An open-label, Phase I study to assess the effect of itraconazole (CYP3A4 and P-gp inhibitor) on the pharmacokinetics of anetumab ravtansine and to assess the ECG effects, safety and immunogenicity of anetumab ravtansine given as a single agent and together with itraconazole in subjects with mesothelin-expressing advanced solid cancers.

Published: 14-08-2017
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Main objective: - Evaluate the effect of itraconazole, a strong cytochrome P450 (CYP) 3A4 inhibitor and a P-glycoprotein (P-gp) inhibitor, on the safety and tolerability (including "thorough" electrocardiogram [ECG] assessment) and...

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

Summary

ID

NL-OMON46366

Source
ToetsingOnline

Brief title
Anetumab ravtansine drug interaction study

Condition

- Other condition

Synonym
Mesothelin-expressing advanced solid cancers

Health condition

Neoplasmata, maligne en niet-gespecificeerd: lokaal gevorderde of metastatische solide kankersoorten met mesotheline-expressie.

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Mesothelin, Phase I, PK DDI, Solid tumors

Outcome measures

Primary outcome

- ECG parameters (PR, QRS, QT/QTcF/QTcP interval duration, abnormal T and U

waves, heart rate)

- Cycle 1+2 AUC (area under the plasma concentration vs. time curve from zero

to infinity after single (first) dose) of BAY94-9343 analytes

- Cycle 1+2 AUC(0-tlast) (AUC from time zero to the last data point > LLOQ

[lower limit of quantification]) of BAY94-9343 analytes

- Cycle 1+2 Cmax (maximum drug concentration in plasma after the first dose

administration) of BAY94-9343 analytes

Secondary outcome

- Incidence of serious and non-serious adverse events

- Incidence of positive anti-drug antibody titer

- Cycle 3 Cmax,md (Cmax after multiple-dose administration) of BAY94-9343

analytes

- Cycle 3 AUC(0-tlast)md (AUC(0-tlast) after multiple-dose administration) of

BAY94-9343 analytes

- Incidence of neutralizing antibody titers

Study description

Background summary

DM4, the cytotoxic toxophore within anetumab ravtansine, is a substrate of CYP3A4, and clinically significant impact of strong CYP3A4 inhibitors or inducers on plasma concentrations of DM4 cannot be ruled out. DM4-Me (the metabolite of DM4) is a P-gp substrate, and an impact of strong P-gp inhibitors or inducers on plasma concentrations of DM4-Me cannot be ruled out. Therefore, one of the purposes of the current study is to evaluate the effect of itraconazole as strong CYP3A4 inhibitor on the safety and PK of anetumab ravtansine.

The other purpose of the current study is to assess the ECG effects of anetumab ravtansine given as a single agent and together with itraconazole. The co-administration of anetumab ravtansine and itraconazole as a potent CYP3A4 inhibitor and an P-gp inhibition may result in an increase in the plasma exposure of DM4 and DM4-Me; therefore, the current study would present an opportune context for the *thorough* QT/QTc assessment together with the DDI assessment.

Study objective

Main objective:
- Evaluate the effect of itraconazole, a strong cytochrome P450 (CYP) 3A4 inhibitor and a P-glycoprotein (P-gp) inhibitor, on the safety and tolerability (including "thorough" electrocardiogram [ECG] assessment) and pharmacokinetics of anetumab ravtansine in subjects with mesothelin-expressing advanced solid cancers.

Secondary objectives:
- Evaluate the general safety and tolerability of anetumab ravtansine in

subjects with mesothelin-expressing advanced solid cancers.
- Evaluate the multiple-dose PK of anetumab ravtansine in subjects with mesothelin-expressing advanced solid cancers.
- Evaluate the immunogenicity of anetumab ravtansine.

Study design

This is a Phase I, multi-center, open-label, non-randomized, uncontrolled, 2-part sequential drug-drug interaction (DDI) study to assess the effect of the CYP3A4 and P-gp inhibitor itraconazole on the PK of anetumab ravtansine and to assess the ECG effects, safety and immunogenicity of anetumab ravtansine given as a single agent and together with itraconazole in subjects with advanced solid cancers.

Intervention

Anetumab ravtansine given intravenous (IV) infusion over 1 hour:

On Day 1 of each 21-day treatment cycle
Part 1:
Cycle 1 Day 1: 6.5 mg/kg of body weight (BW)
Cycle 2 Day 1: 0.6 mg/kg BW

Part 2:
Cycle 1 Day 1: 6.5 mg/kg BW
Cycle 2 Day 1: 6.5 mg/kg BW (planned dose)

Continuous treatment: Cycles >=3 Day 1: 6.5 mg/kg BW once every 3 weeks (Q3W)

Itraconazole/Sporanox, 100 mg oral capsules given by mouth:

Part 1 + 2:
Cycle 1
(Day 18): 200 mg twice daily (BID)
(Days 19 - 21): 200 mg once daily (QD)

Cycle 2 (Days 1-8) 200 mg QD
12 days in total (part 1 and 2)

Study burden and risks

Treatment with anetumab ravtansine may have some therapeutic benefit but this cannot be guaranteed.

Most common risks of anetumab ravtansine are nausea, fatigue, vomiting, anorexia, diarrhea, peripheral neuropathy, increased ALT and AST and eye

toxicity.

Participation in the study involves daily/ weekly / three weekly visits with blood tests and physical exams. Blood samples for PK analysis will be taken 14 times during first 3 cycles (9 of them - at Day 1 of each cycle). Continuous (Holter) ECG monitoring lasting 11 hours will be done 5 times during the first 3 treatment cycles. Visits will continue until the disease progression or intolerable toxicity, further follow up will be done for one more until 1 month.

Examinations including eye examination, ECG and tumor assessments will be performed at specific visits.

Contacts

Public
Bayer

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NL
Scientific
Bayer

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Subjects must have histologically confirmed, locally advanced or metastatic solid cancers of the following histological types:
a.) predominantly epithelial (>=50% tumor component) pleural or peritoneal mesothelioma
b.) epithelial ovarian cancer (fallopian tube and primary peritoneal cancers are eligible)
c.) adenocarcinoma of the pancreas,
d.) triple-negative adenocarcinoma of the breast
e.) non-small-cell adenocarcinoma of the lung
f.) gastric cancer (including gastro-esophageal junction)
g.) colon cancer
h.) cholangiocarcinoma
i.) Thymic carcinoma;- Subjects must have no standard therapy available, or have actively refused standard therapy or, in the investigator*s opinion, treatment in this study is clinically and ethically acceptable for the subject.;- Subjects must provide samples of archival tumor tissue collected and submitted anytime during the study.

- Subjects must have positive mesothelin expression in the archival tumor tissue, defined as the membrane intensity score of 1+, 2+ or 3+ (on the 0-3 scale) expressed on the membrane of >=5% of tumor cells combined.;- Life expectancy of at least 12 weeks.;- ECOG performance status of 0 or 1.;- Subjects must have adequate bone marrow, renal and hepatic function and coagulation;- Subjects must have normal or clinically insignificant ECG at screening.;- Negative pregnancy test if woman of reproductive potential.;- If of reproductive potential, must agree to use adequate contraception as per protocol.

Exclusion criteria

- Previous or concurrent cancer that is distinct in primary site or histology from the cancer being evaluated in this study, except cervical carcinoma in situ, treated basal cell carcinoma, superficial noninvasive bladder tumors or any previous cancer curatively treated greater than or equal to 3 years before the start of anetumab ravtansine.;- New or progressive brain or meningeal or spinal metastases.;- Poor CYP2D6 metabolizers based on the screening test for CYP2D6 genetic polymorphisms.;- Corneal epitheliopathy or any eye disorder that may predispose the subjects to drug-induced corneal epitheliopathy, or may interfere with diagnosis of treatment-emergent corneal epitheliopathy at the ophthalmologist*s or the investigator*s discretion. ;- History or current evidence of:
-- biliary cirrhosis
-- malignant biliary obstruction unless the bile flow to the gastrointestinal tract is maintained by a fully operational biliary stent
-- CTCAE (Common Terminology Criteria for Adverse Events) Grade >=2 bleeding disorder within 4 weeks before the start of anetumab ravtansine
-- uncontrolled cardiovascular disease or uncontrolled hypertension
-- Long QT Syndrome
-- HIV infection

-- Hepatitis B or C infection;- Left ventricular ejection fraction (LVEF) <50% at screening.;- Have QTc >450 ms or heart rate >=100 bpm or <=45 bpm at screening.;- Solid organ or bone marrow transplantation.;- Major surgery or significant trauma within 4 weeks before the start of anetumab ravtansine.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	11-12-2017
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	nvt
Generic name:	Anetumab Ravtansine
Product type:	Medicine
Brand name:	SPORANOX
Generic name:	Itraconazole
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	14-08-2017
Application type:	First submission

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-09-2017
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-11-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-01-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-02-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-02-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	01-05-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	28-05-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Not approved

Date:	14-06-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	02-08-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	21-08-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	18-09-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	27-09-2018
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	EUCTR2017-001978-42-NL
CCMO	NL62577.031.17

Study results

Date completed: 01-01-2022

Results posted: 31-07-2020

First publication
16-07-2020