Phase 1/2 Study to Investigate the Safety, Pharmacokinetics and Efficacy of Tinostamustine, a First-in-Class Alkylating Histone Deacetylase Inhibition (HDACi) Fusion Molecule, in Patients with Advanced Solid Tumors

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The ability to fuse discrete small molecules with different types of pharmacologic activity has created remarkable opportunities in drug discovery and development. Bendamustine itself is a fusion molecule of the nitrogen mustard mechlorethamine and...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON50797

Source
ToetsingOnline

Brief title
Phase * study with tinostamustine in pat. with advanced solid tumors

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Malignant solid tumour

Research involving
Human

Sponsors and support

Primary sponsor: Mundipharma
Source(s) of monetary or material Support: Mundipharma Research Limited

Intervention

Keyword: Pharmacokinetics, Phase 1/2, Safety, Solid tumors

Outcome measures

Primary outcome

Phase 2: Evaluation of Toxicity and Response Rate in Selected Solid Tumor

Cohorts

• To determine the objective response rate (ORR) [complete response (CR)

plus partial response (PR)] of any duration, plus the rate of patients with

stable disease (SD) of at least

4 months duration at a dose of 80 mg/m2 administered over 1 hour on Day 1 and

15 of each

4-week treatment cycle.

Secondary outcome

Phase 2: Evaluation of Toxicity and Response Rate in Selected Solid Tumor

Cohorts

• To evaluate safety and tolerability of 80 mg/m2 of tinostamustine

administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle.

• To determine the progression-free survival (PFS) time for patients who received 80 mg/m2 of tinostamustine administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle.

• To determine the overall survival (OS) for patients who received 80 mg/m2 of tinostamustine administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle.

• To determine duration of response.

• To establish the trough PK profiles of tinostamustine.

Exploratory Objective

• To correlate the extent of gene expression changes in tumor samples with anti-tumor activity.

Study description

Background summary

Initially regarded as *epigenetic modifiers* acting predominantly through chromatin remodeling by maintaining histone acetylation, histone deacetylase (HDAC) inhibitors (HDACi) are recognized to exert multiple cytotoxic actions in cancer cells, often through acetylation of non-histone proteins. Some well-recognized mechanisms of HDACi lethality include, in addition to relaxation of DNA and de-repression of gene transcription, interference with chaperone protein function, free radical generation, induction of deoxyribonucleic acid (DNA) damage, up-regulation of endogenous

inhibitors of cell cycle progression, e.g., p21, and promotion of apoptosis. This class of agents is relatively selective for transformed cells, at least in nonclinical trials. In recent years, additional mechanisms of action of these agents have been uncovered. For example, HDACi compounds interfere with multiple DNA repair processes, as well as disrupt cell cycle checkpoints, critical to the maintenance of genomic integrity in the face of diverse genotoxic insults. Despite their nonclinical potential, the clinical use of HDAC inhibitors remains restricted to certain subsets of T-cell lymphoma. Currently, it appears likely that the ultimate role of these agents will lie in rational combinations, only a few of which have been pursued in the clinic to date.

Multiple lines of recent data have begun to suggest that there is biologically important synergy that exists between alkylating agents and HDAC inhibitors. For example, in one trial the combination of bendamustine, an alkylating agent, and entinostat, a HDAC inhibitor, synergistically inhibits proliferation of multiple myeloma (MM) cells via induction of apoptosis and DNA damage response. In this trial, cell growth assays showed that bendamustine or entinostat inhibited proliferation in a dose-dependent manner, and their combinations synergistically induced growth inhibition in all MM cells tested. An apoptotic enzyme-linked immunoassay (ELISA) and western blot assays on poly (ADP-ribose) polymerase (PARP) cleavage and caspase-8 and caspase-3 revealed that bendamustine in combination with entinostat exhibited a much more potent activity than either agent alone to promote the MM cells undergoing apoptosis in a dose-dependent manner. Flow cytometric analysis found that entinostat exhibited distinct effects on cell cycle progression in different lines and bendamustine mainly arrested the cells at S phase, whereas their combinations dramatically blocked the S cells entering G2/M phase. Furthermore, trials on DNA damage response indicated that phosphohistone H2A.X (P-H2A.X), a hallmark of DNA double strand break, along with phosphorylated CHK2 (P-CHK2) was significantly enhanced by the combinations of bendamustine and entinostat as compared to either agent alone. These molecular changes were correlated with the increases in mitotic catastrophe.

Tinostamustine is a first in class alkylating HDAC inhibitor that is being developed for the treatment of relapsed/refractory hematologic malignancies and solid tumors. The compound underwent broad evaluation in nonclinical models for human cancer. In in vitro and in vivo trials demonstrate efficacy in models of Hodgkin lymphoma, aggressive non-Hodgkin lymphoma, multiple myeloma, T-cell lymphoma and acute myeloid leukemia. In solid tumors activity was seen in models of sarcoma, small cell lung cancer (SCLC), non-small cell lung cancer, breast cancer, ovarian cancer and glioblastoma. The efficacy was independent from p53 status and cell lines resistant to other chemotherapy agents still responded to tinostamustine, including cell lines particularly resistant to bendamustine. Mechanistically, tinostamustine induces a strong DNA damage response, evidenced by a rise of *-pH2AX and p53, while DNA damage response was suppressed.

Consequently, in vitro experiments showed synergy with DNA repair influencing agents such as
PARP inhibitors.

Study objective

The ability to fuse discrete small molecules with different types of pharmacologic activity has created remarkable opportunities in drug discovery and development. Bendamustine itself is a fusion molecule of the nitrogen mustard mechlorethamine and a purine analog based on fludarabine that exhibits unique activity where cancer cells have become resistant to conventional alkylating agents. In fact, randomized clinical trials have established that the combination of rituximab and bendamustine exhibits less toxicity and greater efficacy compared to a conventional R-CHOP based regimen. This concept opens the prospect that other rational fusion molecules could exhibit activity even greater than that seen in the parent molecule.

Tinostamustine is a unique new chemical entity. In the current and ongoing first-in-human dose escalation trial, some patients with relapsed or refractory hematological malignancies, for which there are no available approved therapies, benefited from treatment. The benefit risk assessment is in favour of further development of this molecule in humans.

Study design

The trial is designed as an open label, Phase 1/2 trial of single agent tinostamustine. The Phase 1 portion of the trial was designed to define the MTD by evaluating toxicities during dose escalation until MAD. The Phase 2 portion of the trial is designed to evaluate ORR of the RP2D (80 mg/m2 of tinostamustine administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle) at 4 or 6 months, depending on the type of solid tumor. Secondary objectives are evaluation of safety and tolerability of the RP2D in selected solid tumors. Patients will be eligible for this trial if they have a histologically confirmed solid tumor, sign informed consent and meet the inclusion/exclusion criteria. After enrollment, patients will be screened, and all
procedures will be performed as per protocol.

Intervention

Patients will receive 80 mg/m2 of tinostamustine administered over 1 hour on Day 1 and 15 of each 4-week treatment cycle.

Study burden and risks

There are currently no known drug interactions with Tinostamustine, however not

all possible side effects are known. Furthermore, the risk described below may occur more often or more severely than previously seen. In addition to the possible side effects mentioned below, there is always the possibility of unexpected side effects that you may experience.

Risks Related to Tinostamustine:

Side effects associated with Tinostamustine are summarized below. Side effects with grade 3 or 4 incidence (severe or life-threatening occurrences) are indicated with an asterisk (*). Furthermore, side effects with serious occurrences (serious adverse events) are presented in bold font.

The following adverse events are very common (>=1 in 10 patients):

• Low number of red blood cells that can cause tiredness and shortness of breath* (anemia)
• Condition in which the number of white bloods cells called neutrophils is abnormally low. This increases the risk of infection, which may be serious or life-threatening* (neutropenia)
• Low number of platelets, which may cause bleeding and bruising. Bleeding may be serious or life threatening and may require a blood transfusion* (thrombocytopenia)
• Diarrhea
• Nausea
• Vomiting
• Fatigue*
• Abnormal electrical conduction within the heart which may lead to arrhythmias or irregular heartbeat*
• Loss of appetite
• Headache
• Fever
• Cough

The following adverse events are common (>=1 in 100 and <1 in 10 patients):

• Fever with dangerously low white blood cell count* (febrile neutropenia)
• Condition in which the number of white blood cells circulating in the blood is abnormally low* (leukopenia)
• Decreased number of a type of white blood cells. This is associated with an increased risk of infection* (lymphopenia)
• Irregular heartbeat
• Dry eye
• Blurred vision
• Abdominal pain
• Constipation
• Dry mouth

• Indigestion
• Chronic heartburn and/or acid reflux
• Inflammation of the mouth/mouth sores*
• Feeling weak and having no energy
• Chills
• Influenza-like illness
• Injection site reaction, build-up of fluid in the body or extremities causing swelling
• Fever
• Life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure)*
• Allergic reaction that may include a rash, hives, fever, difficulty breathing, and low blood pressure. Although usually reversible with treatment, it can be severe or life threatening
• Lung inflammation
• Increased risk of infection. This infection may occur anywhere. It may become life-threatening. Symptoms of infection may include fever, pain, redness, and/or difficulty breathing. Infections may include: urinary tract infection, infection of the bone*, infection of the lungs (pneumonia)*, and sepsis (widespread inflammation resulting in poor blood supply to vital organs)*.
• Infusion-related reaction*
• Wound bleeding
• Increased blood level of creatinine, a substance normally eliminated by the kidneys into the urine. This may mean that your kidneys are not functioning properly
• Weight loss
• Low levels of a blood protein called albumin. This can cause generalized swelling (edema)
• Decreased blood calcium level that usually does not cause any symptoms but when severe can cause muscle twitching and/or contractions, abnormal heart beats or seizures
• Low levels of potassium in the blood, which can cause an abnormal heart rate. This could cause an irregular heartbeat, which can be serious and life threatening, Decreased levels of sodium in the blood, which can cause confusion, seizures, fatigue and low levels of consciousness
• Muscle spasms
• Arm/leg pain
• Mental status change (such as memory loss and impaired thinking)
• Dizziness
• Tingling, pricking, chilling, burning, or numb sensation on the skin
• Vision, hearing, taste and smell disturbance
• Frequent urination
• Bloody nose
• Nasal congestion
• Mouth or throat pain
• Collection of fluid around the lungs in the chest cavity, which can cause shortness of breath and may require treatment

• Redness of the skin
• Itching
• Flushing
• Irritation or inflammation of a vein
• Sepsis (also known as infection of the blood leading to weakness, lightheadedness, confusion, uncontrollable shakes) which can lead to organ failure)

The following rare but serious effects have been reported in two drugs like the ones that are combined to make the study drug but have not been seen so far with EDO-S101:
• Release of large amounts of dying tumor cells into the blood which can cause serious problems
• Blood clots in the lungs
• Increased sugar in the blood

Use of allopurinol concomitantly with study drug may cause skin reactions which could be severe and therefore an alternative drug with a different mode of action will be prescribed, if necessary.

When looking at data across all studies with the study drug, the occurrence of some specific ECG abnormalities has been identfied, so called QTc prolongations, which are now closely monitored across the studies. QTc prolongation means a lengthening of the time between certain waves on an ECG. Cardiac monitoring using Holter monitor will be used to determine if there is any significant prolongation. The patient will be continuously checked to see if ECGs show any abnormalities during the infusion and up to 6 hours after the start of infusion. In case of any ECG abnormalities, the doctor may decide to stop the infusion of the drug.

As certain drugs commonly given for side effects of chemotherapy may cause QTc prolongation, the patient may not be able to receive some drugs (such as some anti-nausea drugs, but may be prescribed alternative drugs that do not cause QTc prolongation) during a period of at least 24 hours prior to administration of study drug.

Reproductive risks: The patient should not get pregnant, breastfeed, or father a baby while in this study. The Tinostamustine used in this study could be very damaging to an unborn baby.

The patient should not engage in hazardous activities (like driving a car or operating machinery) requiring mental alertness and motor coordination following drug administration until the patient knows how the study drug will affect him/her.

As a participant, the patient has to come to the clinic for all scheduled visits as requested by the study staff.

4-6 hours per visit per cycle of 28 days, a total of 6 cycles 24-36 hours.
(Cycly 1; 6 visits, following cycles 5 visits).

The patients undergo the following actions during participation:
- physical examination and medical history (weight and height)
- measuring vital functions (pulse, temperature, blood pressure and breathing)
- evaluation of daily activities
- ECG
- Holter ECG
- blood and urine collection and pregnancy test
- Tumor determination by CT scan / MRI
- Infusion research agent

Radiation risk as a result of CT scan / MRI
Blood samples: some known risks, while rare, are pain, bleeding, post-bleeding, burning, discomfort, or bruising or infection where the needle is inserted
Infusion: same as for blood draws
Blood pressure measurement: The cuff that is being inflated may cause discomfort
ECG: The adhesion and removal of the ECG patches (small sticky pads) can cause a transient skin reaction, such as red skin or itching. local skin discomfort and / or hair loss can also be prevented by applying the electrodes.
Side effects of the administered drug / infusion of Tinostamustine (side effects as cytostatics) with special attention to ECG abnormalities, QT prolongation (see above)

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

General Inclusion Criteria:

• Signed informed consent.

• Patients age >=18 years at signing of the informed consent.

• Life expectancy > 3 months

• Histologically confirmed diagnosis of advanced or metastatic solid tumors, disease should have progressed following at least 1 line of therapy and no other standard therapy with proven clinical benefit is available or recommended based on the investigator*s individual risk- benefit assessment for the patient.

• Patients with secondary metastasis to the central nervous system (CNS) are eligible if they have had brain metastases resected or have received radiation therapy ending at least 4 weeks prior to trial day 1 and they meet all of the following criteria:

(1) Residual neurological symptoms <= Grade 1
(2) No glucocorticoids requirement or patients may be receiving low doses of glucocorticoids providing the dose has been stable for at least 2 weeks prior to starting the trial medication
(3) Follow-up imaging studies show no progression of treated lesions and no new lesions

• Evaluable disease; either measurable on imaging or with informative tumor marker as assessed by RECIST version 1.1.

• Eastern Cooperative Oncology Group (ECOG) performance status <=2 (Section 13.1).

• Absolute neutrophil count (ANC) (polymorphonuclear [PMN] cells plus bands)

>1,000 µL.

• Platelets >=100,000 / µL. Platelet transfusions within the 14 days before Day 1 of Cycle 1 is
prohibited.
• Aspartate aminotransferase/alanine aminotransferase (AST/ALT) <=3× upper limit of normal (ULN). In cases with liver involvement ALT/ AST <=5× ULN.

• Total bilirubin <=1.5 mg/dL unless elevated due to known Gilbert*s syndrome.

• Creatinine <=1.5 ULN.

• Serum potassium and magnesium at least at above the lowest limit of normal (LLN) range, before every IMP administration. If it is below LLN, supplementation is permissible.

• Female study participants of child-bearing potential and their partners, and male study participants who intend to be sexually active with a woman of child-bearing potential, must be willing to use at least TWO highly effective forms of contraception
Female study participants of child-bearing potential must continue using contraception for at least six months after the last administration of the IMP.
Male study participants who are sexually active with a woman of child-bearing potential should also use a condom during treatment and for at least ninety (90) days after the last administration of IMP.

Cohort-specific eligibility criteria phase 2 portion of the trial in addition to the general inclusion/exclusion criteria for listed above (refer to protocol page 19-21).
Cohort 1 Patient Population: Relapsed/Refractory Small-cell Lung Cancer (SCLC)
Cohort 2 Patient Population: Relapsed/Refractory Soft Tissue Sarcoma
Cohort 3 Patient Population: Relapsed/Refractory Triple Negative Breast Cancer (RECRUITMENT INTO THIS COHORT HAS NOW BEEN HALTED)
Cohort 4 Patient Population: Relapsed/Refractory Ovarian Cancer
Cohort 5 Patient Population: Relapsed/Refractory Endometrial Cancer (RECRUITMENT INTO THIS COHORT HAS NOW BEEN HALTED)

Exclusion criteria

To be eligible to participate in the trial, a patient cannot meet any of the following exclusion criteria:

• Patients with primary CNS cancer.

• Patients with QTc interval (Fridericia*s formula) >450 ms.

• Patients who are on treatment with drugs known to prolong the QT/QTc interval. Refer to CredibleMeds list of drugs with known risk of Torsade des pointes (TdP): http://crediblemeds.org/new-drug-list.

• Patients who are being treated with valproic acid for any of its indication (epilepsy, mood disorder)

• Any serious medical condition that interferes with adherence to trial procedures.

• Prior history of another solid tumor malignancy diagnosed within the last 3 years of trial enrollment excluding adequately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer, in situ breast cancer, in situ prostate cancer (patients must have shown no evidence of active disease for 2 years prior to enrollment).

• Pregnant or breast feeding women.

• New York Heart Association (NYHA) stage III/IV congestive heart failure (Section 13.2). The following arrhythmias: atrial fibrillation/flutter with poor rate control, documented sustained ventricular tachycardia (defined as >30 seconds or requiring cardioversion before
30 seconds have elapsed) or TdP.

• Significant co-morbidities (e.g., active infection requiring systemic therapy, history of human immunodeficiency virus [HIV] infection, or active Hepatitis B or Hepatitis C).

• Use of other investigational agents or previous anticancer therapies within 28 days prior to the first dose of tinostamustine, provided the patient has recovered from any related toxicities >=Grade 1.

• Steroid treatment within 7 days prior to trial treatment. Patients that require intermittent use of bronchodilators, topical steroids, or local steroid injections will not be excluded from the trial. Patients who have been stabilized to 10 mg prednisolone orally (PO) once daily (QD) (or equivalent), daily (or less) at least 7 days prior to trial drug administration are allowed.

Cohort-specific eligibility criteria phase 2 portion of the trial in addition to the general inclusion/exclusion criteria for listed above (refer to protocol page 19-21).
Cohort 1 Patient Population: Relapsed/Refractory Small-cell Lung Cancer (SCLC)
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Cohort 4 Patient Population: Relapsed/Refractory Ovarian Cancer
Cohort 5 Patient Population: Relapsed/Refractory Endometrial Cancer
(RECRUITMENT INTO THIS COHORT HAS NOW BEEN HALTED)

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	15
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Tinostatumustine
Generic name:	bendamustine-vorinostat fusion molecule EDO-S101

Ethics review

Approved WMO Date:	20-05-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-08-2021
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-09-2021
Application type:	First submission
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
Other	CT.gov https://www.clinicaltrials.gov/ct2/show/NCT03345485
EudraCT	EUCTR2020-004246-11-NL
CCMO	NL75388.078.21

Study results

Results posted: 07-02-2024

Summary results
Trial never started

First publication
06-02-2024