Single-Arm, Phase 2 Study of Valemetostat Tosylate Monotherapy in Subjects with Relapsed/Refractory Peripheral T-Cell Lymphoma

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Valemetostat tosylate may modify epigenetic changes, which plays an important role in the pathogenesis of PTCL. In the ongoing open-label Phase 1 study (DS3201-A-J101, 25 Dec 2019 data cut-off), valemetostat tosylate monotherapy demonstrated...

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

Summary

ID

NL-OMON51259

Source
ToetsingOnline

Brief title
VALENTINE-PTCL01

Condition

- Lymphomas non-Hodgkin's T-cell

Synonym
Non-Hodgkin's lymphoma, PTCL

Research involving
Human

Sponsors and support

Primary sponsor: Daiichi Sankyo Inc.

Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Phase II, Relapsed/Refractory, T-Cell Lymphoma, Valemetostat Tosylate

Outcome measures

Primary outcome

Primary Study Objective:

• To estimate the objective response rate (ORR) with valemetostat tosylate

monotherapy treatment in R/R PTCL, including R/R ATL.

Secondary outcome

Secondary Study Objectives:

• To evaluate the duration of response (DoR)

• To assess the CR rate

• To evaluate the duration of CR (DoCR)

• To assess the PR rate

• To assess the safety and tolerability of valemetostat tosylate monotherapy

Study description

Background summary

For patients with R/R PTCL, the therapeutic options are currently limited. Accelerated approval was granted for belinostat, romidepsin, and pralatrexate for R/R PTCL in the US, which demonstrated 25.8%, 26.2%, and 27% of objective response rate (ORR), respectively. No
drug is approved for R/R PTCL in the European Union (EU). Forodesine, a purine nucleoside phosphorylase inhibitor, was approved in Japan, with 22.5% of ORR. Brentuximab vedotin, an antibody-drug conjugate against CD30, showed 86% of ORR in ALCL, and is the only drug with full approval for R/R PTCL in the US. However, in the US and EU, its indication is limited to ALCL in which CD30 is universally expressed. Although conventional chemotherapy can be used for

patients with R/R PTCL, the durability of response is quite short; bendamustine monotherapy resulted in a median duration of response (DoR) of 3.5 months. Patients who are able to achieve a good response (typically CR) can undergo an allogeneic hematopoietic cell transplantation (HCT) for potential cure, but the modality is limited due to the lack of adequate donor and patients* comorbidities. Thus, there remains a compelling unmet need for improved salvage therapy for patients with R/R PTCL.

For refractory or relapsed ATL, no therapy clearly demonstrated survival benefits. Outside Japan, no drug has been approved for relapsed or refractory ATL. Thus, a high unmet need exists for relapsed or refractory ATL patients.

Recent evidence suggests that PTCL, including ATL, can be driven by epigenetic dysregulation. EZH1 and EZH2, catalytic subunits of the polycomb repressive complex 2, specifically methylate H3K27.Hypertrimethylation of H3K27 is considered to silence tumor suppressor genes and has been associated with lymphoma progression, including PTCL and ATL. Valemetostat tosylate may modify epigenetic changes, which plays an important role in the pathogenesis of PTCL.

Study objective

Valemetostat tosylate may modify epigenetic changes, which plays an important role in the pathogenesis of PTCL. In the ongoing open-label Phase 1 study (DS3201-A-J101, 25 Dec 2019 data cut-off), valemetostat tosylate monotherapy demonstrated approximately 62% ORR (34% CR rate) from 21 evaluable R/R PTCL subjects and approximately 50% ORR (20% CR rate) from 10 evaluable R/R ATL subjects. This Phase 2 study will further characterize the safety and clinical activity of valemetostat tosylate and provide an estimate of the clinical benefit as measured by ORR in subjects with R/R PTCL and R/R ATL.

The primary objective is to evaluate the clinical benefit of valemetostat tosylate monotherapy, by evaluating the objective response rate, as measured by blinded independent central review (BICR) in relapsed/refractory peripheral T-cell lymphoma, including relapsed/refractory ATL participants.

Study design

This global, multicenter, open-label, single-arm, 2-cohort, phase 2 study was designed to evaluate the efficacy and safety of valemetostat tosylate monotherapy.The 2 cohorts are:
• Cohort 1: R/R PTCL
• Cohort 2: R/R ATL
Approximately 176 subjects will be enrolled (128 subjects with R/R PTCL and 48 subjects with R/R ATL).

The interventional phase of the study will be divided into 3 periods:

Screening, Treatment, and Follow-up (which includes the Long-Term Follow-up [LTFU]). The Screening Period will be approximately up to 28 days. Subjects will be enrolled once considered eligible and will then enter the Treatment Period. Subjects will undergo disease assessment by radiographic images at regularly scheduled intervals.

The Follow-up Period begins after the End of Treatment (EOT) Visit, which should occur within 7 days after the last dose of valemetostat tosylate or at the time the decision is made to discontinue valemetostat tosylate (if this is more than 7 days after the last dose of valemetostat tosylate), unless there is a medical condition that prevents subjects from completing the visit within this time, or permanent discontinuation of study drug at any time. In addition, after the EOT visit, a 30-day Safety Follow-up Visit will occur, 30 days (± 7 days) after the last dose of valemetostat tosylate. Subsequently, LTFU visits will occur every 3 months. The Survival Follow-up Period is at least 3 years after the first dose of the study drug in the last subject. However, the sponsor may stop the study at any time. The primary completion date for Cohort 1 is at least 10 months after the first dose of the last subject enrolled into Cohort 1 has occurred. This date is used as the cut-off date for the primary analysis for Cohort 1 in this study. The primary completion date for Cohort 2 is the date at least 10 months after the first dose of the last subject enrolled into Cohort 2. This date is used as the cut-off date for the primary analysis for Cohort 2 in this study. All subjects who are still on treatment or who discontinued study drug at the primary completion date will continue to follow the study schedule of events (Table 1.1) until the overall End of Study (EOS) is reached, or the subject is lost to follow up, or the subject withdraws consent or until death. Overall EOS will occur when the last subject*s last visit has occurred and is defined as the completion of survival follow-up of at least 3 years after the first dose of the last subject either from Cohort 1 or Cohort 2, whichever occurs later. The subject*s EOS is defined as the date of his/her last study visit/contact.

Intervention

DS-3201b (valemetostat tosylate) tablets 50 mg are white, round-shaped, film-coated tablets, each of which contains 50 mg of DS-3201a as the free form of valemetostat tosylate. DS-3201b (valemetostat tosylate) tablets 100 mg are grayish-red, oblong-shaped, film-coated tablets, each of which contains 100 mg of DS-3201a as the free form of valemetostat tosylate.

DS-3201b (valemetostat tosylate) will be administered at a dose of 200 mg once daily.
Subjects are instructed to orally take valemetostat tosylate under fasting conditions (to be taken at least 1 hour

before or at least 2 hours after a meal).

Study burden and risks

In general, study participants can experience physical or psychological discomfort through examination tests and examination procedures. In addition, subjects can experience side effects from the study medication.

The study load consists of:
- Visits to the research location
- Physical examination
- Measuring vital functions and weight
- ECOG and Karnofsky performance status
- ECG
- Blood and urine collection
- Pregnancy test
- CT/MRI
- FDG/PET scan
- Assessment of skin lesions
- Oral mucosa smear
- Upper gastrointestinal endoscopy and possibly colonoscopy
- Bone marrow and tumor biopsy
- Receive study medication

- Beoordeling van huid-laesies
- Mondslijmvlies uitstrijkje
- Bovenste gastro-intestinale endoscopie en eventuele colonscopie

Contacts

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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. Sign and date the ICF, prior to the start of any study-specific qualification procedures.
2. Subjects >=18 years of age or the minimum legal adult age (whichever is greater) at the time the ICF is signed.
3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2
4. Cohort 1 (R/R PTCL): Should be pathologically confirmed by the local pathologist/investigators; local histological diagnosis will be used for eligibility determination, but histology will be centrally reviewed following study entry. Subjects with the following subtypes of PTCL are eligible, according to 2016 World Health Organization classification prior to the initiation of study drug. Any T-cell lymphoid malignancies not listed below are excluded. Below is the complete list of eligible subtypes:
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Primary cutaneous γδ T-cell lymphoma
- Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
- PTCL, not otherwise specified
- Angioimmunoblastic T-cell lymphoma
- Follicular T-cell lymphoma
- Nodal PTCL with TFH phenotype
- Anaplastic large cell lymphoma, ALK positive
- Anaplastic large cell lymphoma, ALK negative
5. Cohort 2 (R/R ATL): (acute, lymphoma, or unfavorable chronic type) with

positive anti-human T-cell leukemia
virus type 1 (anti-HTLV-1) antibody. R/R ATL should be pathologically or hematocytologically confirmed by the local pathologist/investigators. The positivity of anti-HTLV-1 antibody will be locally confirmed.
6. Must have at least 1 of the following lesions which are measurable in 2 perpendicular dimensions on CT (or MRI) based on local radiological read:
- Longest diameter (LDi) >=2.0 cm for a nodal lesion
- LDi >1.0 cm for an extranodal lesion
For Cohort 2 (ATL), subjects who had disease only in peripheral blood or/and skin lesions are eligible, as defined below.
o An abnormal lymphocyte count (actual number) is >=1.0 × 10^9 /L and the abnormal lymphocyte-to-leucocyte ratio is >=5%.
o Skin lesion(s) measured by modified severity weighted assessment tool (mSWAT) score.
7. Documented failure to achieve CR (or uncertified CR [CRu] for ATL) from prior systemic lymphoma therapy, or relapsed disease (after CR or CRu for ATL), or progressive disease (after PR or stable disease).
8. Must have at least 1 prior line of systemic therapy for PTCL or ATL.
- Subjects must also be considered as HCT-ineligible during Screening due to disease status (active disease), comorbidities, or other factors; in case of other factors, the eligibility should be discussed with the study medical monitor, and the reason must be clearly documented.
- In Cohort 1, subjects with ALCL must have prior brentuximab vedotin treatment.

Please refer to the protocol for the full list of inclusion criteria.

Exclusion criteria

1. Diagnosis of mycosis fungoides, Sézary syndrome, and primary cutaneous ALCL and systemic dissemination of primary cutaneous ALCL
2. Diagnosis of precursor T-cell lymphoblastic leukemia and lymphoma (T-cell acute lymphoblastic leukemia and T-cell lymphoblastic leukemia), T-cell prolymphocytic leukemia, or T-cell large granular lymphocytic leukemia
3. Prior malignancy active within the previous 2 years except for locally curable cancer that is currently considered as cured, such as cutaneous basal or squamous cell carcinoma, superficial bladder cancer, or cervical carcinoma in situ, or an incidental histological finding of prostate cancer
4. Presence of active central nervous system (CNS) involvement of lymphoma
5. History of autologous HCT within 60 days prior to first dose of study drug
6. History of allogeneic HCT within 90 days prior to the first dose of study drug
7. Clinically significant graft-versus-host disease (GVHD) or GVHD requiring initiation of systemic treatment or systemic treatment escalation
8. Inadequate washout period from prior lymphoma-directed therapy before enrollment, defined as follows:

- Prior systemic therapy (eg, chemotherapy, immunomodulatory therapy, or monoclonal antibody therapy) within 3 weeks prior to the first dose of study drug
- Had curative radiation therapy or major surgery within 4 weeks or palliative radiation therapy within 2 weeks prior to the first dose of study drug
9. Uncontrolled or significant cardiovascular disease, including the following:
- Evidence of prolongation of QT/QTc (eg, repeated episodes of QT corrected for heart rate using Fridericia*s method [QTcF] >450 ms) (average of triplicate determinations)
- Diagnosed or suspected long QT syndrome, or known family history of long QT syndrome
- History of clinically relevant ventricular arrhythmias, such as ventricular tachycardia, ventricular fibrillation, or Torsade de Pointes
- Uncontrolled arrhythmia (subjects with asymptomatic, controllable atrial fibrillation may be enrolled), or asymptomatic persistent ventricular tachycardia
- Subject has clinically relevant bradycardia of <50 bpm unless the subject has a pacemaker
- History of second- or third-degree heart block. Candidates with a history of heart block may be eligible if they currently have pacemakers, and have no history of fainting or clinically relevant arrhythmia with pacemakers, within 6 months prior to Screening
- Myocardial infarction within 6 months prior to Screening
- Angioplasty or stent graft implantation within 6 months prior to Screening
- Uncontrolled angina pectoris within 6 months prior to Screening
- New York Heart Association (NYHA) Class 3 or 4 congestive heart failure
- Coronary/peripheral artery bypass graft within 6 months prior to Screening
- Uncontrolled hypertension (resting systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg)
- Complete left or right bundle branch block
10. History of treatment with other EZH inhibitors
11. Current use of moderate or strong cytochrome P450 (CYP)3A inducers (Table 10.4)
12. Systemic treatment with corticosteroids (>10 mg daily prednisone equivalents). Note: Short-course systemic corticosteroids (eg, prevention/treatment for transfusion reaction) or use for a non-cancer indication (eg, adrenal replacement) is permissible.

Please refer to the protocol for the full list of exclusion criteria.

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):	01-02-2022
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Valemetostat Tosylate
Generic name:	Valemetostat Tosylate

Ethics review

Approved WMO

Date:	06-05-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	27-10-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	23-11-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	08-12-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	19-03-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	06-04-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	29-07-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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	EUCTR2020-004954-31-NL
ClinicalTrials.gov	NCT04703192
CCMO	NL76530.058.21