A Phase 1 Study of SEA-CD70 in Myeloid Malignancies

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This study has been transitioned to CTIS with ID 2023-506945-42-00 check the CTIS register for the current data. Primary* Evaluate the safety and tolerability of SEA-CD70* Identify the maximum tolerated dose (MTD) or recommended expansion dose of...

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

Summary

ID

NL-OMON54392

Source
ToetsingOnline

Brief title
SGNS70-101

Condition

- Leukaemias

Synonym
Acute Myeloid Leukemia, Myelodisplastic syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Seagen Inc
Source(s) of monetary or material Support: Seattle Genetics;Inc is de sponsor van het onderzoek

Intervention

Keyword: Myeloid malignancies, Phase I

Outcome measures

Primary outcome

CR rate, CRh rate, ORR, MRD-negative ORR, rate of conversion to TI, and maintenance of TI will be presented with corresponding binomial exact 95% Cis using the All Treated Subjects set. For MDS, binomial exact 95% Cis will also be provided for HI rate and blast clearance rate. For AML, binomial exact 95% Cis will also be provided for CRi rate.

DOR, EFS, TTR, and OS will be estimated using the all treated subjects set using Kaplan-Meier methodology, and Kaplan-Meier plots will be provided. Medians will be calculated, where possible. The 95% Cis may also be calculated, as appropriate. Detailed methodology will be provided in the SAP.

Secondary outcome

NA

Study description

Background summary

AML is a genetically heterogeneous bone marrow malignancy defined by the dysregulation of differentiation and proliferation of hematopoietic progenitor cells. This results in the uncontrolled proliferation of immature malignant cells (blasts) and a deficiency in normal blood cells (i.e., red blood cells [RBCs], white blood cells [WBCs], and platelets). If untreated, AML generally causes death in weeks to months due to infection, bleeding, or complications related to a large volume of abnormal cells in the marrow/vasculature. In 2019, it is estimated that over 20,000 new cases of AML will be diagnosed in the United States and nearly 11,000 deaths due to AML will occur (American Cancer Society (ACS) 2019). Similarly, over 18,000 new cases of AML are diagnosed per

year in Europe (Visser 2012). The prognosis for AML depends heavily on disease factors such as the presence or absence of specific cytogenetic abnormalities, gene mutations or overexpression, antecedent myelodysplasia, and patient factors such as age and comorbidities. The 5-year survival rate for AML patients ages 18 to 60 years is approximately 40% whereas the corresponding 5-year survival rate for AML patients older than 60 years is 15%.

MDS represents a group of heterogeneous hematopoietic disorders derived from an abnormal multipotent progenitor cell. MDS is characterized by ineffective hematopoiesis, bone marrow failure, peripheral blood cytopenias, and predisposition to myeloid leukemia. MDS may be classified as indolent or aggressive (lower- or higher-risk) depending on life expectancy and likelihood of progression to AML. The annual age-adjusted incidence of MDS is approximately 2 to 4 per 100,000 in the EU and US, but rises substantially to 7 per 100,000 in people aged 60*69 and 36 per 100,000 in people 80 years of age or older (Visser 2012; Zeidan 2019).
Prognosis in MDS depends on the number of bone marrow blasts, cytogenetic abnormalities, and the amount and severity of peripheral blood cytopenias. For patients with Low or Intermediate-1 risk MDS per the IPSS (Greenberg 1997), standard treatment is usually supportive care. Symptomatic anemia is treated with growth factors as appropriate. Among patients who are intolerant of or fail to respond to treatment with erythropoiesis-stimulating agents, those with low serum erythropoietin levels (<500 mU/mL) may be candidates for immunosuppressive therapy (IST) with antithymocyte globulin/cyclosporine. HMA treatment (azacitidine or decitabine) in lower risk MDS are typically reserved for patients who are not candidates for IST and those who are intolerant of or fail to respond to IST. HMA treatment generally continues for at least 4-6 cycles with maintenance treatment until disease progression (Greenberg 2017).
For patients with Intermediate-2 or High risk MDS per IPSS, allogeneic hematopoietic cell transplant (allo-HCT) is the preferred treatment for patients who are candidates and have a donor stem cell source available. However, the majority of higher-risk MDS patients are not eligible for allo-HCT due to age, comorbidities, and/or donor availability. For patients who are not candidates for allo-HCT, treatment with HMA therapy as described above is appropriate. In this setting, azacitidine has demonstrated an improvement in OS (24.5 months; 95% confidence interval [CI]: 9.9-not reached) when compared to previous standard of care (15.0 months; 95% CI: 5.6-24.1) in a randomized controlled trial (Fenaux 2009). There is no standard treatment for patients who do not respond to or relapse following HMA treatment (Greenberg 2017).

Study objective

This study has been transitioned to CTIS with ID 2023-506945-42-00 check the CTIS register for the current data.

Primary
* Evaluate the safety and tolerability of SEA-CD70

* Identify the maximum tolerated dose (MTD) or recommended expansion dose of SEA-CD70
Secondary
* Assess the pharmacokinetics (PK) of SEA-CD70
* Assess the immunogenicity of SEA-CD70
* Assess the antitumor activity of SEA-CD70
Exploratory
* Assess biomarkers of biological activity, resistance, and predictive biomarkers of response
* Assess SEA-CD70 PK/pharmacodynamic relationships of interest

Study design

This is a phase 1, open-label, multicenter, dose-escalation, and cohort expansion study designed to evaluate the safety, tolerability, pharmacokinetic (PK), and antitumor activity of SEA-CD70 in adults with myeloid malignancies.

Intervention

Subjects will receive an active dose SEA-CD70

Study burden and risks

SEA-CD70 is never tested on humans. What is expected from animal test results is:

Low levels of neutrophils (neutropenia).
Low levels of lymphocytes (lymphopenia).
Infusion-related reactions can happen while the drug is being given or afterwards, like fever, chills, rash, feel faint, or feel out of breath.
Changes in the liver.
immunogenicity.
an allergic reaction to the drug.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

SEA-CD70 dose-escalation cohort in relapsed/refractory (HMA-failure) MDS, Part A:
1. Subjects with cytologically/histologically confirmed MDS according to the 2016 World Health Organization (WHO) classification with the following:
* Measurable disease per WHO MDS with excess blasts (MDS-EB) criteria as defined either:
* 5%-9% blasts in the bone marrow or 2%-4% blasts in the peripheral blood (MDS-EB-1), or
* 10%-19% blasts in the bone marrow or 5%-19% blasts in the peripheral blood (MDS-EB-2)
* MDS that is relapsed or refractory and must not have other therapeutic options known to provide clinical benefit in MDS available.
* Treatment failure after prior HMA therapy for MDS, defined as one of the following:
* Progression (per 2006 IWG criteria) at any time after initiation of HMA therapy.
* Lack of response (failure to achieve CR, PR, or hematologic improvement [HI] per 2006 IWG criteria) after at least 6 cycles of azacitidine (or equivalent oral HMA) or 4 cycles of decitabine (or equivalent oral HMA).
* Relapse after achievement of CR, PR, or HI (per 2006 IWG criteria).
* Intolerance of HMA (Grade 3 or higher non-hematologic toxicity leading to treatment discontinuation).
* Subjects with isolated 5q-/5q- syndrome must have progressed, failed, relapsed, or not tolerated lenalidomide in addition to HMA.
2. Must be off all treatments for MDS (including HMAs) for >=4 weeks; growth

factors (e.g., G-CSF, erythropoietin and thrombopoietin) and transfusions are allowed before and during the study as clinically indicated.
3. Age >=18 years.
4. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0-1

SEA-CD70 expansion cohort in relapsed/refractory (HMA-failure) MDS, Part B:
5. Subjects with cytologically/histologically confirmed MDS according to the 2016 WHO classification with the following:
* Measurable disease per WHO MDS with excess blasts (MDS-EB) criteria as defined either:
* 5%-9% blasts in the bone marrow or 2%-4% blasts in the peripheral blood (MDS-EB-1), or
* 10%-19% blasts in the bone marrow or 5%-19% blasts in the peripheral blood (MDS-EB-2)
* MDS that is relapsed or refractory and must not have other therapeutic options known to provide clinical benefit in MDS available.
* Treatment failure after prior HMA therapy for MDS defined as one of the following:
* Progression (per 2006 IWG criteria) at any time after initiation of HMA therapy.
* Lack of response (failure to achieve CR, PR, or HI per 2006 IWG criteria) after at least 6 cycles of azacitidine (or equivalent oral HMA) or 4 cycles of decitabine (or equivalent oral HMA).
* Relapse after achievement of CR, PR, or HI (per 2006 IWG criteria).
* Intolerance of HMA (Grade 3 or higher non-hematologic toxicity leading to treatment discontinuation).
* Subjects with isolated 5q-/5q- syndrome must have progressed, failed, relapsed, or not tolerated lenalidomide in addition to HMA.
6. Must be off all treatments for MDS (including HMAs) for >=4 weeks; growth factors (e.g., G-CSF, erythropoietin and thrombopoietin) and transfusions are allowed before and during the study as clinically indicated.
7. At least one cytopenia (ANC <1800/µL or platelet count <100,000/µL or hemoglobin [Hgb] <10 g/dL).
8. Age >=18 years.
9. ECOG Performance Status of 0-2

SEA-CD70 expansion cohort in relapsed/refractory AML, Part C:
10. Subjects with relapsed/refractory AML according to the WHO 2016 classification (Arber 2016)(except for acute promyelocytic leukemia [APL]):
* Who have received either 2 or 3 previous regimens to treat active disease. Post-remission treatments, intrathecal chemotherapy, and radiotherapy are not considered previous regimens.
* Who have received 1 previous regimen to treat active disease and have at least one of the following:
* Age >60 and <=75 years.
* Primary resistant AML (defined as failure to achieve CR after 1-2 courses of induction therapy).

* First CR duration <6 months.
* Adverse-risk per European Leukemia Net (ELN) genetic risk stratification
* Secondary AML (prior history of MDS or therapy-related).
11. Age 18-75 years.
12. ECOG Performance status of 0-2

All Subjects
13. The following baseline laboratory data:
a. WBC count <20,000/µL; use of hydroxyurea to control WBC is acceptable.
b. Serum bilirubin <=1.5 x upper limit of normal (ULN) or <=3 x ULN for subjects with Gilbert*s disease, or direct bilirubin <=2 x ULN if total bilirubin is abnormal.
c. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <=3 x ULN.
d. Estimated glomerular filtration rate (GFR) >60 mL/min using the Modification of Diet in Renal Disease (MDRD) study equation as applicable.
14. Subjects of childbearing potential, under the following conditions:
a. Must have a negative serum or urine pregnancy test (minimum sensitivity 25 mIU/mL or equivalent units of beta human chorionic gonadotropin [β-hCG]) result within 3 days prior to the first dose of SEA-CD70. Subjects with false positive results and documented verification that the subject is not pregnant are eligible for participation.
b. Must agree not to try to become pregnant during the study and for at least 2 months after the final dose of study drug.
c. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 2 months after the final dose of study drug.
d. If sexually active in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control starting at time of informed consent and continuing throughout the study and for at least 2 months after the final dose of study drug.
15. Subjects who can father children, under the following conditions:
a. Must agree not to donate sperm starting at time of informed consent and continuing throughout the study and for at least 2 months after the final dose of study drug.
b. If sexually active with a person of childbearing potential in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control starting at time of informed consent and continuing throughout the study and for at least 2 months after the final dose of study drug.
c. If sexually active with a person who is pregnant or breastfeeding, must consistently use one of 2 contraception options starting at time of informed consent and continuing throughout the study and for at least 2 months after the final dose of study drug.
16. The subjects must provide written informed consent.

Exclusion criteria

1. History of another malignancy within 3 years before the first dose of study drug or any evidence of residual disease from a previously diagnosed malignancy. Exceptions are malignancies with a negligible risk of metastasis or death (e.g., 5-year OS >=90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer.
2. Previous exposure to CD70-targeted agents.
3. Prior allogeneic hematopoietic stem cell transplant, for any condition.
4. Central nervous system leukemia based on imaging or documented positive cytology in cerebral spinal fluid.
5. Any uncontrolled Grade 3 or higher (per the National Cancer Institute*s Common Terminology Criteria for Adverse Events [NCI CTCAE], version 5.0) viral, bacterial, or fungal infection within 14 days prior to the first dose of study treatment. Antimicrobial prophylaxis or ongoing treatment of resolving/controlled infection is permitted.
6. Subjects who have experienced major surgery (defined as requiring general anesthesia and hospitalization for >24 hours) or significant traumatic injury that would place the subject at undue risk from study procedures, in the opinion of the investigator, within 14 days before the first dose of study treatment. Subjects must have recovered adequately from the surgery/injury, or complications thereof, prior to starting treatment.
7. Positive for hepatitis B by surface antigen expression. Active hepatitis C infection (positive by PCR or on antiviral therapy for hepatitis C within the last 6 months). Subjects who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks.
8. Known to be positive for human immunodeficiency virus (HIV).
9. Known active or latent tuberculosis.
10. History of clinically significant sickle cell anemia, autoimmune hemolytic anemia, or idiopathic thrombocytopenic purpura.
11. History of clinically significant chronic liver disease (e.g., liver cirrhosis) and/or ongoing alcohol abuse.
12. Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association Class III-IV (Appendix F) within 6 months prior to their first dose of SEA-CD70.
13. chemotherapy, systemic radiotherapy, biologics, other anti-neoplastic or investigational agents, and/or other antitumor treatment with immunotherapy that is not completed 4 weeks prior to first dose of SEA-CD70. Focal radiotherapy that is not completed 2 weeks prior to the first dose of SEA-CD70. Hydroxyurea or 6-mercaptopurine used for cytoreduction may be given up to 24 hours prior to treatment.
14. Subjects with either of the following:
a. A condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone or equivalent) or other immunosuppressive medications within 2 weeks of first dose of SEA-CD70 (inhaled, topical, intraocular, intranasal, and intraarticular steroids are permitted in the absence of active immune disease, and steroid premedication for prevention of hypersensitivity reactions to

radiographic contrast is permitted).
b. Active known or suspected clinically significant autoimmune disease or clinically significant autoimmune-related toxicity from prior immune-oncology-based therapy (exceptions include vitiligo, controlled type 1 diabetes mellitus, residual hypothyroidism requiring hormone replacement, and conditions not expected to recur in the absence of an external trigger).
15. Subjects who are breastfeeding, pregnant, or planning to become pregnant from time of informed consent until 2 months after final dose of study drug.
16. Known hypersensitivity to any excipient contained in the drug formulation of SEA-CD70.
17. Estimated life expectancy <12 weeks.
18. Other serious underlying medical condition that, in the opinion of the investigator, would impair the subject*s ability to receive or tolerate the planned treatment and follow-up.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	21-01-2022
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	SEA-CD70
Generic name:	CD-70

Ethics review

Approved WMO Date:	04-11-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-05-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-04-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	CTIS2023-506945-42-00
EudraCT	EUCTR2019-001917-18-NL
CCMO	NL74832.056.20