Absorption, metabolism, excretion, and the determination of absolute bioavailability of Niraparib in subjects with cancer

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Objectives:Primary:• To determine the absolute bioavailability of niraparib by using an intravenous (IV) niraparibmicrodose of 100 µg (containing approximately 1 µCi of [14C]-niraparib) in subjects with cancer.Secondary:• To characterize the...

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

Summary

ID

NL-OMON41940

Source
ToetsingOnline

Brief title
Tesaro PR-30-5015-C

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
and that may benefit from treatment with a PARP inhibitor, cancer; metastatic or locally advanced solid tumors that have failed to respond to standard therapy, have progressed despite standard therapy, or for which no standard therapy exists, refuse standard therapy

Research involving
Human

Sponsors and support

Primary sponsor: TESARO, Inc
Source(s) of monetary or material Support: TESARO;Inc

Intervention

Keyword: Niraparib, PARP inhibitor, solid tumor

Outcome measures

Primary outcome

The absolute bioavailability of niraparib in subjects with cancer (part 1).

Plasma niraparib concentrations will be used to determine the following PK parameters: maximum observed plasma concentration (Cmax); time to reach Cmax (Tmax); and area under the plasma concentration-time curve (AUC) from time 0 to the last quantifiable concentration (AUC0-last); and if the data allow: AUC from time 0 to infinity (AUC0-inf); apparent oral volume of distribution (Vd/F); apparent oral clearance (CL/F); and half-life (t*). Absolute bioavailability of niraparib will be calculated as the ratio of dose normalized oral to IV niraparib exposure.

Secondary outcome

Pharmacokinetics, safety and tolerability of niraparib in subjects with cancer (part 2 and extension study).

Whole blood and plasma total radioactivity and niraparib concentration-time data will be used to determine the following PK parameters: Cmax, Tmax, and AUC0-last. The plasma niraparib concentration will be used to determine the

following PK parameters: Cmax, Tmax, and AUC0-last, and if the data allow: AUC0-inf, Vd/F, CL/F, and t*. Additionally, the following PK parameters will be determined: amount of drug excreted in the urine in a 24-hour period, Ae (day), and total amount of drug excreted in the urine, Ae (total). Urine and fecal elimination of radioactivity will be determined, and total recovery of radioactivity over the collection period will be calculated. Data interpolation will be used to project recovery estimates. Other PK parameters, such as the extent of absorption (f), could be estimated, if appropriate. Selected plasma, urine, and fecal samples will also be subjected to metabolic profiling.
Extension study: Plasma niraparib concentrations will be used to determine the following PK parameters: Cmax, Tmax, AUC0-last, AUC0-inf, and t*.
Safety: Safety will be assessed based on adverse events (AEs), physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory results.

Study description

Background summary

The rationale for the study is described in the protocol:

Niraparib is an orally active poly (adenosine diphosphate [ADP]-ribose) polymerase
(PARP)-1 and -2 inhibitor with nanomolar potency that is being developed for tumors with
defects in the homologous recombination (HR) deoxyribonucleic acid (DNA) repair pathway or
that are driven by PARP-mediated transcription factors.
The potential benefit of niraparib treatment for patients with cancer is tumor regression.
This is an open-label study with 2 parts, including an extension study

following completion of
Parts 1 or 2, that is being conducted in approximately 12 subjects (6 subjects in Part 1; 6 subjects
in Part 2) with cancer to examine the absorption, metabolism, excretion, and absolute
bioavailability of niraparib.
This study will be performed because the oral bioavailability of niraparib has been determined in rats and dogs, but has yet to be determined in human subjects, including those with cancer.
This study will be the first-in-human administration of the IV formulation of niraparib. Data from the nonclinical studies did not demonstrate any safety issues that would preclude testing of IV niraparib in humans, and a microdose (100 µg) of niraparib is being administered in the current study.

Study objective

Objectives:
Primary:
• To determine the absolute bioavailability of niraparib by using an intravenous (IV) niraparib
microdose of 100 µg (containing approximately 1 µCi of [14C]-niraparib) in subjects with cancer.
Secondary:
• To characterize the absorption, metabolism, and excretion of [14C]-niraparib administered as a
single, 300-mg oral dose (containing approximately 100 µCi of [14C]-niraparib) to subjects with
cancer.
• To evaluate the safety and tolerability of niraparib in subjects with cancer.

Study design

The current study is a phase I, single-center, non-randomised, open label study with two parts including an extension study after completing part 1 or part 2, which will be performed with 12 subjects (6 in part 1; 6 in part 2) with cancer to determine the Absorption, Metabolism, Excretion, and the Determination of Absolute Bioavailability of Niraparib

Refer to section Intervention for detailed information.

Intervention

This is an open-label study with 2 parts, plus an extension study following completion of Part 1 or 2, to be conducted in subjects with cancer at a single study center in conformance with Good Clinical Practice (GCP).
Part 1: The Screening Visit will occur within the 3 weeks prior to study drug

administration. Clinical laboratory assessments must occur within 72 hours prior to study drug administration. Subjects have the option of reporting to and/or staying t at the study center on Day -1 for the fasting period. Subjects not staying at the study center on Day -1 must report to the study center at least 2 hours prior to study drug administration. After an overnight fast of at least 10 hours, subjects will receive a single, 300 mg (3 × 100-mg capsules) oral dose of niraparib (unlabeled active pharmaceutical ingredient) on Day 1. Two hours after the oral dose, subjects will receive a 15-minute IV infusion of 100 µg niraparib, containing approximately 1 µCi of radioactivity. Subjects will continue fasting until 2 hours after the start of the IV infusion, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after oral study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to the morning of Day 4, and subjects will undergo safety assessments and pharmacokinetic (PK) blood sampling during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 5, 7, 9, 11, 13, 15, and 22 for safety assessments and PK blood sampling.
Part 2: The Screening Visit will occur within the 3 weeks prior to study drug administration. Clinical laboratory assessments must occur within 72 hours prior to study drug administration. Subjects have the option of reporting to and/or staying overnight at the study center on Day -1 for the fasting period. Subjects not staying at the study center on Day -1 must report to the study center at least 2 hours prior to study drug administration. After an overnight fast of at least 10 hours, subjects will receive a single, 300 mg oral dose of niraparib, containing approximately 100 µCi of radioactivity (3 × 100-mg capsules, labeled active pharmaceutical ingredient [3 x 33.3 µCi of radioactivity]), on Day 1. Subjects will continue fasting until 4 hours after administration of study drug, at which time a light meal will be served. A physician will be present for study drug administration and will remain on site for 5 hours after study drug administration. All subjects will be confined to the study center and under appropriate medical supervision from Day 1 to the morning of Day 10, and subjects will undergo safety assessments, PK and metabolite profile blood sampling, and collection of urine and fecal samples during the confinement period. No strenuous physical activity will be permitted during the confinement period. Subjects will return to the study center on Days 11, 15, and 22 for safety assessments and PK and metabolite profile blood sampling. Participation in Part 2 of the study may extend beyond Day 22 based on the amount of radioactivity recovered.
Extension Study: On the same day that subjects complete Part 1 or 2 of the study, subjects may be eligible to participate in the extension study following re-review of the entry criteria and completion of the screening assessments. Note that if a subject becomes non-evaluable for PK during Part 1 or Part 2, the subject may be considered for the extension study without continuing through Day 22 of Part 1 or Part 2, as long as that subject still meets all inclusion/exclusion criteria. If laboratory values are outside of the range

specified in the inclusion criteria, the subject may continue to participate in the study at the discretion of the Sponsor and Investigator with consideration for a reduced dose as described in Table 6. The Screening Visit should occur within 7 days after the End of Part 1 or Part 2. Assessments performed at the End of Part 1 or Part 2 that are completed within 7 days of Screening do not need to be repeated at Screening (with the exception of complete blood count [CBC] and coagulation/blood chemistry tests, which must be performed within 72 hours prior to first extension study dose). The Cycle 1/Day 1 Visit can also occur on the same day as the Screening Visit and the End of Part 1 or 2 Visit. At the Cycle 1/Day 1 Visit, subjects will receive study drug (300 mg [3 × 100 mg capsules, unlabeled active pharmaceutical ingredient] of niraparib) once a day (QD) and will undergo safety assessments. No fasting period is required during the extension study. Subjects will return to the study center during Cycle 1 on Days 8, 15, and 22 to undergo safety assessments. Subjects will return on the first day of every treatment cycle (28 [±3] days) to receive study drug and for safety assessments, and an Eastern Cooperative Oncology Group (ECOG) performance status assessment. Visits will continue approximately every 4 weeks until treatment discontinuation. Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the subject (Section 7.4). Dose interruptions or reductions will not affect the timing and completion of study assessments. Subjects will continue in the extension study until the subject meets 1 of the withdrawal criteria (Section 8.4), or until the subject can be transitioned to the roll-over study (if eligible, see below). At end of treatment (EOT), safety assessments, and an ECOG performance status assessment will be completed. No new capsules will be dispensed at EOT.
Roll-over Study (all eligible subjects): Subjects who have completed the main objectives of Part 1 or Part 2 may be eligible to enroll in a roll-over study when the protocol becomes available.

Study burden and risks

Most common side effects experienced by patients taking niraparib:

The following side effects were experienced by 10% or more patients who took niraparib as a single drug therapy:

• Decrease in blood cells (red blood cells) that carry oxygen; this may make the subject feel tired or short of breath (*)
• Decrease in blood cells (white cells) that fight infection; this may decrease the subject*s ability to fight infections (*)
• Decrease in blood cells (platelets) that help stop bleeding; this may increase the subject*s risk of bleeding (*)
• Loose/liquid stools (diarrhea)
• Infrequent hard stools (constipation)
• Feeling sick to the stomach (nausea)
• Vomiting

• Feeling tired, lack of energy (fatigue)
• Feeling not hungry; decreased appetite (anorexia)
• Decreased kidney function as measure by increase in creatinine levels (blood markers of kidney function) in the blood

The following side effects were experienced by 5% < 10% of patients who took niraparib as a single drug therapy:

• Shortness of breath
• Low level of salt in the blood that may cause the subject to feel tired, confused, or experience headache or muscle cramps
• Disturbances in the electrical activity of the heart; this may be a lengthening of time between heart beats and/or an abnormal heart beat that is either faster or slower than normal
• Sleeplessness, trouble sleeping (insomnia)
• Headache
• Hair loss
• Irritation and redness of the lining of the mouth (stomatitis)
(*) The levels of each type of blood cell (red and white) and the cells responsible to help stop bleeding in the subject*s body will be closely monitored during the study. Patients must tell the doctor if they take any medicine to prevent blood clotting. If the subject experiences unusual bruising of the skin, bleeding of the gums or nose, the subject should tell his/her doctor.

Most Common Serious side effects experienced by patients taking niraparib that have required immediate medical intervention

The following side effects most commonly resulted in the need for immediate medical intervention:

• Decrease in blood cells (platelets) that help stop bleeding and may increase the risk of bleeding
• Decrease in blood cells (red blood cells) that carry oxygen which may the subject feel tired or short of breath
• Decrease in blood cells (white cells) that fight infection; this may decrease the subject*s ability to fight infections

Potential for new blood cancer (pre-leukemia, leukemia):
Leukemia can be caused by repeated chemotherapies the subject may have already taken for the subject*s cancer. If the subject has experienced pre-leukemia or leukemia before entering this study, the subject is at increased risk for developing leukemia again.

Risk to fetus/newborn:
Niraparib may have adverse effects on a fetus in utero. Furthermore, it is not

known if niraparib has transient adverse effects on the composition of sperm. Patients may not receive niraparib in the study if they are pregnant, planning to become pregnant, or nursing a child. Patients must agree to use contraception for 90 days after the last dose of niraparib and must inform the investigator immediately if they or their partner become pregnant.

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

To be considered eligible to participate in this study, all of the following requirements must be
met:
1. Subject is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.

2. Subject, male or female, is at least 18 years of age.
3. Subject has histologically or cytologically confirmed diagnosis of metastatic or locally advanced solid tumors that have failed to respond to standard therapy, have progressed despite standard therapy, refuse standard therapy, or for which no standard therapy exists, and that may benefit from treatment with a poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor. The diagnosis must be
confirmed with a previous computed tomography (CT) scan.
4. The subject has adequate organ function:
a. Absolute neutrophil count >=1500/µL
b. Platelets >=150,000/µL
c. Hemoglobin >=9 g/dL (5.6 mM)
d. Serum creatinine <=1.5 × the upper limit of normal (ULN) or a calculated creatinine clearance >=60 mL/min using the Cockcroft-Gault equation
e. Total bilirubin <=1.5 × ULN or direct bilirubin <=1 × ULN
f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <=2.5 × ULN unless liver metastases are present, in which case AST
and ALT must be <=5 × ULN
5. Subject must have an ECOG performance status of 0 to 2.
6. Female subjects of childbearing potential must have a negative serum pregnancy test (beta human chorionic gonadotropin [hCG]) within 72 hours prior to receiving the first dose of study drug.
7. Male and female subjects of reproductive potential must use adequate birth control for the duration of study participation (Section 8.3).
8. Subject is able to take oral medications.
9. Subject must agree to blood samples during screening and at the end of treatment for cytogenetic analysis.

Exclusion criteria

Subjects will not be eligible for study entry if any of the following criteria are met:
1. Subject has undergone palliative radiotherapy within 1 week of study drug administration, encompassing >20% of the bone marrow.
2. Subject has persistent >Grade 2 toxicity from prior cancer therapy.
3. Subject has any known, persistent (>4 weeks) >=Grade 3 hematological toxicity or fatigue from prior cancer therapy.
4. Subject has symptomatic uncontrolled brain or leptomeningeal metastases. To be considered *controlled,* the subject must have undergone treatment (eg, radiation or chemotherapy at least 1 month prior to study entry) for the central nervous system (CNS) disease. The subject must have no new or progressive signs or symptoms related to the CNS disease and must be taking a stable dose of steroids or no steroids. A scan to confirm the absence of brain metastases is not required. Subjects with spinal cord compression may be considered if they have received definitive treatment and there is evidence of the disease being clinically stable for 28 days.
5. Subject has known hypersensitivity to the components of niraparib.
6. Subject has had major surgery within 3 weeks of study drug administration or has not

recovered from all effects of any major surgery.
7. Subject is considered a medical risk due to a serious, uncontrolled medical disorder; nonmalignant systemic disease; or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days of the Screening Visit) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.
8. Subject received (or is anticipated to receive) a platelet transfusion within 4 weeks of study drug administration.
9. Subject has a history or current evidence of any condition, therapy, or laboratory abnormality (including active or uncontrolled myelosuppresion [ie, anemia, leukopenia, neutropenia,
thrombocytopenia]) that might confound the results of the study, interfere with the subject*s participation for the full duration of the study treatment, or suggests it is not in the best interest of the subject to participate.
10. Subject has any known history of myelodysplastic syndrome (MDS)
or a pre-treatment cytogenetic testing result at risk for a diagnosis of
MDS/acute myeloid leukemia (AML).
11. Subject is pregnant, breastfeeding, or expecting to conceive children within the projected duration of the study treatment.
12. Subject is immunocompromised with an active event and is being treated with medications.
13. Subject has confirmed or suspected hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).
14. Subject has a corrected QT interval (QTc) prolongation of >470 msec at the Screening Visit.
15. Subject is receiving concomitant medication(s) that prolong QTc and is unable to discontinue use for the duration of the study.
16. Subject is starting chemotherapy within 3 weeks of study drug administration.
17. Subject is taking proton pump inhibitors, antacids, or H2 blockers within 48 hours prior to study drug administration, and/or within 6 hours after study drug administration.
18. Subject has a history of illicit drug use.
19. Subject has a past or current history of chronic alcohol use (3 or more drinks per day for the 30 days prior to study drug administration) or dependence or is unable to abstain from alcohol for the duration of the study.
20. Subject is currently participating in another clinical study and has received an investigational drug, or has participated in a clinical study and has received an investigational drug within 21 days of study drug administration.
21. Subject has participated in a radioactive clinical study and has received an investigational radiolabeled drug within 6 months prior to study drug administration (for subjects participating in Part 1) or within 30 days prior to study drug administration (for subjects participating in Part 2).

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):	24-02-2015
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	[14C]-niraparib (IV formulation, radiolabeled)
Generic name:	-
Product type:	Medicine
Brand name:	[14C]-niraparib oral
Generic name:	-

Ethics review

Approved WMO Date:	22-10-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-12-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	08-04-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-04-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-11-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-01-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-02-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-06-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2014□002011□41-NL
CCMO	NL49915.031.14