A Phase I/II Study of brentuximab vedotin (SGN-35) in Pediatric Patients With Relapsed or Refractory Systemic Anaplastic Large-Cell Lymphoma or Hodgkin Lymphoma

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Primary• To assess the safety profile and determine the pediatric maximum tolerated dose and/or recommended phase 2 dose of brentuximab vedotin• To assess the pharmacokinetics of brentuximab vedotin• To determine the overall response rate (complete...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lymphomas Hodgkin's disease
Study type	Interventional

Summary

ID

NL-OMON37406

Source
ToetsingOnline

Brief title
Brentuximab Vedotin (SGN-35)

Condition

- Lymphomas Hodgkin's disease

Synonym
Anaplastic Large-Cell Lymphoma or Hodgkin Lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Millenium Pharmaceuticals
Source(s) of monetary or material Support: Millenium

Intervention

Keyword: brentuximab vedotin, Hodgkin Lymphoma, Phase I/II, Systemic Anaplastic Large-Cell Lymphoma

Outcome measures

Primary outcome

Primary Endpoints

• Adverse events (AEs), serious adverse events (SAEs), assessments of clinical

laboratory values, and vital sign measurements

• Plasma concentrations of brentuximab vedotin, total therapeutic antibody, and

MMAE

• Overall response rate (CR, PR) as determined by an IRF using PET, CT, and

clinical assessment according to IWG revised response criteria

Secondary outcome

Secondary Endpoints

• Anti-therapeutic antibody (ATA) titer and neutralizing ATA titer

• Overall response rate (CR, PR) as determined by an independent review

facility (IRF) using positron emission tomography (PET), computed tomography

(CT), and clinical assessment, according to International Working Group (IWG)

revised response criteria

• Time to progression

• Time to response

• Duration of response

• Event-free survival

• Progression-free survival

• Overall survival

Adverse events, serious adverse events, assessments of clinical laboratory values, and vital sign measurements

• Plasma concentrations of brentuximab vedotin, total therapeutic antibody, and MMAE

• Anti-therapeutic antibody (ATA) titer and neutralizing ATA titer

Exploratory Endpoints

• Immune reconstitution (enumeration of the total lymphocyte count and lymphocyte subsets, total immunoglobulin and IgG, IgM, IgA levels, levels of the antibodies to tetanus, HiB, and polioserotypes) at baseline, end of treatment, and 6- and 12-months post-last dose.

Study description

Background summary

Classical Hodgkin lymphoma (HL) is defined histopathologically by the presence of malignant Hodgkin-Reed-Sternberg (H/RS) cells in a background of inflammatory cells. H/RS cells are characterized by the expression of CD30, a surface tumor marker and cell membrane protein belonging to the tumor necrosis factor (TNF) receptor superfamily. HL occurs in patients in all age groups and presents a bimodal distribution with peaks at 15 to 35 years of age and over the age of 60. The median age at diagnosis is 38 years in adults and 13.5 years in the pediatric population. The disease is very uncommon in children under 4 years of age and almost nonexistent in those under 2 years of age.
Painless cervical lymphadenopathy is the most common presenting sign (> 70%)(5)

in children with HL, often with a fluctuating course leading to a delay in diagnosis. Mediastinal masses are frequent (about 60% of pediatric patients) and sometimes discovered after routine chest X-rays. Patients with mediastinal adenopathy may present with respiratory symptoms such as shortness of breath, chest pain, or cough. Fewer than 5% present with disease limited to the upper cervical lymph nodes, above the level of the hyoid bone. Disseminated lymphadenopathy is rare in patients with HL.
Approximately 25% of patients will have systemic B symptoms at presentation (as defined by the Ann Arbor system), typically fatigue, fever, weight loss, and night sweats. Pruritus and intermittent fever usually associated with night sweats are classic symptoms of HL. The frequency of these symptoms increases with advanced stage of the disease. Accurate disease staging and classification of the histological subtype determine the most favorable treatment options and prognosis. The stage of the disease is assigned according to the Ann Arbor staging system with Cotswold modifications for HL. All cases are subclassified to indicate the absence (A) or presence (B) of the systemic symptoms at presentation. Pediatric patients are more likely than adults to present with stage I/II disease and less likely to present with stage IV disease.
Adolescents are more likely to have B symptoms than pediatric patients younger than 10 years and have a much higher
relapse rate.

Transplantation-related mortality rates of more than 20% and even higher relapse rates in pediatric and adult series compromise the survival benefit. Patients who experience relapse or progressive HL post-alloSCT fare dismally. A pooled analysis from 5 international transplant centers of 756 patients who experienced relapsed HL after autologous stem cell transplant (ASCT) revealed a median survival of 2.4 years, with fewer than 10% of patients alive at 5 years. When the collected data were analyzed by decade in which treatment was received, no difference in treatment outcome was apparent, suggesting that introduction of novel treatment approaches and allogeneic transplantation has not meaningfully improved OS (overall survival). Current therapies for pediatric HL have changed dramatically to reduce these toxicities - high-dose radiation therapy is no longer utilized, chemotherapy regimens utilize lower doses of alkylating agents, hybrid regimens allow for lower doses of anthracycline and bleomycin - minimizing the current late effects in patients receiving modern therapy. However, there is still a need to investigate the efficacy and safety of these regimens versus chemotherapy alone in children and adolescents. Because late effects may take 10 to 30 years or more to become clinically apparent, it is too early to conclude on the long-term safety of these
treatments. The proposed pediatric study has been designed to study brentuximab vedotin in patients with relapsed or refractory HL, where adult data in this disease setting are presently available and where an unmet medical need for new treatments currently exists.

Study objective

Primary
• To assess the safety profile and determine the pediatric maximum tolerated dose and/or recommended phase 2 dose of brentuximab vedotin
• To assess the pharmacokinetics of brentuximab vedotin
• To determine the overall response rate (complete remission, partial remission) with brentuximab vedotin.

Secundary

• To determine the overall response rate (complete remission, partial remission) with brentuximab vedotin.
• To determine the time to progression, time to response, duration of response, and eventfree, progression-free, and overall survival with brentuximab vedotin.

Explorative
• To assess immume reconstitution

Study design

This is a phase I/II, open-label, single-agent, multicenter, dose escalation study of brentuximab vedotin in children with relapsed or refractory sALCL or HL. Patients with primary mediastinal B cell lymphoma will be eligible during phase I. The primary objectives of the study are to assess the safety and pharmacokinetics, and determine the pediatric maximum tolerated dose (MTD) and/or RP2D of brentuximab vedotin in children.
In addition, the immunogenicity and antitumor activity of brentuximab vedotin will be evaluated in children. Overall response will be evaluated after 2 cycles of therapy. Objective response is to be assessed by an independent review facility (IRF) according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma.(1) Children who respond or experience stable disease may receive up to 16 cycles of brentuximab vedotin. Children who experience disease progression or have unacceptable toxicity at any time will be withdrawn from treatment. All children will be followed for 12 months following the last dose of brentuximab vedotin to assess overall survival. Brentuximab vedotin will be administered by intravenous (IV) infusion once every 21 days in this study. Each 21-day treatment cycle is composed of 1 day of study drug treatment, followed by a monitoring period of 21 days. The starting dose will be 1.4 mg/kg and escalation will proceed using a traditional 3 + 3 design to a maximum dose of 1.8 mg/kg.

Intervention

Patient can have up to 16 cycles of 21 days. On day one of each cycles patients

will get study medication. Dose is depending on the weight of the patient.

Study burden and risks

Please refer to section E8.

Contacts

Public
Millenium Pharmaceuticals

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Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. Male or female patients aged 2 to < 18 years (5 to < 18 years for patients with HL).;2. Have a diagnosis of systemic anaplastic large-cell lymphoma, or Hodgkin lymphoma for which standard, curative, life-prolonging, or palliative treatment does not exist or is no longer

effective. (Patients diagnosed with any relapsed or refractory CD30+ hematological malignancy [eg, primary mediastinal B-cell lymphoma] may be included in phase 1 of the study.);3. Patients with sALCL must have documented anaplastic lymphoma kinase (ALK) status.;4. Patients with HL must be in their second or later relapse, have failed systemic chemotherapy either as induction therapy for advanced stage disease or salvage therapy, and were ineligible for, refused, or previously received a stem cell transplant.;5. Patients with relapsed or refractory sALCL must be beyond first remission or refractory to front-line chemotherapy.;6. Performance score >= 60 from Lansky Play Performance Scale if <= 16 years;7. Female patients who are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form (ICF) through 6 months after the last dose of study drug, or agree to completely abstain from heterosexual intercourse;8. Male patients, even if surgically sterile, who agree to practice effective barrier
contraception during the entire study treatment period and through 6 months after the last dose of study drug, or agree to completely abstain from heterosexual intercourse;9. Voluntary written consent (and institution-specific assent as appropriate based upon patient comprehension) must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent/assent may be withdrawn by the patient or patient guardian at any time without prejudice to future medical care.;10. Suitable venous access for the study-required procedures.;11. Clinical laboratory values as specified below within 14 days before the first dose of
study drug:
• Absolute neutrophil count greater than or equal to 1,500/µL.
• Platelet count greater than or equal to 75,000/µL.
• Serum bilirubin level less than or equal to 1.5 * upper limits of normal (ULN).
• Serum creatinine less than or equal to 1.5 * ULN.
• Alanine aminotransferase (ALT or SGPT) and aspartate aminotransferase (AST or SGOT) less than or equal to 2.5 * ULN.;12. Patients must have a radiographically or clinically evaluable tumor per the IWG(1)
criteria.

Exclusion criteria

1. Current diagnosis of primary cutaneous ALCL those with systemic ALCL are eligible.
2. Received an allogeneic stem cell transplant < 6 months prior to first dose of study medication, or presence of polymerase chain reaction (PCR)-detectable CMV in any post-allogeneic transplant patient. (Prior PCR positivity that was successfully treated is acceptable provided the baseline PCR result is negative prior to first dose of study drug.)
3. Receiving immunosuppressive therapy.
4. Receiving systemic therapy for chronic graft-versus-host disease (topical therapy is allowed).
5. Previous treatment with any anti-CD30 antibody.

6. Therapeutic monoclonal antibody use within the longer of 6 weeks or 5 plasma half lives.
7. Symptomatic cardiac disease including ventricular dysfunction, coronary artery disease, or arrhythmias, if this would, in the opinion of the investigator or medical monitor, interfere with assessment of efficacy or safety of the drug.
8. History of another primary malignancy not in remission for at least 3 years. (The following are exempt from the 3-year limit: nonmelanoma skin cancer and cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on Pap smear)
9. Known cerebral/meningeal disease, including signs or symptoms of progressive multifocal leukoencephalopathy (PML).
10. History of cirrhosis.
11. Active systemic viral, bacterial, or fungal infection requiring antimicrobial, antiviral therapy or antifungal therapy within 2 weeks prior to first dose of study drug (routine antimicrobial prophylaxis is acceptable).
12. Concurrent therapy with other anti-neoplastic or experimental agents.
13. System corticosteroid therapy <14 days prior to first dose of study medication.
14. Any serious underlying medical condition that, in the opinion of the investigator or medical monitor, would impair patient*s ability to receive or tolerate the planned treatment.
15. Known hypersensitivity to recombinant proteins, murine proteins, or any excipient contained in the drug formulation.
16. Received nitrogen mustard agents, melphalan, or BCNU therapy within 6 weeks prior to first study dose.
17. Prior autologous hematopoietic stem cell infusion < 6 weeks prior to first study dose.
18. Grade 2 or greater unresolved toxicity from prior antineoplastic therapy.
19. Received a strong inhibitor of CYP3A4 < 2 weeks prior to first study dose.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-10-2012

Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	SGN-35
Generic name:	Brentuximab vedotin

Ethics review

Approved WMO Date:	12-01-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-10-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-01-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-02-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-04-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-05-2014

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-08-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-10-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-07-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-08-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	24-04-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-02-2018
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
EudraCT	EUCTR2011-001240-29-NL
CCMO	NL38209.078.11