Phase II trial of nivolumab for pediatric and adult relapsing/refractory ALK+ anaplastic large cell lymphoma, for evaluation of response in patients with progressive disease (Cohort 1) or as consolidative immunotherapy in patients in complete remission after relapse (Cohort 2)

Published: 01-03-2022
Last updated: 19-08-2024

Primary objectivesCohort 1 Estimate the efficacy of nivolumab treatment in patients with relapsed/refractory ALK+ ALCL in terms of best objective response rate within thefirst 24 weeksCohort 2 Estimate the efficacy of nivolumab treatment as...

Ethical review	Approved WMO
Status	Pending
Health condition type	Lymphomas non-Hodgkin's T-cell
Study type	Interventional

Summary

ID

NL-OMON56001

Source
ToetsingOnline

Brief title
NIVO-ALCL

Condition

- Lymphomas non-Hodgkin's T-cell

Synonym
ALCL

Research involving
Human

Sponsors and support

Primary sponsor: Gustave Roussy
Source(s) of monetary or material Support: sponsor Gustave Roussy

Intervention

Keyword: ALCL, Nivolumab, Phase 2

Outcome measures

Primary outcome

Cohort 1

Best objective response rate (CR+PR) within the first 24 weeks, according to adapted Lugano 2014 Criteria for Malignant Lymphoma. In case of PETpositive residual masses after 24 weeks of induction treatment, a resection/biopsy must be performed by week 24. A residual mass proven to be pathologically negative for disease after resection or limited biopsy is considered as CR after discussion with the Coordinating investigator.

Cohort 2

3-year PFS

PFS is defined as the time since the inclusion in the trial, to the first event among relapse (see definition below) and death, whatever the cause of death

Definition of relapse: In case of developpement of new lesion(s) based on CT

scan and/or MRI and/or PET-CT:

- In patients with clinical deterioration, a biopsy should be performed whenever possible, in order to obtain histological confirmation of the relapse. Additional MRD assessment (with quantitave PCR) is also recommended. In patient in whom a biopsy is not feasisible, an increase of MRD quantitative PCR at 2 consecutive measures qualifying for a significant increase according to the same reference laboratory, along with clinical signs and symptoms suggestive of progressing disease and new lesion(s) on imagings will be considered as a relapse. In this case, relapsed status must be reviewed and confirmed by the international coordinating investigator.

- In patients without clinical deterioration (scheduled assessment imaging), a confirmatory CT scan and/or MRI (+ optional PET-CT), along with MRD assessment (with quantitave PCR) and a biopsy (whenever possible), should be performed 4 weeks later on, in order to confirm or not the relapse.

Secondary outcome

Cohort 1

- Time between the first dose of treatment and the confirmed CR/PR according to adapted Lugano 2014 Criteria for Malignant Lymphoma.
- Duration of response (CR/PR), defined as the time between the CR or PR (first met of these criteria of measurement), evaluated according to adapted Lugano 2014 Criteria for Malignant Lymphoma, until confirmed progression, or death.
- Progression-free survival, defined as the time since the inclusion in the

trial, to the first event among confirmed progression, relapse, and death, whatever the cause of death.

- Confirmed progression is defined according to Lugano 2014 Criteria for Malignant Lymphoma. However:

- In patients with clinical deterioration, a biopsy should be performed whenever possible, in order to obtain histological confirmation of the progression. Additional MRD assessment (with quantitave PCR) is also recommended. An increase of MRD quantitative PCR at 2 consecutive measures qualifying for a significant increase according to the same reference laboratory, along with clinical signs and symptoms suggestive of progressing disease and progression on imagings will be considered as a progression/relapse. In this case, progressive/relapse status must be reviewed and confirmed by the international coordinating investigator.

- In patients without clinical deterioration (scheduled assessment imaging), a confirmatory CT scan and/or MRI (+ optional PET-CT), along with MRD assessment (with quantitave PCR) and a biopsy (whenever possible), should be performed 4 weeks later on, in order to confirm or not the progression/relapse.

See chapt 7.3 for details

- Overall survival, defined as the time since the inclusion in the trial to death, whatever the cause of death.

- Minimal residual disease (MRD) measured by quantitative PCR for NPM1-ALK in the blood at various time-points (see Table 1 to Table 4)

Cohort 2

- Overall survival, defined as the time since the inclusion in the trial to death, whatever the cause of death
- Progression-free survival, defined as the time since the inclusion in the trial to the first event among confirmed relapse and death, whatever the cause of death. (For definition of relapse, see primary criteria) Overall survival, defined as the time since the inclusion in the trial to death, whatever the cause of death
- Minimal residual disease (MRD) measured by quantitative PCR for NPM1-ALK in the at various time-points (see Table 1 to Table 4)

In cohort 1 and cohort 2

Acute toxicity (according to NCI-CTCAE v5, Appendix 3) during treatment (induction treatment, and maintenance treatment), and one month after the end of treatment

- description of all observed adverse events (grade 1 to 5)
- rate of patients with at least one grade 3-4 AE
- rate of patients with at least one grade 4 AE rate of patients with at least one grade 3-4 immune-related AE
- rate of SUSAR and rate of patients with at least one SUSAR
- rate of death related to AE
- rate of patients with at least one or more doses of nivolumab cancelled due to AEs
- rate of patients with treament with nivolumab definitively stopped due to AEs

Long-term toxicity (according to NCI-CTCAE v5) defined by toxicity during the off-therapy period up to 5 years after study inclusion:

- description of all observed adverse events grade >= 3
- rate of patients with at least one grade 3-4 AE
- rate of patients with at least one grade 3-4 immune-related AE
- duration of grade 3-4 immune-related AE
- rate of grade 3-4 immune-related AEs lasting more than one year
- rate of patients who need immune modulating medication,
- > 10 mg prednisone equivalents

Modification of biomarkers, at various time-points (see Table 1 to Table 4), in tumor tissues, in blood and in bone marrow: PDL1 and PDL2 expression, tumor infiltrating lymphocytes, anti-ALK antibody, and leucocytes populations/ cytokines.

Objective response rate and PFS in cohort 1, PFS in cohort 2

Study description

Background summary

Systemic anaplastic large cell lymphoma (ALCL) is a rare, aggressive, CD30-positive non-Hodgkin lymphoma (NHL) affecting mostly children/adolescents and young adults (Turner et al., 2016). Most patients with systemic ALCL present at advanced stages (stages III-IV) with peripheral intraabdominal or mediastinal lymph node involvement frequently associated with B symptoms and extranodal spread including skin, liver, lung, soft tissue and bone localization. ALK+ ALCL results from chromosomal translocations involving the ALK gene and different partners

(Swerdlow et al., 2016). The most common ALK fusion protein is nucleophosmin (NPM1)-ALK resulting from the t(2;5) translocation. This translocation induces a constitutive phosphorylation of ALK associated with the activation of multiple pathways such JAK/STAT3, AKT/PI3K, RAS/ERK leading to growth-factor independent cell proliferation and inhibition of apoptosis.
Accumulating evidence indicates that the immune system plays a major role in both the pathogenesis and final control of ALK+ ALCL. Antibodies against ALK and cytotoxic T-cell and CD4 T-helper responses to ALK have been detected in patients with ALK+ ALCL both at diagnosis and
during remission with a significant inverse correlation between ALK-antibody titers and the incidence of relapses. Moreover, vaccination using trunked cDNA ALK has been reported to induce potent and long lasting protection from local and systemic lymphoma growth. However, it has also been shown that ALK+ ALCL cells strongly express the immunosuppressive cell-surface protein PD-L1 (B7-H1), as determined on the mRNA and protein level in ALK-positive ALCL cell lines. Furthermore, results of PD-L1 immunostaining on all patient tissue samples reported so far showed a strong PD-L1 expression (Marzec et al., 2008). Analysis revealed that PD-L1 expression is induced by the chimeric NPM1/ALK tyrosine kinase, by activating STAT3, confirming a unique function for NPM/ALK as a promoter of immune evasion by inducing PD-L1. These observations provide a strong rationale to target PD1/PD-L1 in a subset of relapsed/refractory ALK+ ALCL.

Study objective

Primary objectives

Cohort 1
Estimate the efficacy of nivolumab treatment in patients with relapsed/refractory ALK+ ALCL in terms of best objective response rate within the
first 24 weeks

Cohort 2
Estimate the efficacy of nivolumab treatment as consolidative therapy after CR in patients with relapsed/refractory ALK+ ALCL in terms of PFS

Study design

Prospective, non-randomized, single arm phase II trial with 2 cohorts of ALK+ ALCL treated with nivolumab, according to patient status after previous treatment (patients in progression, into the Cohort 1; patients in CR, into the Cohort 2)

Intervention

Cohort 1
Induction: nivolumab 3 mg/kg (maximal unitary dose: 240 mg) iv Q2W until CR
Evaluation of response as defined below, including biopsy in case of residual masses at Week 24
Maintenance: nivolumab 3 mg/kg (maximal unitary dose: 240 mg) Q4W
Total duration of treatment (induction + maintenance) = 24 months

Cohort 2
Induction: nivolumab 3 mg/kg iv Q2W for 4 doses (Wk0, Wk2, Wk4 and Wk6)
Maintenance: nivolumab 3 mg/kg Q4W, for 25 doses, starting at Week 8 (14 days after the last induction dose)
Total duration of treatment (induction + maintenance) = 24 months

Duration of treatment:
Patients will continue on study treatment up to progression, unacceptable toxicities, patient refusal or for a total duration of treatment (induction + maintenance) of 24 months.

Study burden and risks

Risks associated with this study are mainly the anticipated side-effects of nivolumab (an overview of the adverse effects are found in the investigator brochure (IB). However, due to the remarkable immunogenic properties of the disease, the strong PD-L1 expression by tumors cells, the good tolerance profile and the success of anti-PD1 therapies in other immunogenic diseases, the option to use consolidative anti-PD1 immunotherapy rather than HSCT for refractory/relapsed ALK+ ALCL with the highest risk of failures should be considered.
The PK, clinical activity, and safety of nivolumab have been assessed in completed Phase I and ongoing Phase II and III studies in adults with several tumor types. Preliminary data show that the toxicity and PK profiles in children are similar to those in adults. During the study, side effects will be closely monitored and reported.

Additional blood tests are performed. Other additional tests (e.g. urinalysis, pregnancy tests, compared to standard treatment) are not invasive.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

I-1. Histologically confirmed evidence of relapsed/refractory ALK+ ALCL. If biopsy could not be performed, relapsed/refractory status should be confirmed by molecular analysis whenever possible (increase of MRD quantitative PCR at 2 consecutive measures qualifying for a significant increase according to the same reference laboratory, with clinical signs and symptoms suggestive of progressing disease). In this case, relapsed/refractory status must be reviewed and confirmed by the international coordinating investigator.
I-2. Age at inclusion > 6 months
I-3. No washout needed, but patients must have recovered from acute toxic effects of all prior therapy before enrollment into the study. A short course of steroids is allowed at the beginning of Nivolumab if it is clinical indicated
I-4. Adequate organ function:
* Peripheral absolute neutrophil count (ANC) >=750/µL in patients without bone marrow involvement and >=500/µL in patients with bone marrow involvement (unsupported)
* Platelet count >=75,000/µL in patients without bone marrow involvement and 50

000 in patients with bone marrow involvement (unsupported)
* Hemoglobin >=8.0 g/dL (transfusion is allowed)
* Serum creatinine <=1.5 x upper limit of normal (ULN) for age
* Total bilirubin <=1.5 x ULN in patients without liver involvement and < 2.5 ULN in patients with liver involvment
* Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT) <=3 x ULN in patients without liver involvement and < 5 ULN in patients with liver involvement
* Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase/SGOT <=3 x ULN in patients without liver involvement and < 5 ULN in patients with liver involvment
I-5. Performance status: Karnofsky performance status (for patients >12 years of age) or Lansky Play score (for patients <=12 years of age) >= 40%.
I-6. Able to comply with the scheduled disease management (treatment and follow-up), and with the management of toxicity
I-7. Females of childbearing potential must have a negative serum β-HCG pregnancy test within 24 hours prior to initiation of treatment. Sexually active women of childbearing potential must agree to use acceptable and appropriate contraception during the study and for at least 5 months after the last study treatment administration. Sexually active males patients must agree to use condom during the study and for at least 7 months after the last study treatment administration. Acceptable contraception is listed in Appendix 5.
I-8. Written informed consent from parents/legal representative, patient, and age-appropriate assent before any study-specific screening procedures are conducted according to local, regional or national guidelines.
I-9. Patient affiliated to a social security regimen or beneficiary of the same according to local requirements.
I-10. Patients will prior allogeneic HSCT may be included if clinically indicated (see non-inclusion criteria regarding prior allogeneic HSCT). In this case, study inclusion must be confirmed by the international coordinating investigator.
Cohort 1:
For being enrolled in Cohort 1, all criteria from C1.I-1 to C1.I-2 are required, in addition of I-1 to I-10 criteria
C1.I-1. Measurable progressive disease with at least one lesion measuring more than 1.5 cm and/or evaluable disease on PET-CT
C1.I-2. Previous treatment including chemotherapy and ALK inhibitor or brentuximab vedotin, if available.
Cohort 2:
For being enrolled in Cohort 2, all criteria from C2.I-1 to C2.I-2 are required, in addition of I-1 to I-10 criteria
C2.I-1. Complete response (disappearance of all disease except for possible detection of MRD in blood and/or bone marrow) with an on-going treatment of at least 2 months with ALK inhibitor or brentuximab vedotin, if available combined or not with chemotherapy
C2.I-2. High-risk relapsed/refractory ALK+ ALCL for whom an hematopoietic stem

cell transplantation is considered after CR (see Appendix 1 for criteria according to the age) Of note, the inclusion of patients who have received more than 12 months of ALK inhibitor or brentuximab will be closed after 8 patients

Exclusion criteria

E-1. Patients with prior allogeneic HSCT less than 3 months before study inclusion
E-2. Patients with prior allogeneic HSCT and any active graft versus host disease (GVHD) and/or any prior grade 3 or 4 GVHD according to International Bone Marrow Transplant Registry (ITBMR)
E-3. Previous organ transplantation
E-4. Significant hemophagocytosis in bone marrow, spleen, lymph nodes, or liver must be discussed with the Coordinating Sponsor before inclusion
E-5. Presence of any >= CTCAE grade 2 treatment-related toxicity with the exception of alopecia, fatigue and peripheral neuropathy.
E-6. History or evidence of severe uncontrolled illness that contra-indicates use of an investigational drug, or places the patient at unacceptable risk from treatment complications
E-7. History or evidence of severe acute or chronic infection unless fully healed at least four weeks prior to screening
E-8. Known human immunodeficiency virus (HIV) infection
E-9. Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection.
E-10. History or evidence of any auto-immune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of
an external trigger are permitted to enroll.
E-11. Subjects with another pathology requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
E-12. Known hypersensitivity to any component of the products (study drug or ingredients)
E-13. Concurrent administration of any other antitumor therapy
E-14. Clinically significant, uncontrolled heart disease (including history of any cardiac arrhythmias, e.g., ventricular, supraventricular, nodal arrhythmias, or conduction abnormality within 12 months of screening).
E-15. Vaccinated with live attenuated vaccines within 4 weeks of the first dose of the study drug
E-16. Pregnant or breast-feeding female patient
E-17. Patient under guardianship or deprived of his liberty by a judicial or

administrative decision, patients under safeguards of justice or incapable of giving its consent, patients undergoing psychiatric care under duress
E-18. Participation in another clinical study with an investigational product during 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:	Pending
Start date (anticipated):	15-05-2022
Enrollment:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	Nivolumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	01-03-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	22-06-2022

Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	28-07-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-11-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-10-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	31-10-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-06-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-07-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2018-001447-31-NL
ClinicalTrials.gov	NCT03703050
CCMO	NL68699.041.22