Open-Label, Multi-Center, Randomized Study of Anti-CCR4 Monoclonal Antibody KW 0761 (mogamulizumab) Versus Vorinostat in Subjects with Previously Treated Cutaneous T-Cell Lymphoma (CTCL)

Published: 19-06-2013
Last updated: 18-07-2024

The main purpose of this study is to determine if KW-0761, an investigational drug will work against cutaneous T-cell lymphoma (CTCL) that has failed to respond to other treatments, and to evaluate its side effects. An investigational drug is one...

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

Summary

ID

NL-OMON44789

Source
ToetsingOnline

Brief title
KYOWA 0761-010 study

Condition

- Lymphomas non-Hodgkin's T-cell
- Lymphomas non-Hodgkin's T-cell

Synonym
Cutaneous T-cell lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Kyowa Kirin Pharmaceutical Development Inc.
Source(s) of monetary or material Support: Kyowa Hakko Kirin Pharma

Intervention

Keyword: Anti-CCR4 Monoclonal Antibody KW 0761, Cutaneous T-Cell Lymphoma, Vorinostat

Outcome measures

Primary outcome

• To compare the progression free survival of KW-0761 versus vorinostat for

subjects with relapsed or

refractory Cutaneous T-Cell Lymphoma (CTCL).

Secondary outcome

To compare the overall response rate of KW-0761 versus vorinostat in subjects

with relapsed or refractory

CTCL;

• To evaluate and compare improvements in Quality of Life (QoL) measurements,

Skindex-29, FACT-G, and

EQ-5D-3L for subjects receiving KW-0761 versus vorinostat;

• To evaluate and compare improvements in the Pruritus Evaluation (Likert scale

& Itchy QoL) for subjects

receiving KW-0761 versus vorinostat;

• To estimate the duration of response for both the KW-0761 and vorinostat arms

for those subjects with

relapsed or refractory CTCL responding to treatment;

• To determine if subjects who relapse on vorinostat can achieve response upon

cross over to treatment with

KW-0761;

• To further assess the safety of KW-0761;

• To describe the immunogenicity of KW-0761;

To compare the overall survival of KW-0761 versus vorinostat for subjects with

relapsed or refractory

CTCL.

• To conduct exploratory evaluation of KW-0761exposure-response relationships

Study description

Background summary

T-cell non-Hodgkin*s lymphoma (NHL) comprises approximately 10 - 15% of all adult
NHL.1
The T-cell lymphomas are a highly heterogeneous group of disorders with a highly
variable prognosis, response to therapy and geographic distribution, of which the two most
common forms of cutaneous T-cell Lymphoma (CTCL) are mycosis fungoides (MF) and
Sézary syndrome (SS).
The estimated incidence of CTCL in the U.S. based on the Surveillance Epidemiology and
End Results (SEER) data from 2001 - 2007 is 0.5/100,000 or about 2,400 new cases per year,
which represents about 25% of all T-cell lymphomas.2
From 1973 to 2002, there appears to
have been at least a three-fold rise in the incidence of CTCL,3 although this may partially
represent a greater degree of awareness and reporting of the disease.
Unlike other forms of NHL, CTCL mainly affects the skin. It can present as patches, plaques,
tumors or erythroderma and may be associated with severe pruritus.4,5
The type and extent of

skin involvement as well as the presence of extracutaneous disease are significant prognostic
factors in this subject population.6
Cutaneous T-cell Lymphoma can cause significant
morbidity and adversely affect the subject*s quality of life (QoL).7,8,9
Cutaneous T-cell lymphoma is staged according to four anatomical compartments: involvement of skin (T), nodes (N), visceral metastases (M) and peripheral blood (B). Blood
involvement is further divided into three categories, B0 (absence of significant blood
involvement where <= 5% of peripheral blood lymphocytes are atypical [Sézary] cells), B1
(low blood tumor burden where >5% of peripheral blood lymphocytes are atypical [Sézary]
cells without meeting the criteria of B2) and B2 (high blood tumor burden with > 1,000/µl
Sézary cells).10
At presentation, up to 50% of subjects with MF will have limited disease, while only 10-20%
present with erythrodermic involvement.11 Survival, as would be expected, is related to stage.
Subjects with early stage MF have median survivals in excess of 25 years; median survival of
advanced disease is very variable, with some reporting median survival as little as 1.5 years.6

Study objective

The main purpose of this study is to determine if KW-0761, an investigational drug will work against cutaneous T-cell lymphoma (CTCL) that has failed to respond to other treatments, and to evaluate its side effects. An investigational drug is one which has not been approved for sale for the treatment of disease being studied but is currently being tested. Currently, KW-0761 is approved by the Government Health Agency in Japan for use in patients with another type of T-cell lymphoma. KW-0761 is an antibody. Antibodies are proteins which the immune system, your body*s defense system, uses to recognize foreign or unwanted material, such as infection or some cancers. Antibodies are used to try to destroy cancer cells while causing little harm to normal cells. The cancer cells of many patients with T-cell lymphoma contain a protein called CCR4. KW-0761 is an antibody that finds T-cells that have a protein called CCR4 on their surface and attempts to destroy them. KW-0761 will be tested in this study versus vorinostat which is a drug that has been approved by the US FDA for treatment of CTCL. Vorinostat has not been approved in Europe and would be considered as an investigational drug in Europe.

Study design

This is an open-label, multi-center randomized, Phase 3 study with 1:1 randomization of study drug, KW-0761
versus the comparator, vorinostat.

Intervention

Subjects will be randomized 1:1 to receive either KW-0761 or vorinostat. Treatment will be administered on an
outpatient basis. The dose of KW-0761 will be 1.0 mg/kg. The dose of vorinostat will be the recommended dose
of 400 mg (once daily with food).
Each treatment cycle is 28 days. Subjects will receive KW-0761 as an iv infusion over at least 1 hour on Days 1,
8, 15 and 22 of the first cycle and on Days 1 and 15 of subsequent cycles. Vorinostat will be administered orally
daily beginning on Day 1.

Subjects may remain in the treatment phase up until progressive disease (PD), drug intolerance or unacceptable
toxicity, or until any of the other criteria for study removal are met.

Subjects in the Vorinostat arm who have received at least two full treatment cycles and demonstrate progression of disease on
treatment with vorinostat at the 8 week (cycle 2, Day 26-28) or anytime thereafter assessment may cross over to treatment with
KW-0761 after discussion with KKD Medical Monitor and receipt of approval for cross over from KKD. In cases where a subject's disease progresses rapidly (i.e. prior to 8 weeks), the medical monitor should be contacted and may consider the possibility of early crossover, if appropriate for that subject. All subjects must undergo full extent of disease evaluations (including computed tomography scanning) to document progressive disease prior to crossover.

Upon notification from the study doctor, if the subject is receiving study treatment at the time the study data is formally reviewed by KKD to look at side effects and how the study drug works, the subject may continue on study and his/her disease evaluation assessments will be followed according to his/her study doctor*s institutional standard of care.

Study burden and risks

The minimal study cycles is 28 days. Patient can remain in the study until the overall complete response or disease progression.
These are the following study procedures:

Physical examination, Vital signs, ECG, Serum sample for KW-0761 concentration assesment, Blood sample for determination of natural ligands, Saliva sample for genetic analysis, CT scans, Skin photographs, Pruritus Evaluation and Skindex-29, FACT-G & EQ-5D-3L questionnaires;

Contacts

Public
Kyowa Kirin Pharmaceutical Development Inc.

212 Carnegie Center Suite 101
Princeton NJ 08540
US
Scientific
Kyowa Kirin Pharmaceutical Development Inc.

212 Carnegie Center Suite 101
Princeton NJ 08540
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1) Voluntarily signed and dated Institutional Review Board / Ethics Committee approved informed consent form in accordance with regulatory and institutional guidelines. Written informed consent must be obtained prior to performing any study-related procedure;
2) Males and female subjects >= 18 years of age at the Pre-treatment Visit, i.e., at the time that written informed consent is obtained, except in Japan where subjects must be >= 20 years of age;

3) Histologically confirmed diagnosis of MF or SS;
For SS (defined as meeting T4 plus B2 criteria), where the biopsy of erythrodermic skin may only reveal suggestive but not diagnostic histopathologic features, the diagnosis may be based on either a node biopsy or fulfillment of B2 criteria including a clone in the blood that matches that of the skin.
4) Stage IB, II-A, II-B, III and IV;
5) Subjects who have failed at least one prior course of systemic therapy (e.g., interferon, denileukin diftitox, bexarotene, photopheresis, anti-neoplastic chemotherapy, etc.); Psoralen plus ultraviolet light therapy (PUVA) is not considered to be a systemic therapy;
6) Eastern Cooperative Oncology Group (ECOG) performance status score of <= 1;
7) The subject has resolution of all clinically significant toxic effects of prior cancer therapy to Grade <= 1 by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI-CTCAE, v.4.0) excluding the specifications required in 8, 9 and 10 below.
8) Adequate hematological function:
a. absolute neutrophil count (ANC) >= 1,500 cells/µL (>= 1,500/mm3)
b. platelets >= 100,000 cells/µL; (>= 100,000/mm3)
c. in subjects with known bone marrow involvement, ANC must be >= 1,000 cells/µL (>= 1,000/mm3) and platelets >= 75,000 cells/µL. (>= 75,000/mm3)
9) Adequate hepatic function:
a. bilirubin <= 1.5 times the specific institutional upper limit of normal (ULN), except for subjects with Gilbert*s syndrome;
b. aspartate transaminase (AST) and alanine transaminase (ALT) each <= 2.5 x ULN or <= 5.0 x ULN in the presence of known hepatic involvement by CTCL.
10) Adequate renal function:
a. serum creatinine <= 1.5 x ULN; OR
b. calculated creatinine clearance > 50 mL/min using the Cockcroft-Gault formula.
11) Subjects previously treated with anti-CD4 antibody or alemtuzumab are eligible provided their CD4+ cell counts are >= 200/mm3.
12) Subjects with MF and a known history of non-complicated staphylococcus infection/colonization are eligible provided they continue to receive stable doses of prophylactic antibiotics.
13) Women of childbearing potential (WOCBP) must have a negative pregnancy test within 7 days of receiving study medication.
14) WOCBP must agree to use effective contraception, defined as oral contraceptives, double barrier method (condom plus spermicide or diaphragm plus spermicide) or practice true abstinence from sexual intercourse (periodic abstinence, e.g., calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception) during the study and for 3 months after the last dose. WOCBP includes any female who has experienced menarche and who has not undergone successful surgical sterilization or is not postmenopausal (defined as amenorrhea >= 12 consecutive months without an alternative medical cause);
15) Male subjects and their female partners of child bearing potential must be willing to use an appropriate method of contraception defined as oral contraceptives, double barrier method (condom plus spermicide or diaphragm plus spermicide) or practice true abstinence from sexual intercourse (periodic abstinence, e.g., calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception) during the

study and for 3 months after the last dose.
NOTE: For subjects continuing to receive study treatment as of protocol Amendment 8, the period of contraceptive use should be extended to 6 months after the last dose of KW-0761.

Exclusion criteria

1) Current evidence of large cell transformation (LCT). Subjects with clinical features suggestive of LCT must have a biopsy performed within 4 months prior to Cycle 1 Day 1 to rule out transformed disease. Subjects with a history of LCT but without current aggressive disease and no current evidence of LCT on pathology in skin or lymph nodes would be eligible;;2) Diagnosed with a malignancy in the past two years. However, subjects with non-melanoma skin cancers, melanoma in situ, localized cancer of the prostate with current prostate-specific antigen of < 0,1 ng/mL, treated thyroid cancer or cervical carcinoma in situ or ductal/lobular carcinoma in situ of the breast with in the past two years may enroll as long as there is no current evidence of disease.;3) Clinical evidence of central nervous system (CNS) metastasis.;4) Psychiatric illness, disability or social situation that would compromise the subject*s safety or ability to provide consent, or limit compliance with study requirements.;5) Significant uncontrolled intercurrent illness including, but not limited to:;a. uncontrolled infection requiring antibiotics;;b. clinically significant cardiac disease (class III or IV of the New York Heart Association classification);;c. unstable angina pectoris;;d. angioplasty, stenting, or myocardial infarction within 6 months;;e. uncontrolled hypertension (systolic blood pressure (BP) > 160 mm Hg or diastolic BP
> 100 mm Hg, found on two consecutive measurements separated by a 1-week period) despite two anti-hypertensive medications;;f. clinically significant cardiac arrhythmia; or;g. uncontrolled diabetes.;6) Known or tests positive for human immunodeficiency virus, human T-cell leukemia virus, hepatitis B or hepatitis C.;7) Active herpes simplex or herpes zoster. Subjects on prophylaxis for herpes who started taking medication at least 30 days prior Pre-treatment visit, and have no active signs of active infection, and whose last active infection was more than 6 months ago, may enter the study, and should continue to take the prescribed medication for the duration of the study.;8) Experienced allergic reactions to monoclonal antibodies or other therapeutic proteins.;9) Known active autoimmune disease will be excluded. (For example; Graves* disease; systemic lupus erythematosus; rheumatoid arthritis; Crohn*s disease; psoriasis).;10) Is pregnant (confirmed by beta human chorionic gonadotrophin [β-HCG]) or lactating.;11) Prior treatment with KW-0761.;12) Prior treatment with vorinostat. Patients who were exposed to vorinostat for a short time, did not progress while on treatment, and did not have intolerable toxicity but were discontinued for another reason (e.g. comorbidity) may be permitted to enter the study after discussion with the Medical Monitor.;13) Have had any therapy directed against the subject*s underlying cancer or any investigational medications within four weeks of randomization (skin directed treatments, including topicals and radiation within two weeks of randomization). However, subjects with rapidly progressive malignant disease may be enrolled prior to this period after discussion with the Medical Monitor.;14) Subjects on a stable dose of a low dose systemic corticosteroid (<= 20 mg prednisone equivalent) for at least 4 weeks prior to Pre-treatment Visit may continue use although the investigator should attempt to taper the use to the lowest dosage tolerable while on study. Initiation of treatment with systemic corticosteroids

or increase in dose while on study is not permitted except to treat an infusion reaction. Subjects may receive intra-articular corticosteroid injections, intraocular corticosteroid drops, inhalation or nasal corticosteroids and replacement doses of systemic corticosteroids as needed.;15) Subjects on a stable dose of medium or low potency topical corticosteroids for at least 4 weeks prior to Pre-treatment Visit may continue use at the same dose, although the investigator should attempt to taper the use to the lowest dosage tolerable while on study. Initiation of treatment with topical corticosteroids while on study is not permitted except to treat an acute rash.;16) History of allogeneic transplant.;17) Autologous hematopoietic stem cell transplant within 90 days of Pre-treatment Visit.;18) Subjects on any immunomodulatory drug for concomitant or intercurrent conditions other than T-cell lymphoma or who have received any of these agents within 4 weeks of treatment, including but not limited to the following, will be excluded: low dose or oral methotrexate; azathioprine; intravenous;(iv) immunoglobulin; low dose or oral cyclophosphamide; cyclosporine; mycophenolate; infliximab;etanercept; leflunomide; adalimumab; lenalidomide; abatacept; rituximab; anakinra; interferon-β; IL-2 and natalizumab.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-07-2015
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	KW-0761
Generic name:	Mogamulizumab
Product type:	Medicine
Brand name:	Zolinza
Generic name:	Vorinostat

Ethics review

Approved WMO Date:	19-06-2013
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	21-11-2013
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	14-04-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	12-05-2014
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	22-05-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	18-05-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	26-05-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	06-06-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	10-06-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	26-04-2017
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	13-07-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	11-05-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	28-05-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	05-09-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	18-02-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	05-03-2019
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2012-004766-17-NL
CCMO	NL44747.058.13