A phase I, open-label, multi-center study to evaluate the pharmacokinetics and safety of oral panobinostat in patients with advanced solid tumors and varying degrees of renal function

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON36258

Source
ToetsingOnline

Brief title
PK of panobinostat in solid tumors with varying renal function

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
pharmacokinetic of panobinostat in solid tumors with varying degrees of renal function

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma

Intervention

Keyword: panobinostat, pharmacokinetics, renal function, solid tumors

Outcome measures

Primary outcome

To assess the effect of varying degrees of renal function (as defined by

creatinine clearance) on the pharmacokinetics of panobinostat.

Secondary outcome

* To assess the effect of varying degrees of renal function on the safety of

panobinostat.

* To evaluate whether there is a relationship between PK and safety parameters

in patients with varying degrees of renal function

Exploratory objective:

* To explore anti-tumor activity associated with panobinostat (extension phase)

Study description

Background summary

Panobinostat (LBH589) is a deacetylase inhibitor (DACi) which belongs to a structurally novel cinnamic hydroxamic acid class of compounds. It is a potent class I/II pan-DAC inhibitor (pan-DACi) that has shown anti-tumor activity in pre-clinical models and patients with solid tumors and hematological malignancies.
Panobinostat is administered orally on days 1, 3, and 5, every week of a 21-or 28-day cycle. The recommended phase II dose has been defined as 40 mg oral

panobinostat given three times a week every week or 60 mg three times a week every other week in patients with primary diagnosis of lymphoma or multiple myeloma. Analysis of data pooled from multiple trials across various doses and schedules provided additional information regarding the adverse event profile of panobinostat at 40 mg dose. Based on this pooled analysis, there is a high likelihood of Grade 3 and 4 thrombocytopenia (50%) and fatigue (57%) apart from other adverse events in patients receiving the 40 mg dose given three times a week every week. The median time to grade 3 thrombocytopenia is approximately 20 days at the 40 mg dose. Thus, this
dose may be considered high for use in a population of patients with underlying organ dysfunction. After treatment of patients with 30 mg
panobinostat, although the overall number patients treated with 30 mg is small, the median time to Grade 3 thrombocytopenia is considerably longer (70 days) and the incidence of Grade 3 or 4 fatigue is very low.

To date, the pharmacokinetics (PK) of panobinostat has been characterized in patients with solid tumors and hematological malignancies participating in several phase I/II clinical studies. Panobinostat PK does not appear to be different in patients with solid tumors and hematological malignancies.
The balanced elimination and absence of a single major route of panobinostat metabolism suggest that clinically significant drug-drug interaction is minimized and altered organ functional status is not expected to have a major impact on panobinostat PK. However, the effect of organ dysfunction on PK of panobinostat is yet to be elucidated in patients with solid tumors and hematological malignancies.

Study objective

As results from a recently completed radio-labeled human ADME study [CLBH589B2108] in patients indicated that both kidney and liver are involved in the elimination and metabolism of panobinostat, understanding the impact of altered organ function status on panobinostat PK
has become important and thus provides a rationale for this study.
Panobinostat is likely to be utilized in cancer patients with co-existing morbidities such as impaired renal function. Patients with renal impairment may be at risk with decreased ability to eliminate panobinostat. Decreased elimination of the drug as a result of impaired organ
function may lead to an increased systemic exposure and possible toxicity.
Although, a number of patients with mild or moderate renal dysfunction have been included in prior clinical studies of single agent panobinostat, currently, there has been no formal evaluation of the disposition of panobinostat in patients with cancer and impaired renal function.
The purpose of this study is to characterize the pharmacokinetics of panobinostat administered as a single oral dose and to evaluate the safety profile of panobinostat administered as single and multiple oral doses in adult patients with advanced solid tumors with varying degrees of renal impairment.
The degree of renal impairment in study patients will be classified as mild,

moderate or severe based on pre-dose (screening) 24-hour urine creatinine clearance determination.

Study design

This is a phase I, open-label, multi-center study to evaluate the PK and safety of oral panobinostat in patients with advanced solid tumors with varying degrees of renal function. Initially, patients with normal renal function and mild or moderate renal dysfunction will be enrolled in the study. A decision to enroll patients with severe renal impairment will be made following review of the preliminary safety data of all patients dosed and completed the core phase and cycle 1 of treatment (extension) phase, of which at least three (3) patients must be from the moderate group. In an unlikely scenario, the first 3 patients enrolled in the study may all belong to the moderate renal dysfunction group and may not, exhibit major toxicities. Such a case, historical data from prior studies of oral panobinostat, where patients with normal renal function and mild renal dysfunction have been enrolled, will be taken into account prior to making a decision to open enrollment for the severe renal dysfunction patients.

Intervention

Core (PK) phase (days 1-7):
A single dose of 30 mg panobinostat will be administered orally following breakfast on day 1 to all patients enrolled in the study and starting treatment. The study starts with a core phase lasting 7 days (day 1 to day 7). If clinically significant toxicities are noted in the core phase, patients will be discontinued from the study. Reduced dose administration will not be permitted in the core phase.

Extension phase (cycle 1 (day 1) and subsequent cycles):
An oral panobinostat dose of 30 mg will be administered with or without food three times a week on days 1, 3 and 5 (e.g., Monday, Wednesday and Friday) as part of a 28-day cycle to all patients enrolled into Groups 1, 2, or 3.
Patients should be advised to maintain fed or fasting status for all subsequent dosing. If excessive thrombocytopenia is encountered (>50% grade 3 or 4), the starting dose will be reduced.

Dose reductions demanded by toxicities will be allowed in the extension phase only.
Based on the observed safety from patients enrolled in the study prior to initiation of enrollment in Group 4, the starting dose for extension phase in severe renal impairment (group 4) patients may be 20 mg
The lowest dose permitted in this study will be 20 mg of panobinostat given on day 1, 3, 5 every other week, regardless of renal function status. Patients requiring a dose reduction below the above lowest possible dose will be

withdrawn from the study.

Study burden and risks

The patient can get side effects of panobinostat, the main side effects are:
* Decrease in platelet count.
* Mild to moderate nausea, vomiting, and diarrhea.
* Decreased appetite
* Fatigue, feeling weak or tired.

In addition, the patient will need to visit the hospital more frequently, this is every day in the first week for pharmacokinetics. At home the patient needs to collect urine samples two times during 24 hours (one time for creatine clearance and one time for pharmacokinetics)

The drawing of blood can hurt or might cause bruising.

Contacts

Public
Novartis

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Scientific
Novartis

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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. Patient is * 18 years of age
2. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of * 2
3. Patient has documented diagnosis of advanced solid tumor for which no standard systemic therapy exists
4. Patient has the following laboratory values within 2 weeks of starting study drug (labs may be repeated, if needed, to obtain acceptable values before failure at screening is concluded)
a. Creatinine clearance according to a 24-hour urine CrCL (specific criteria for allocation of patients by renal function):
* * 80mL/min for the normal renal function patients
* *50 - <80 mL/min for the mildly renal impaired patients
* *30 - <50 mL/min for the moderately impaired patients
* < 30mL/min for severely renal impaired patients, if applicable
b. Urinalysis: protein (proteinuria) * +2 by dipstick method, or < 100 mg/dL by quantitative method and blood (hematuria) * +1 by dipstick method for normal renal function group patients
c. Hemoglobin * 9 g/dL
d. Absolute neutrophil count (ANC) * 1.5 x 109 /L
e. Platelet count * 100 x 109 /L
f. AST/SGOT and ALT/SGPT * 2.5 x ULN (or * 5 x ULN if transaminase elevation is due to disease involvement)
g. Serum total bilirubin * 1.5 ULN
h. Patient with normal renal function should have serum potassium, magnesium, phosphorus, total calcium (corrected for serum albumin) or ionized calcium within normal limits
5. Patient is able to swallow capsules
6. Patient, if sexually active (men and women of child bearing potential WOCBP), is agreeing to use double barrier method of contraception during the course of the study and for 3 months after completing study treatment. WOCBP are defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months
7. Patient has signed a written informed consent prior to any screening procedures

Exclusion criteria

1. Patient has received prior treatment with DAC inhibitors including panobinostat
2. Patient is needing valproic acid for any medical condition including during the study or within 5 days prior to the first dose of panobinostat
3. Patient is taking any anti-cancer therapy concomitantly
4. Patient is requiring diuretics unless patient is taking potassium sparring diuretics

5. Patient has active CNS disease or brain metastasis, except those previously treated and stable for at least 3 months
6. Patient has evidence of another malignancy not in remission or history of such a malignancy within the last 3 years (except for treated basal or squamous cell carcinoma, or in situ cancer of the cervix)
7. Patient has received:
a. prior chemotherapy * 3 weeks prior to start of treatment. Patient must have recovered from all therapy-related toxicities
b. biologic immunotherapy including monoclonal antibodies or experimental therapy * 4 weeks prior to start of study
c. radiation therapy * 4 weeks or limited field radiotherapy * 2 weeks prior to start of treatment
8.Patient has not recovered from all therapy-related toxicities to * grade 1 CTCAE or baseline
9. Patient has undergone major surgery * 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy to * grade 1 CTCAE or baseline
10. Patient has unresolved diarrhea * CTCAE grade 2
11. Patient has impaired cardiac function, including any one of the following:
a. LVEF < the lower limit of institutional norm, as determined by ECHO or MUGA
b. obligate use of a permanent cardiac pacemaker
c.congenital long QT syndrome
d. history or presence of ventricular tachyarrhythmias
e. resting bradycardia defined as < 50 beats per minute
f. QTcF > 450 msec on screening ECG
g. Complete left bundle branch block (LBBB), bifasicular block (RBBB with either left anterior hemiblock or left posterior hemiblock)
h. Any clinically significant ST segment and/or T-wave abnormalities
i. Presence of unstable atrial fibrillation (ventricular response rate > 100 bpm). Patients with stable atrial fibrillation are allowed in the study provided they do not meet the other exclusion criteria
j. Myocardial infarction or unstable angina pectoris * 6 months prior to starting study drug
k. Congestive heart failure (New York Heart Association class III-IV)
l. Other clinically significant heart disease and vascular disease (e.g. uncontrolled hypertension)
12. Patient is taking medications with relative risk of prolonging the QT interval or inducing torsade de pointes, if such treatment cannot be discontinued or switched to a different medication prior to starting study drug
13. Patient has acute renal failure (e.g., acute nephritis, nephritic syndrome, acute tubular necrosis, glomerolunephritis, pyelonephritis, active hydronephrosis), history of renal transplant, end stage renal disease (ESRD). However, ESRD is acceptable, if Group 4 (severe) patients are enrolled.
14. Patient is requiring dialysis
15. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of panobinostat (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, mal-absorption syndrome, obstruction, or major stomach and/or small bowel resection)
16. Patient has any other concurrent severe and/or uncontrolled medical conditions (e.g.,

uncontrolled diabetes, active or uncontrolled infection, chronic obstructive or chronic restrictive pulmonary disease including dyspnea at rest from any cause, uncontrolled thyroid dysfunction) that could cause unacceptable safety risks or compromise compliance with the protocol
17. Patient has a known history of HIV seropositivity or history of activated/treated hepatitis B or C; test for screening is not required
18. Patient is a woman who is pregnant or breast feeding
19. Patient is a male whose sexual partner(s) are WOCBP not willing to use a double method of contraception, one of which includes a condom), during the study and for 3 months after the end of treatment
20. Patient is unwilling or unable to comply with the protocol

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-06-2010
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nvt
Generic name:	Panobinostat

Ethics review

Approved WMO

Date:	25-03-2010

Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	03-06-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-01-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-05-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	07-06-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-06-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-03-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-04-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	20-08-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-05-2013

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2009-012263-34-NL
ClinicalTrials.gov	NCT00997399
CCMO	NL30729.041.10