A randomized, double-blindphase 3 study of vadastuximab talirine (SGN-CD33A)versus placebo in combination with azacitidine or decitabine in the treatment of older patients with newly diagnosed acute myeloid leukemia (AML)

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Primary* To compare the composite complete remission (CRc) rate (morphologic complete remission [CR] and morphologic CR with incomplete hematologic recovery [CRi]) between treatment arms * To compare overall survival (OS) between treatment...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON45635

Source
ToetsingOnline

Brief title
SGN33A-005

Condition

- Leukaemias

Synonym
acute myelogenous leukemia, cancer of the blood

Research involving

Human

Sponsors and support

Primary sponsor: Seattle Genetics, Inc.
Source(s) of monetary or material Support: Seattle Genetics;Inc.

Intervention

Keyword: azacitidine or decitabine, combination with, newly diagnosed acute myeloid leukemia (AML), talirine, vadastuximab

Outcome measures

Primary outcome

The primary efficacy endpoint of this study is

CRc rate

OS.

Secondary outcome

The secondary endpoints are:

* MRD-negative CRc rate

*Duration of remission

* EFS

* LFS

* Type, incidence, severity, seriousness, and relatedness of adverse events

* Laboratory abnormalities

* Time to CR or CRi

* Mortality rates at Day 30 and Day 60 post the first study treatment

Study description

Background summary

see protocol pages 11-13

Study objective

Primary
* To compare the composite complete remission (CRc) rate (morphologic complete remission [CR] and morphologic CR with incomplete hematologic recovery [CRi]) between treatment arms
* To compare overall survival (OS) between treatment arms
Secondary
* To compare the minimal residual disease-negative remission (MRD-negative CRc) rate between treatment arms
* To evaluate the duration of remission in the 2 treatment arms
* To evaluate event-free survival (EFS) in the 2 treatment arms
* To evaluate leukemia-free survival (LFS) in the 2 treatment arms
* To evaluate the safety profiles in the 2 treatment arms
* To evaluate the time to response in the 2 treatment arms
* To evaluate the 30- and 60-day mortality rates in the 2 treatment arms

Additional
* To evaluate the treatment effect of vadastuximab talirine compared to the control group on the change in patient reported outcomes (PRO) and medical resource utilization (MRU)
* To assess the incidence of antitherapeutic antibodies (ATA)
* To assess exploratory markers of clinical outcome and the pharmacodynamics of vadastuximab talirine in combination with a hypomethylating agent (HMA)

Study design

This is a randomized, double-blind, placebo-controlled phase 3 study designed to compare the OS between patients treated with HMA plus vadastuximab talirine (experimental arm) versus patients treated with HMA plus placebo (comparator arm). Patients will be randomized in a 1:1 manner to one of the study arms. Investigators may select either HMA (azacitidine or decitabine).
Response will be assessed by bone marrow examination and complete blood counts (CBC) between Day 22 to 28 of even numbered cycles until CR or CRi. The response assessment window may be up to Day 42 in the event of a delay in the start of the next cycle of treatment. After CR or CRi, response assessment will continue to be performed by CBC surveillance. In addition, bone marrow examination will be conducted according to the following schedule:
* 2 cycles after initial confirmation of CR or CRi
* At the time of conversion from CRi to CR
* At the time of suspected relapse
* End of treatment (EOT), if not performed within the previous 4 weeks

Patients may continue on study treatment until progression, leukemic recurrence, or unacceptable toxicity, whichever comes first. Patients who achieve stable disease or better should receive a minimum of 4 cycles of study treatment. Progression is defined after 4 or more cycles of treatment as either a >25% absolute rise in the percent of bone marrow blasts from baseline (or a proportional increase of >25% in patients with baseline bone marrow blasts >75%), or appearance of new extramedullary disease. Patients who fulfill the criteria for progression but who are still deriving clinical benefit in the opinion of the investigator may continue on study treatment.
After discontinuation of study treatment, patients will be followed for survival status every 2 months (or more frequently as needed to support analysis of the study endpoints) after EOT until death or study closure, whichever comes first. Patients who have not experienced progression or leukemic recurrence will continue to be assessed for response by CBC surveillance every 2 months through 24 months after EOT, and every 4 months thereafter, until initiation of another anticancer treatment (excluding stem cell transplant and maintenance therapy in the absence of relapse), progression, or leukemic recurrence, whichever comes first.
Two interim analyses for OS are planned: the first interim analysis is to evaluate futility and the second interim analysis is to evaluate the superiority of vadastuximab talirine.
Safety will be monitored over the course of the study by an Independent Data Monitoring Committee (IDMC).

Intervention

Both Arms
HMA, either:
* Azacitidine 75 mg/m2 given subcutaneously (SC) or intravenously (IV) x 7 (7 consecutive days or 5 days on/2 days off/2 days on), every 4 weeks, or
* Decitabine 20 mg/m2 given IV daily x 5, every 4 weeks
Experimental Arm
Blinded study treatment: vadastuximab talirine, 10 mcg/kg, every 4 weeks (on the last day of HMA administration) via IV push
Comparator Arm
Blinded study treatment: placebo, volume equivalent to 10 mcg/kg, every 4 weeks (on the last day of HMA administration) via IV push

Study burden and risks

Events observed in >=10% of patients receiving vadastuximab talirine (may affect more than 1 in 10 people):
• Anxiety
• Back pain
• Bleeding into the skin (seen as small red or purple dots or bruising
• Chills

• Constipation
• Cough*
• Diarrhea
• Dizziness
• Decreased appetite
• Dry mouth
• Fall
• Insomnia
• Fever*
• Fluid around the lungs
• Headache
• Hypertention
• Infections*
• Itching
• Kidney failure*
• Hypotension
• Low electrolytes
• Low levels of oxygen*
• Low platelets in the blood*
• Low levels of protein in the blood
• Low red blood cells*
• Low white blood cells*
• Nausea
• Nose bleeds
• Pneumonia*
• Palpitation
• Rash
• Sepsis (a serious complication of infection)*
• Shortness of breath*
• Stomach pain
• Swelling of extremities
• Swelling or irritation of mucus membranes
• Swelling of sinuses/sinus infection
• Taste alterations
• Tiredness
• Vomiting
• Weakness or lack of energy
• Weight loss

Detailed information regarding the above risks can be found in attachment 2 of the informed consent form

Contacts

Public
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US
Scientific
Seattle Genetics, Inc.

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Patients with newly diagnosed, previously untreated, cytologically or histologically confirmed de novo or secondary AML according to WHO classification (except for acute promyelocytic leukemia [APL]).
2. Age >=18 years.
3. Life expectancy of at least 12 weeks.
4. Patient is eligible for therapy with either decitabine or azacitidine.
5. For patients <80 years, an ECOG performance status <=2 (Appendix C). Patients >=80 years must be have an ECOG performance status of 0 or 1.
6. The following baseline laboratory data:
* White blood cell (WBC) count <30,000/µL; use of hydroxyurea to control WBC is acceptable.
* Serum bilirubin <=1.5 x upper limit of normal (ULN) or <=3 x ULN for patients with Gilbert*s disease, or direct bilirubin <= 2 x ULN if total bilirubin is abnormal.
* Serum creatinine <=2.5 x ULN and estimated creatinine clearance >=30 mL/min.
* Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <=3 x ULN.
7. Female patients (for those of childbearing potential as defined in Section 4.3), the following

stipulations apply:
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 7 days prior to the first dose of study treatment. Females with false positive results and documented verification that the patient is not pregnant are eligible for participation.
b. Must agree not to try to become pregnant during the study and for at least 6 months after the final dose of study drug administration.
c. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 6 months after the final dose of study drug administration.
d. If heterosexually active, must consistently use 2 highly effective methods of birth control (as defined in Appendix G) starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of study drug administration.
8. Male patients under the following conditions:
a. Must agree not to donate sperm starting at time of informed consent and continuing throughout the study period and for at least 6 months after the final study drug administration.
b. If heterosexually active with non-pregnant, pregnant, or breastfeeding partner, must consistently use 2 highly effective methods of birth control (as defined in Appendix G) starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of study drug administration.
9. Patients must provide written informed consent.

Exclusion criteria

1. AML associated with favorable risk karyotypes including inv(16), t(8;21), t(16;16), or t(15;17).
2. Patients who are medically fit and willing to receive standard intensive induction chemotherapy.
3. Patients who are candidates for allogeneic stem cell transplant at the time of enrollment.
4. Patients with a history of one of the following myeloproliferative neoplasms: essential thrombocythemia, polycythemia vera, and primary myelofibrosis.
5. Received prior treatment with HMA or chemotherapy for antecedent MDS. Prior hydroxyurea or 6-mercaptopurine is permitted, as is prior lenalidomide treatment for MDS.
6. History of allogeneic stem cell transplant.
7. History of clinically significant chronic liver disease (e.g. liver cirrhosis) and/or ongoing alcohol abuse.
8. Patient with supplemental oxygen requirement or resting oxygen saturation of <90%.
9. Concurrent active malignancy other than nonmelanoma skin cancer or carcinoma in situ of the following: bladder, stomach, colon, cervix, endometrium, melanoma, or breast. Patients with previous malignancies are eligible if the malignancy has been confined and surgically resected (or treated with other modalities) with curative intent. Any active systemic therapy must have been completed > 1 year from enrollment (except for hormonal/anti hormonal treatment, e.g., breast cancer).
10. Central nervous system leukemia based on imaging or documented positive cytology in cerebral spinal fluid.

11. Any uncontrolled Grade 3 or higher (per NCI CTCAE, Version 4.03) 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.
12. Patients with any of the following:
* Known positive hepatitis B polymerase chain reaction (PCR) assay who have also tested positive for hepatitis B surface antigen and/or anti-hepatitis B core antibody; patients with a negative PCR assay are permitted with appropriate antiviral prophylaxis.
* Known or suspected active hepatitis C infection (positive by PCR or on antiviral therapy within the last 6 months).
* Known human immunodeficiency virus (HIV) infection.
13. Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, or myocardial infarction within 6 months prior to their first dose of study drug, or cardiac symptoms consistent with New York Heart Association (NYHA) Class III-IV within 6 months prior to the first dose of study treatment (see Appendix F).
14. Current therapy with other systemic anti-neoplastic or investigational agents, with the exception of hydroxyurea.
15. Females who are breastfeeding.
16. Known hypersensitivity to any excipient contained in the drug formulation of any study treatment.
17. Significant history of pulmonary, renal, neurologic, psychiatric, endocrine, metabolic, immunologic, hepatic, cardiovascular disease, or any other condition which, in the opinion of the investigator, would adversely affect participation in this study, compromise patient safety or interfere with data interpretation.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	6

Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Dacogen
Generic name:	DECITABINE
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	vadastuximab talirine
Generic name:	nap
Product type:	Medicine
Brand name:	Vidaza
Generic name:	AZACITIDINE
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	22-11-2016
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-05-2017
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-06-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2015-003482-28-NL
ClinicalTrials.gov	NCT02785900
CCMO	NL59333.068.16