Open-Label, Multi-Center, Phase 2 Study of Anti-CCR4 Monoclonal Antibody KW 0761 (mogamulizumab) in Subjects with Previously Treated Peripheral T-cell Lymphoma (PTCL)

Published: 15-08-2012
Last updated: 26-04-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Haematopoietic neoplasms (excl leukaemias and lymphomas)
Study type	Interventional

Summary

ID

NL-OMON39990

Source
ToetsingOnline

Brief title
KKP 0761-007

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
Peripheral T-Cell Lymphoma, PTCL

Research involving
Human

Sponsors and support

Primary sponsor: Kyowa Hakko
Source(s) of monetary or material Support: Pharmaceutical Industry Farmaceutische industrie

Intervention

Keyword: CCR4, Mogamulizumab, PTCL, T-Cell Lymphoma

Outcome measures

Primary outcome

The primary objective of this study will be:

* To determine the overall response rate of KW-0761 for the treatment of

patients with relapsed or refractory

PTCL;

Secondary outcome

The secondary objectives of this study will be:

* To determine the duration of response, progression-free survival, and overall

survival of patients with

relapsed or refractory PTCL treated with KW-0761;

* To further assess the safety of KW-0761;

* To describe the immunogenicity of KW-0761.

Study description

Background summary

PTCL is a rare and heterogeneous disease that remains difficult to diagnose and treat. In the majority of PTCL
subtypes, patients are of older age (>60 years) and present with advanced stage disease. With the exception of

the ALCL-ALK-positive subtype that responds well to CHOP combined chemotherapy, most PTCL subtypes
become refractory even to aggressive chemotherapy regimens or relapse. Overall survival of PTCL patients is
poor compared with that of aggressive B-cell lymphomas. Thus, novel and effective therapies are needed.
KW-0761has been shown to be safe and tolerable in several clinical trials in subjects with a variety of T-cell
malignancies and represents a promising and novel therapeutic agent for the treatment of patients with relapsed
or refractory PTCL.

Study objective

The primary objective of this study will be:
* To determine the overall response rate of KW-0761 for the treatment of patients with relapsed or refractory
PTCL;
The secondary objectives of this study will be:
* To determine the duration of response, progression-free survival, and overall survival of patients with
relapsed or refractory PTCL treated with KW-0761;
* To further assess the safety of KW-0761;
* To describe the immunogenicity of KW-0761.

Study design

This open-label, multi-center study, Phase 2 study will enroll subjects with previously treated PTCL.
Patients are refractory or have relapsed the previous treatment

Study Treatment

Treatment will be administered on an outpatient basis. Subjects will receive 1.0 mg/kg of KW-0761 as an iv
infusion over 1 hour on Days 1, 8, 15 and 22 of the first cycle and on Days 1 and 15 of subsequent cycles.
No other investigational or commercial agents or therapies other than the study treatment and those described in
Section 5.8.1 of the protocol may be administered with the intent to treat the subject*s malignancy.

Definition of Treatment Cycle

Each treatment cycle is 28 days.
Inter-Cycle Delays

A subject*s next cycle should begin within 2 weeks of the completion of the prior cycle. The start of a new
cycle may be delayed to allow resolution of treatment-related toxicities or for non-medical reasons (holidays,
vacations, etc.). Delay of the start of a new cycle greater than 2 weeks must be discussed with the KKP Medical
Monitor.

Duration of Treatment

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.
In cases where the definition of PD is met in one disease compartment but the clinical impression is
questionable, subjects may remain on study after consultation with the KKP Medical Monitor for a period of at
least 28 days. Review of additional disease assessments at that time by the investigator and KKP Medical
Monitor will then determine if additional treatment or study removal is warranted.
Subjects who experience a CR may be treated for up to 2 additional cycles beyond CR. After that the subject
may continue to receive an infusion of KW-0761 monthly at the discretion of the investigator.

Replacement of Subjects

Subjects who withdraw prior to completing Day 26-28 visit in the first treatment cycle for reasons other than
progression will be replaced.
Dose Modifications
No dose modifications of the KW-0761 will be permitted in this study.

Intervention

Patients will be treated with Mogamulizumab (KW-0761) as described above in the section study design. There is no placebo group.

Study burden and risks

To date, a total of 218 subjects have been given mogamulizumab (KW-0761). The adverse events experienced by the patients were generally mild.

Adverse reactions associated with the use of mogamulizumab (KW-0716):

- One patient who had received Mogamulizumab (KW-0761) suffered from Stevens-Johnson syndrome; a serious disease where the skin and mucous membranes strongly respond to medication or infection leading to flaking of the skin and can cause skin to waste
- Two persons, with a T-cell lymphoma have developed a different type of T-cell lymphoma. It is difficult to ascertain whether this was a consequence of the natural course of their illness or the use of mogamulizumab (KW-0761) was involved.

Common side effects (occur in more than 10% of patients)

- Infusion reaction (an allergic reaction to the drug can cause the following symptoms: itching and rashes in the form of hives, back pain, fever, chills, headache, nausea and sometimes shortness of breath and low blood pressure);
- A low white blood cell (possible increased risk of infections)
- A low neutrophil count (possible increased risk of infections)
- Low platelet count (leading to a higher risk of bleeding may lead)
- Fever
- Rash
- Colds
- Nausea
- Headache
- Abnormal liver function
- Tachycardia (rapid heartbeat)
- Hypotension
- Deviating-oxygen tension in the blood, as measured by the pulse

Other disadvantages, risks and side effects of participating in this study are:

- Blood samples and injections, which may possibly result in bruising, bleeding or (sometimes) infection, fainting or nerve damage.
- When a PET and/or CT scan is performed one comes into contact with radiation. Since radiation can be of disadvantage, the aim is to the amount of radiation to a minimum.
- The most common adverse reactions to contrast materials used in the CT scan used include:
o Allergic reaction
o Blozen/roodheid
o Hives
o Aspiration of bone marrow / biopsy, the consequences can include bleeding, infection, pain at the place where the biopse welcomed. One can also possible reactions to the anesthetic.
- Biopsy of a lymph node and a piece of skin can cause bleeding, infection, pain at the spot where the biopsy was carried out, problems with healing of the wound or reactions to anesthesia may result.
- Reactions to anesthesia may be possible allergic reactions, nausea, or

irregular heartbeat.

Contacts

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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 Ethics Committee (EC) 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 time of enrollment;;3)Histologically confirmed diagnosis of PTCL according to World Health Organization (2008) classification as specified below;;a.PTCL-NOS;b.Angioimmunoblastic T-cell lymphoma;c.Anaplastic large cell lymphoma, ALK-positive;d.Anaplastic large cell lymphoma, ALK-negative;e.Transformed mycosis fungoides;4)Failed or intolerant of at least one prior systemic anticancer therapy;;5)Eastern Cooperative Oncology Group (ECOG) performance status score of * 2 at study entry;;6)At

least one site of disease measurable in two dimensions by computed tomography (CT). Both nodal and extranodal disease will be considered (lymph nodes must have long axis of 1.5 cm regardless of short axis or long axis 1.1 to 1.5 cm and short axis >1.0 cm);7)Subjects who are positive for CCR4 by immunohistochemistry.;8)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 (NCICTCAE, v.4.0) excluding the specifications required in 9, 10, and 11 below;;9)Adequate hematological function:;a.absolute neutrophil count (ANC) * 1,500/mm3;;b.platelets * 100,000 / mm3 or *75,000 in the presence of known bone marrow involvement.;Note: Retesting for values out of criteria will be permitted;;10)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 malignancy.;Note: Retesting for values out of criteria will be permitted;;11)Adequate renal function as evidenced by serum creatinine of *1.5 x the ULN or a calculated creatinine clearance of * 60 ml based on the Cockroft-Gault algorithm.;Note: Retesting for values out of criteria will be permitted;;12)Women of childbearing potential (WOCBP) must have a negative pregnancy test within 7 days of receiving study medication;;13) 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);;14) 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.

Exclusion criteria

1)Subject with the following PTCL diagnoses are excluded;;a.Precursor T/NK neoplasms;b.Adult T-cell leukemia-lymphoma;c.T-cell prolymphocytic leukemia;d.T-cell large granular lymphocytic leukemia;e.Aggressive NK-cell leukemia;f.Systemic EBV-positive T-cell lymphoproliferative disorder of childhood;g.Hydroa vacciniforme-like lymphoma;h.Mycosis fungoides, other than transformed mycosis fungoides;i.Sezary Syndrome;j.Primary cutaneous CD30+ disorders: Anaplastic large cell lymphoma and lymphatoid papulosis;k.Primary cutaneous CD8+ aggressive epidermotropic cytoxic T-cell lymphoma;l.Primary cutaneous CD4+ small/medium T-cell lymphoma;m.Primary cutaneous gamma-delta T-cell lymphoma;n.Extranodal NK /TT-cell lymphoma-nasal type;o.Enteropathy-associated T-cell lymphoma;p.Hepatosplenic T- cell lymphoma;q.Subcutaneous panniculitis -like T-cell lymphoma;r.Chronic lymphoproliferative disorder of NK cells;2)Have had an invasive solid tumor malignancy in the past five years except non-melanoma skin cancers, melanoma in

situ, cervical carcinoma in situ, ductal/lobular carcinoma in situ of the breast, or;localized prostate cancer with a current PSA of * 0.1 ng/ml who is currently without evidence of disease.;3)Relapsed less than 75 days of autologous stem cell transplant;4)History of allogeneic stem cell transplant;5)Evidence of central nervous system (CNS) metastasis.;6)Psychiatric illness, disability or social situation that would compromise the subject's safety or ability to provide consent, or limit compliance with study requirements.;7)Subjects with a history of moderate or severe psoriasis (covering >3% body surface area) or with psoriasis associated with systemic symptoms;e.g. arthropathy, or with a 1st degree relative with history of psoriasis that required medical intervention.;8)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 [NYHA] classification);;c.unstable angina pectoris;;d.angioplasty, stenting, or myocardial infarction within 6 months;;e.uncontrolled hypertension (systolic blood pressure >160 mm Hg or;diastolic BP >100 mmHg, 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.;9)Known or tests positive for human immunodeficiency virus (HIV), hepatitis B or hepatitis C.;10)Active herpes simplex or herpes zoster:;a.Subjects with a history of herpes zoster who have had an outbreak;within the last 3 months will also be excluded;;b.Subjects on prophylaxis for herpes who started taking medication at least 30 days prior to study entry, should continue to take the prescribed;medication for the duration of the study. ;11)Experienced allergic reactions to monoclonal antibodies or other therapeutic proteins;;12)Known active autoimmune disease will be excluded (For example: Grave's disease; systemic lupus erythematosus; rheumatoid arthritis; Crohn's disease);;13)Is pregnant (confirmed by beta human chorionic gonadotrophin [*-HCG]) or lactating.;14)Prior treatment with KW-0761;;15)Initiation of treatment with systemic corticosteroids while on study is only permitted for acute and brief complications of underlying disease (e.g.,hypercalcemia) or for treatment related side effects. Subjects on systemic corticosteroids prior to enrollment must be off for 7 days before initiation of treatment with KW-0761. All tests to document extent of disease must be performed after completion of corticosteroid treatment and prior to first infusion of KW-0761 (subjects may receive intra-articular corticosteroid injections, intraocular corticosteroid drops, inhalation nasal corticosteroids and replacement doses of systemic corticosteroids as needed);;16)Initiation of treatment with topical corticosteroids while on study is not permitted except to treat an acute rash. Assessment of skin disease must be documented after completion of corticosteroid treatment and before treatment with KW-0761 is reinitiated;;17)Have had anti-neoplastic chemotherapy, radiation, immunotherapy, or investigational medications within 4 weeks of commencing treatment;;18)Subjects treated with any immunomodulatory drug, for concomitant or
intercurrent conditions other than T-cell lymphoma or who received any of these
agents within 4 weeks of treatment including, but not limited to low dose or oral
methotrexate; azathioprine; intravenous (iv) immunoglobulin; low dose or oral
cyclophosphamide; cyclosporine;
mycophenolate; infliximab; etanercept; leflunomide; adalimumab; abatacept;
rituximab; anakinra; interferon-*; IL-2, lenalidomide and natalizumab.

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):	01-12-2012
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Mogamulizumab
Generic name:	Mogamulizumab (KW-0761 a recombinant humanized glycosylated defucosylated immunoglobin G subclass 1

Ethics review

Approved WMO Date:	15-08-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-11-2012

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-04-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2011-004151-39-NL
CCMO	NL41526.029.12