toxicity profile of NX-5948 in non human primates, at doses up to 100 mg/kg for 28 consecutive days is generally consistent with BTK inhibition.
Toxicities associated with BTKi include an increased risk of bleeding, particularly for patients receiving concurrent anticoagulation. Additional AEs associated with use of BTKi include serious and opportunistic infections, cytopenias, cardiovascular complications such as cardiac arrhythmias and hypertension, and tumor lysis syndrome.
The study protocol contains entry criteria, DLT definitions, and Safety Review Committee oversight to minimize risk to study participants. Patients will be monitored for signs and symptoms of toxicities throughout the study.
The study will utilize an Safety Review Committee. Decisions on dose escalation will be made by the SRC. The Safety Review Committee will be comprised of representatives of the Sponsor, the Sponsor*s Medical Monitor, the CRO*s Medical Monitor (if applicable), and at a minimum, a quorum of Investigators with subjects under review.
Given that the main expected adverse effects of NX-5948 are anticipated to be similar to BTKi, NX-5948 has an acceptable risk/benefit profile for use in patients with treatment relapsed/refractory malignant disease.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Patients must be >= 18 years of age, and mentally competent

Patients in Phase 1a (Dose Escalation) must have 1 of the following histologically confirmed R/R B-cell malignancies: R/R CLL, SLL, DLBCL of the following subgroups: DLBCL, not otherwise specified (NOS), geminal center B-cell type, activated B-cell type (includes transformed indolent lymphoma [eg, grade 3b/transformed FL] and Richter-transformed DLBCL, high-grade B-cell lymphoma (HGBL) with MYC and BCL-2 and/or BCL-6 rearrangements, high-grade B-cell lymphomas NOS), (note: other subgroups of DLBCL or LBCL from the 2016 WHO classification of lymphoid malignancies are excluded), FL (grade 1-3a; eligibility for systemic treatment as determined by the Groupe d*Etude des Lymphomes Folliculaires [GELF] criteria), MCL, MZL (eligible subtypes include EMZL, MALT, NMZL and SMZL), WM, PCNSL.
- Patients in Phase 1a must meet the following:
a. For non-PCNSL indications, received at least 2 prior lines of therapy and have no other therapies known to provide clinical benefit.
b. For PCNSL, received at least 1 prior line of therapy.

Patients in Phase 1b (Safety Expansion) must have 1 of the following histologically documented R/R B-cell malignancies, must meet criteria for systemic treatment, and must have received the following prior therapies based on indication:

CLL/SLL arm:
• CLL or SLL with prior exposure to both a BTKi and BCL-2 inhibitor, unless previously deemed ineligible for those therapies.

MCL arm:
• MCL with prior exposure to a BTKi and an anti-CD20 monoclonal antibody (mAb)-based chemo-immunotherapy regimen.

MZL arm:
• MZL (EMZL, MALT, NMZL, SMZL) with prior exposure to an anti-CD20 mAb-based chemo-immunotherapy regimen and an additional line of therapy.

WM arm:
• WM with prior exposure to a BTKi and an additional line of therapy.

DLBCL arm:
• DLBCL of the following subgroups with prior exposure to an anthracycline (unless previously deemed ineligible to receive), an anti-CD20 mAb based chemo-immunotherapy regimen, and an additional line of therapy:
o NOS, germinal center B-cell type, activated B-cell type (includes transformed indolent lymphoma [eg, grade 3b/transformed FL] and Richter-transformed DLBCL.
o HGBL with MYC and BCL-2 and/or BCL- 6 rearrangements, and HGBL NOS
(note: other subgroups of DLBCL or LBCL from the WHO classification of lymphoid malignancies

FL arm:
FL (grade 1-3a; eligibility for systemic treatment as determined by the GELF criteria) with prior exposure to an anti-CD20 mAb-based chemo-immunotherapy regimen and an additional line of therapy.

PCNSL/SCNSL arm:
• PCNSL patients who have progressed or had no response to at least 1 prior line of therapy.
• SCNSL patients meeting criteria for non-CLL/SLL arms above with secondary CNS involvement of lymphoma.

Exclusion criteria

- Known or suspected prolymphocytic leukemia or Richter*s transformation to Hodgkin*s lymphoma at any time preceding enrollment.
- Prior treatment for the indication under study for anti-cancer intent that includes:
a. Radiotherapy within 2 weeks of planned start of study drug (excluding limited plaliatiev radiation).
b. Prior systemic chemotherapy within 2 weeks of planned start of study drug.
Note: Use of intrathecal chemotherapy is allowed per institutional guidelines.
c. Prior mAb therapy within 4 weeks of planned start of study drug.
d. Prior small molecule therapy within 5 half-lives or 2 weeks (whichever is shorter) of planned start of study drug.
e. Autologous or allogeneic stem cell transplant within 100 days prior to planned start of study drug.
f. Chimeric antigen receptor (CAR) T-cell therapy within 100 days prior to start of study drug (within 60 days prior to start of study drug for Phase 1b).
g. Use of systemic corticosteroids outside of dosing limits described below and within 14 days prior to initiation of study treatment excepting those used as prophylaxis for radio diagnostic contrast. Patients with central nervous system lymphoma (CNSL, including both primary and secondary CNSL): no greater than 40 mg/day prednisone, or equivalent; CNSL patients using greater than 20 mg/day prednisone, or equivalent must be clinically stable at that dose for 14 days.

All other diagnoses: no greater than 20 mg/day prednisone or equivalent.
h. Use of systemic immunosuppressive drugs other than systemic corticosteroids for any medical condition within 60 days, prior to first dose of study drug.
i. Previously treated with a BTK degrader.
- Active, uncontrolled autoimmune hemolytic anemia or autoimmune thrombocytopenia.
- Patient has any of the following:
a. Myocardial infarction, unstable angina, unstable symptomatic ischemic heart disease, or placement of a coronary arterial stent within 6 months of planned start of study drug.
b. Uncontrolled atrial fibrillation or other clinically significant arrhythmias, conduction abnormalities, or New York Heart Association (NYHA) class III or IV heart failure within 6 months of planned start of study drug.
c. Thromboembolic events (eg, deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events), stroke, or intracranial hemorrhage within 6 months of planned start of study drug.
d. Any other significant cardiac condition (eg, pericardial effusion, restrictive cardiomyopathy, severe untreated valvular stenosis, severe congenital heart disease, or persistent uncontrolled hypertension defined as systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg despite optimal medical management) within 6 months of planned start of study drug.
- Bleeding diathesis, or other known risk for acute blood loss.
- History of Grade >= 2 hemorrhage within 28 days of planned start of study drug.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-10-2023
Enrollment:	40

Type:	Actual

Ethics review

Approved WMO Date:	05-10-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-12-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-01-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-04-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-12-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-02-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-10-2023
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-11-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-12-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-02-2024
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	CTIS2023-510541-25-00
EudraCT	EUCTR2021-003125-29-NL
ClinicalTrials.gov	NCT05131022
CCMO	NL78598.078.21