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Sponsor protocol number: NX-5948-301

EudraCT number: 2021-003125-29

Protocol title: 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

Text for the HOVON website:

Naam	NX-5948-301
Titel	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
Status	Recruiting
Medicatie	BTK-degrader (oral)
Populatie	Relapsed/Refractory B-Cell Malignancies **Phase 1a**: CLL/SLL, DLBCL, FL, MCL, MZL, WM, PCNSL who have received at least 2 prior lines of therapy (1 prior line for PCNSL) and secondary CNS involvement in any disease listed is permitted (and have no other therapies known to provide clinical benefit. **Phase 1b**: CLL/SLL (prior exposure to both a BTKi and BCL-2 inhibitor), MCL (prior exposure to a BTKi and an anti-CD20 monoclonal antibody based chemo-immunotherapy regimen), MZL (prior exposure to an anti-CD20 mAb-based chemo-immunotherapy regimen and additional line of therapy), WM (prior BTKi and additional line of therapy), DLBCL (prior exposure to an anthracycline, andti-CD20 mAb-based chemo-immunotherapy regimen, and an additional line of therapy), FL (prior exposure to an anti-CD20 mAb-based chemo-immunotherapy regimen and an additional line of therapy), PCNSL (1 prior line of therapy) and SCNSL (secondary CNS involvement of lymphoma) meeting criteria for non-CLL/SLL arms above.
Documenten	Link provided to Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

- Patients must be ≥ 18 years of age.
- 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), germinal 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, HGBL NOS

(note: other subgroups of DLBCL or large B-cell lymphoma (LBCL) from the 2016 WHO classification of lymphoid malignancies [Swerdlow 2016] are excluded)

- FL (grade 1–3a; eligibility for systemic treatment as determined by the Groupe d'Etude des Lymphomes Folliculaires [GELF] criteria; Section 15.8)
- MCL
- MZL (eligible subtypes include EMZL, MALT, NMZL, and SMZL)
- WM
- PCNSL

- Patients in **Phase 1a** must meet the following:
  - For non-PCNSL indications, received at least 2 prior lines of therapy and have no other therapies known to provide clinical benefit.
  - 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:
- NOS, germinal center B-cell type, activated B-cell type (includes transformed indolent lymphoma [eg, grade 3b/transformed FL] and Richter-transformed DLBCL)
- HGBL with *MYC* and *BCL-2* and/or *BCL-6* rearrangements, and HGBL NOS

(note: other subgroups of DLBCL or LBCL from the 2016 WHO classification of lymphoid malignancies [Swerdlow 2016] are excluded).

FL arm:

- FL (grade 1–3a; eligibility for systemic treatment as determined by the GELF criteria; Section 15.8) 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.

- Patients must have measurable disease per response criteria specific to the malignancy. For patients with NHL, must have either at least 1 metabolically active lesion defined as fluorodeoxyglucose (FDG)-avid (5PS score of 4 or 5) as assessed by PET-CT or at least 1 target lesion that is >1.5 cm for lymph nodes or >1.0 cm for extranodal lesion(s) in the longest diameter as assessed by CT. For patients with WM, serum monoclonal immunoglobulin M (IgM) paraprotein >0.5 g/dL.

Key Exclusion Criteria:

- Individuals who meet any of the following exclusion criteria at Screening will not be eligible to participate in the study:
- 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:
    - Radiotherapy within 2 weeks of planned start of study drug (excluding limited palliative radiation).
    - Prior systemic chemotherapy within 2 weeks of planned start of study drug. Note: Use of intrathecal chemotherapy is allowed per institutional guidelines.
    - Prior mAb therapy within 4 weeks of planned start of study drug.
    - Prior small molecule therapy within 5 half-lives or 2 weeks (whichever is shorter) of planned start of study drug.
    - Autologous or allogeneic stem cell transplant within 100 days prior to planned start of study drug.
    - 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).
    - 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.
    - Use of systemic immunosuppressive drugs other than systemic corticosteroids for any medical condition within 60 days, prior to first dose of study drug.
    - 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.