An open-label randomized two-arm Phase I dose-escalation study to characterize the safety, tolerability, pharmacokinetics, and maximum tolerated dose of oral BAY 1217389 in combination with weekly intravenous paclitaxel given in an intermittent dosing schedule in subjects with advanced malignancies

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Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON45121

Source
ToetsingOnline

Brief title
Phase I study of oral BAY 1217389 in combination with IV paclitaxel

Condition

- Other condition

Synonym
advances cancer (solid tumors)

Health condition

advanced malignancies

Research involving
Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: Bayer HealthCare AG

Intervention

Keyword: advanced malignancies, BAY1217389, MPS1 inhibitor, paclitaxel

Outcome measures

Primary outcome

The primary study outcome is the MTD. The MTD is defined as the highest dose

that can be given such that the DLT rate of the combination treatment is not

more than 10% higher than the cumulative DLT rate of the standard single-agent

treatment across all previous and the current cohort.

Secondary outcome

NA

Study description

Background summary

BAY 1217389 is a potent and highly selective inhibitor of monopolar spindle 1

(MPS1) kinase activity. Human MPS1 is a serine threonine kinase, which functions as a core component of the spindle-assembly checkpoint (SAC), a key surveillance mechanism that monitors the attachment of spindle microtubules to the kinetochores of the chromosomes during pro-metaphase and halts the transitions to anaphase until all chromosomes are bioriented, fully attached, and correctly tensed at the metaphase plate. MPS1 is expressed in the mitosis phase of the cell cycle in proliferating cells. Overexpression of MPS1 has been observed in several cancer cell lines and tumor types, including lung and breast cancers.

Established anti-mitotic drugs such as vinca alkaloids, taxanes, or epothilones activate the SAC either by destabilizing or stabilizing spindle microtubules resulting in mitotic arrest. Prolonged arrest in mitosis forces a cell either into a mitotic exit without cytokinesis or into a mitotic catastrophe leading to cell death. In contrast, MPS1 inhibitors inactivate the SAC and accelerate progression of cells through mitosis eventually resulting in severe chromosomal missegregation, mitotic catastrophe, and cell death. Consequently, MPS1 inhibition leads to failure of cells to arrest in mitosis in response to anti-mitotic drugs. Thus, the combination of microtubule-interfering agents and MPS1 inhibition strongly increases chromosomal segregation errors and cell death and therefore, constitutes an efficient strategy for selectively eliminating tumor cells.

MPS1 inhibition in combination with microtubule-interfering agents is expected to improve therapeutic efficacy of anti-mitotic drugs and to overcome paclitaxel resistance.

Further details of BAY 1217389 can be found in the investigator*s brochure (IB), which contains comprehensive information about BAY 1217389. The IB in its most current version is available in the study file.

Study objective

The primary objectives of this study are to:
* Determine the safety, tolerability, maximum tolerated dose (MTD), and recommended Phase 2 dose (RP2D) of oral BAY 1217389 given in combination with intravenous (IV) paclitaxel using an intermittent dosing schedule (2 days on / 5 days off) in subjects with advanced malignancies.
* Characterize the pharmacokinetics (PK) of oral BAY 1217389 and IV paclitaxel.

The exploratory objective of this study is to:
* Determine any preliminary clinical efficacy of oral BAY 1217389 given in combination with IV paclitaxel compared to paclitaxel given alone.
* Determine pharmacodynamic (PD) target modulation effects (decrease in phosphorylated kinetochoreassociated protein pKNL1 and potentially other biomarkers like activation of the p53 system) of oral BAY 1217389 in mandatory paired fresh tumor biopsies (or in mandatory paired fresh skin punch biopsies

depending on the status of the subject and the accessibility of the tumor) taken on Day 2 of Cycle 1 (C1D2) and on C1D3.
* Evaluate the effect of oral BAY 1217389 on the activation of p53 in blood samples as PD biomarker (blood samples will be taken as a mandatory procedure to monitor PD effects on C1D-4, C1D-3, and C1D-2).
* Evaluate the effect of BAY 1217389 on levels of tumor-derived free circulating deoxyribonucleic acid (DNA) in blood samples taken before the first dose of study treatment and on C1D3, C1D8, and C1D15.

Study design

The expected mean sample size is up to 48 subjects with solid tumors. This study will have 2 treatment arms, investigating the combination of oral BAY 1217389 given in combination with IV paclitaxel in an intermittent dosing schedule compared to IV paclitaxel given alone. In the standard treatment arm, weekly IV paclitaxel will be given as single-agent treatment in Cycle 1. From Cycle 2 onwards, they will receive the
combination treatment at the oral BAY 1217389 dose of their cohort. In Cohort 1, subjects will be randomized to combination and single-agent treatments in Cycle 1 in a 1:1 allocation ratio. From Cohort 2 onwards, subjects will be randomized to combination and single-agent treatment in
Cycle 1 in a 3:1 allocation ratio.

A treatment cycle in this study is defined as a period of 28 days. Based on nonclinical pharmacology results, a 2 days on / 5 days off dosing schedule for oral BAY 1217389 administered every 12+/-1 hours is most promising and will initially be used for this study. However, if based on e.g. initial human safety and tolerability, PK, or PD results, a 2 days on / 5 days off dosing schedule for oral BAY 1217389 is not feasible, an alternative intermittent dosing schedule may be used. The alternative intermittent dosing schedule will stay within a 7-day dosing schedule, i.e. treatment will be administered at least on 1 day per week. Paclitaxel will be given IV once per week on D1, D8, and D15 of the 28-day cycles. During the fourth week of each cycle, no study drug will be administered.

Pharmacokinetics
In the experimental treatment arm, serial blood sampling for the assessment of single- and multiple-dose PK of BAY 1217389 will be collected on C1D-4 and C1D9 respectively. Serial blood sampling for the assessment of single-dose PK of BAY 1217389, paclitaxel, and 6-alpha-hydroxy-paclitaxel in the experimental treatment arm will be collected on C1D8. In both treatment arms, serial blood sampling for the assessment of paclitaxel and 6-alpha-hydroxy-paclitaxel PK will be collected on C1D1. In addition, blood samples will be collected on D1, pre-dose and 2 hours post-BAY 1217389 dose, in even number cycles (i.e. Cycles 2, 4, and 6) for monitoring the PK of BAY 1217389.

Determination of the MTD

Cohorts of subjects will be enrolled in an adaptive doseescalation manner. Each cohort will include 3 subjects in the experimental treatment arm receiving oral BAY 1217389 in combination with IV paclitaxel. In the first cohort, 3 additional subjects will be enrolled in the standard treatment arm receiving IV paclitaxel alone. In all subsequent cohorts, only 1 subject will be enrolled in the standard treatment arm receiving IV paclitaxel alone.
From Cohort 2 onwards, all subjects will be randomized to combination treatment or single-agent treatment in Cycle 1. The purpose of the dose escalation will be to determine the MTD of the combination treatment with oral BAY 1217389 and IV paclitaxel. It will be based on the dose-limiting toxicities (DLTs) reported during Cycle 1. The MTD is defined as the highest dose that can be given such that the DLT rate of the combination treatment is not more than 10% higher than the cumulative DLT rate of the standard single-agent treatment across all previous and the current cohort.
Each cohort will be evaluated after all subjects have completed the first 28 days of treatment (which will subsequently be referred to as *Cycle 1*) or discontinued prematurely.
Safety monitoring will occur by telephone conferences with participation of the investigators and the sponsor on a regular basis.
At the time of dose escalation, the available clinical safety and PK information is discussed in a telephone conference by the involved investigators and representatives from the sponsor, including the Study Medical Expert as well as representatives of other clinical and if required further contributing functions. During this telephone conference, it will be judged if dose escalation can proceed as planned. Dose escalation for subsequent cohorts will only be considered after full evaluation of at least Cycle 1 safety data from the previous cohort.

Intervention

NA

Study burden and risks

BAY 1217389:
Based on animal studies BAY 1217389 may have an effect causing all or some of the following side effects:
• Decrease in blood cells (white blood cells, red blood cells, blood platelets) that may cause infection, bleeding, and bruising
• Nausea, vomiting, mouth sores
• Maldigestion symptoms such as abdominal (tummy) pain, gas, bloating (abdominal distention), diarrhea and foul-smelling ,greasy stools
Paclitaxel:
Common side-effects associated with paclitaxel are:
• Hair loss
• Nausea, vomiting and diarrhea

• Allergic reactions such as flushing, skin rash, itching and other general infections
• Changes in heart beat rate or rhythm, high or low blood pressure
• Decrease in blood cells (white blood cells, red blood cells, blood platelets) that may cause infection, bleeding, and bruising
• Numbness and/or tingling in hands and/or feet, muscle and joint pain
• Soreness of the mouth and tongue
• Raised temperature
• Temporary changes to the nails and skin
• Pain, swelling and possibly skin peeling at the site of injection
• Inflammation of a vein (occurs less commonly)
• Chest pains and or shortness of breath may occur if you are receiving other chemotherapy agents and/or radiotherapy
• Bowel disorders, abdominal pain, increased sweating and pain in limbs
Rare side effects associated with paclitaxel may include:
• Dehydration and anaphylaxis (swelling of the face/throat, wheezing, feeling faint, and shortness of breath)
• Chills and back pain associated with allergic reaction
• Pneumonia and other lung disorders
• Swelling and/or weakness in the hands and/or feet
• Peritonitis (serious abdominal pain)
• Heart failure is rare and usually occurs in patients who have received other chemotherapy such as an anthracycline or trastuzumab
Very rare side-effects associated with paclitaxel may include:
• Severe infections
• Disturbance to sight and hearing
• Vertigo (dizziness)
• Severe allergic reactions which may be fatal
• Rash affecting limbs, hands, feet and mouth
• Confusion, fainting, seizures, lack of coordination and other effects on the brain
• Liver disorders, abnormal kidney laboratory tests
• Loss of appetite (anorexia), weight loss and constipation
• Weakness, difficulty coordinating movement
• Hearing and/or balance effects
• Fast heat beat
Most of these side effects will occur during treatment and may go away during treatment as your body adjusts to the medicine. Your study doctor may be able to tell you about ways to prevent or reduce some of these side effects. If you notice any of these, or any other side effects, between courses of treatment or after your treatment has finished tell your study doctor. If any of these side effects continues to gets serious immediately tell your study doctor.
BAY 1217389 + Paclitaxel
The combination of paclitaxel and BAY 1217389 has not been studied before in humans, and there may be side effects, including allergies and interactions, that are not yet known when these medications are given together. Combining drugs may cause unexpected side effects, may alter the likelihood, or may

worsen known side effects of paclitaxel. Initial clinical data suggests that the combination of BAY 1217389 and paclitaxel may increase the chance of neutropenia [decrease in neutrophils, a type of white blood cells] and febrile neutropenia [fever associated with low neutrophil level, usually caused by infection]. There is also a potential that the BAY 1217389 study drug could reduce the cancer-fighting capacity of paclitaxel. This is why it is important that you notify you study doctor / study staff of any new symptoms you may have even if you do not think it is related to the study medication.
We do not know yet whether the study drug might be harmful to an unborn child. If you want to participate in this study, you are not allowed to get pregnant or, if you are a man, to impregnate a woman. You must agree to the use of suitable contraception (as discussed with the study doctor) and monitoring for possible pregnancy by means of blood/urine tests.

There may be significant risks for newborns or for the unborn child of a woman who participates in this study. This is why all sexually active female patients who may become pregnant must agree to the use of a suitable form of birth control in accordance with the study doctor*s instructions. This is mandatory during participation in the study and for 30 days after the end of the treatment. Breastfeeding must be stopped during the treatment and for at least 90 days after the last dose of the study drug.

Women who may become pregnant must take a pregnancy test with blood or urine before they participate in this study. For the pregnancy test with blood, a needle is used to take a blood sample from a vein in your arm. You will be informed of the result of the pregnancy test. If the result of the pregnancy test is positive, you cannot participate in the study.

You must agree to the use of a suitable form of birth control in accordance with the study doctor*s instructions to prevent pregnancy, because we are not sure whether the drug you receive has a negative effect on sperm. This is mandatory during participation in the study and for 30 days after the end of the treatment.

If you suspect that your partner is pregnant during your participation in the study or during the 3 months afterwards, you must inform the study doctor. Contact the investigator or your doctor immediately. This study might have consequences for your unborn child. The study doctor will ask you and your female partner to fill out a consent form to give permission for the collection of coded data about the pregnancy and the birth of the child.

Contacts

Public

Bayer

Bayer Boulevard 100
Wippany NJ 07981
US
Scientific
Bayer

Bayer Boulevard 100
Wippany NJ 07981
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion criteria (selected):
(1) Male or female subjects aged > or = 18 years
(2) Study population
For the dose-escalation cohorts: Subjects with histologically or cytologically confirmed advanced malignancies (solid tumors), refractory to any standard therapy, have no standard therapy available, or subjects actively refused any standard treatment and/or if, in the judgement of the investigator, experimental treatment is clinically acceptable.
For the expansion cohort: Subjects with advanced, histologically or cytologically confirmed TNBC, relapsed on a paclitaxel-containing regimen within 12 months prior to enrollment and refractory to any standard therapy, have no standard therapy available. Other malignancies where paclitaxel is part of the standard of care may be considered upon agreement of the investigator and the sponsor.
(3) Subjects must have evaluable or measurable disease.
(4) Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
(5) Life expectancy of at least 12 weeks
(6) Adequate bone marrow, liver, and renal functions

Exclusion criteria

Exclusion criteria (selected)
(1) Known hypersensitivity to the study drugs or excipients of the preparations or any agent given in association with this study
(2) Evidence of peripheral neuropathy of Grade >2
(3) History of cardiac disease: congestive heart failure New York Heart Association (NYHA) class >II, unstable angina (anginal symptoms at rest), new-onset angina (within the past 3 months before study entry), myocardial infarction within the past 3 months before study entry, or cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers, calcium channel blockers, and digoxin are permitted)
(4) Uncontrolled hypertension defined as systolic blood pressure >150 mmHg or diastolic blood pressure >90 mmHg, despite optimal medical management
(5) Moderate or severe hepatic impairment, i.e. Child-Pugh class B or C
(6) History of human immunodeficiency virus, hepatitis B, or hepatitis C infection
(7) Active clinically serious infections of Grade >2
(8) Central nervous system metastases

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	18-04-2015
Enrollment:	15
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	MPS1 inhibitor
Product type:	Medicine
Brand name:	Pactlitaxel
Generic name:	NA
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	13-04-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-09-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-11-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-11-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-02-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	16-02-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-08-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-10-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-01-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-02-2017
Application type:	Amendment
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
EudraCT	EUCTR2014-004821-41-NL
CCMO	NL52644.078.15