An open-label, first-in-human, multi-center study to evaluate the safety, tolerability, pharmacokinetics and anti-tumor activity of a thorium-227 labeled antibody-chelator conjugate, BAY 2287411 Injection, in patients with solid tumors known to express mesothelin

Published: 10-01-2018
Last updated: 12-04-2024

The purpose of this study is to evaluate, in patients with tumors known to express the protein mesothelin, the following properties of BAY2287411 injection: - safety (to identify, assess, minimize, and appropriately manage the risks associated to...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON50671

Source
ToetsingOnline

Brief title
MSLN-TTC

Condition

- Other condition

Synonym
mesothelin positive tumor cells in malignancies with multiple indications

Health condition

mesotheline expressie solide tumoren. (epithelioid mesothelioma, sereuze ovarium carcinoma, pancreas adenocarcinoma).

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Mesothelin expression, Solid Tumors, Thorium-227 labeled antibody chelator conjugate

Outcome measures

Primary outcome

The primary study variable is the incidence of DLTs during the first 6 weeks of

treatment (Cycle 1) following administration of BAY 2287411 Injection.

Secondary outcome

- Cmax of Thorium-227 after single dose of Cycle 1

- Cmax of Radium-223 after single dose of Cycle 1

- Cmax of Total antibody after single dose of Cycle 1

- AUC(0-42 days) of Radium-223 after single dose of Cycle 1

- AUC(0-42 days) of Total antibody after single dose of Cycle 1

- AUC(0-42 days) of Thorium-227 after single dose of Cycle 1

Study description

Background summary

BAY 2287411 Injection is a radiolabeled tumor targeting biopharmaceutical, which belongs to the Targeted Thorium Conjugates (TTC). TTCs are a novel class of compounds, which provides a unique approach to deliver directly to tumor cells a localized lethal dose of α- radiation by decay of the α particle emitter thorium 227, using targeting molecules such as monoclonal antibodies (mAb).

BAY 2287411 Injection comprises the mesothelin (MSLN) targeted, fully human mAb anetumab, which is conjugated with the octadentate 3, 2 HOPO chelator and an α particle emitting radionuclide. The antibody chelator conjugate is radiolabeled with the tetravalent ion of the α particle emitting nuclide thorium 227, resulting in the formation of a stable complex of thorium-227 with the antibody-chelator conjugate. The mode of action of BAY 2287411 consists in the specific binding of the mAb to tumor cells expressing MSLN, which enables the targeted delivery of thorium 227 to the tumor and the release of a localized lethal dose of α radiation.

MSLN is physiologically expressed on mesothelial cells lining the pleura, peritoneum and pericardium. MSLN is pathologically expressed on a number of solid tumors, including mesothelioma, ovarian and pancreatic cancers, and certain subsets of triple negative breast cancer, cholangiocarcinoma and non small cell lung cancer.

Despite an impressive increase in treatment options, clinical benefit in patients with MSLN positive tumors has remained limited and there is still a high unmet medical need for treatments that offer durable clinical benefit and further improve overall survival. BAY 2287411 Injection is being developed for patients with tumors known to express MSLN, which have exhausted available therapeutic options.

The purpose of the sub study is to learn how the Zr-89-MSLN imaging agent (BAY 2616506) administered in combination with different doses of the cold antibody (BAY 2287409) is distributed through the body and how much enters the tumor. This will help in selecting the antibody dose for the development of the thorium-227 labeled study drug.

Study objective

The purpose of this study is to evaluate, in patients with tumors known to express the protein mesothelin, the following properties of BAY2287411 injection:
- safety (to identify, assess, minimize, and appropriately manage the risks associated to the study drug)
- tolerability (the degree to which side effects can be tolerated by your body)
- maximum tolerated dose
- pharmacokinetics (the effect of your body on the study drug)
- anti-tumor activity

- recommended dose (to determine the recommended dose for further clinical development)

Study design

This is an open-label, multi-center, Phase 1 study, comprising 2 parts:
- a dose escalation part, with the objective to define the MTD of BAY 2287411 Injection
- a dose expansion part, with the objectives to investigate the PK and determine the recommended dose for further clinical development of BAY 2287411 Injection.

There is a sub study available for the 18795 participants with the purpose to learn how the Zr-89-MSLN imaging agent (BAY 2616506) administered in combination with different doses of the cold antibody (BAY 2287409) is distributed through the body and how much enters the tumor.

Intervention

BAY 2287411 Injection will be administered intravenously on Day 1 of each cycle lasting 6 weeks (42 days). Subjects will receive a starting dose of thorium-227 of 1.5 MBq with antibody doses within the range of 10 to 400 mg. The thorium-227 dose will be escalated in a stepwise fashion up to the MTD or to the maximum feasible dose

After the MTD has been determined, the dose-expansion phase starts to define the recommended dose for further clinical development.

Also in the expansion part, subjects receive an intravenous BAY2287411 Injection on day 1 of each cycle.

Once the screening period for the main study is completed the subject will receive the first dose of the Zr-89-MSLN imaging agent in addition to a dose of the cold antibody which is not labeled with thorium-227. This is administered by an intravenous injection. The second dose will be given about 6 weeks later, after completion of the first cycle of treatment with the thorium-227 labeled antibody.

Study burden and risks

This first-in-human study of BAY 2287411 Injection is to be performed in patients with advanced malignant epithelioid mesothelioma, advanced recurrent serous ovarian cancer or metastatic pancreatic adeno carcinoma, who have exhausted available therapeutic options. In the escalation part it is aimed to evaluate the safety, tolerability and MTD or maximum feasible dose of BAY 2287411 Injection. After establishment of the maximum feasible dose BAY2287411

the sponsor will define the recommended dose in conjunction with the investigator for further development in the expansion part of the study.

A therapeutic benefit in monotherapy in MSLN-expressing tumors is anticipated based on preclinical observations in vitro and in in vivo xenograft models.

All subjects enrolled in this study will be closely monitored for safety and tolerability with visits planned for 3 times during the first week after each dosing followed by weekly visits up to the end of treatment visit. Risks for the patients will be minimized by intensive safety monitoring and patients will only be enrolled in the study if they have already exhausted available therapeutic options.

Close monitoring of patients will be performed, especially for bone marrow toxicity (blood count), liver toxicity, as well as cardiac toxicity (QT prolongation and LVEF) and any ophthalmologic side effects.

Men and women of childbearing potential must use adequate barrier birth control measures, starting from before the study and continuing during the entire course of the study and for at least 6 months after the last administration of MSLN-TTC.

Safety calls and dose escalation safety calls will be performed, in which the decision to escalate the dose of thorium-227 will be based on the collective analysis of all available safety and PK data and benefit-risk assessment.

Due to the small amount of radioactivity administered with the Zr-89-MSLN imaging agent, there should be no exposure problems for others. However, as soon as the patient participates in the main study and receives the thorium 227-labeled antibody, it is important to follow the hygiene guidelines that the patient has received from the research team.

Contacts

Public
Bayer

Energieweg 1
Mijdrecht 3641 RT
NL
Scientific
Bayer

Energieweg 1

Mijdrecht 3641 RT
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion Criteria:
- Signed informed consent
- Male or female subjects >= 18 years of age
- ECOG (Eastern Cooperative Oncology Group) PS of 0 or 1
- Patients with advanced malignant epithelioid mesothelioma or advanced recurrent serous ovarian cancer, who have exhausted available therapeutic options; in addition, in the dose expansion part of the study, patients with metastatic pancreatic adenocarcinoma, who have exhausted available therapeutic options
- Availability of fresh or archival tumor samples
- Adequate bone marrow, liver, and renal function, as assessed by the following laboratory requirements (within 28 days before start of study drug treatment)
- Negative serum pregnancy test in women of childbearing potential (WOCBP) performed within 7 days before the start of study drug administration. Women and men of reproductive potential must agree to use highly effective methods of contraception, when sexually active.

Exclusion criteria

Exclusion Criteria:
- Impaired cardiac function or clinically significant cardiac disease
- Pericarditis (any CTCAE grade) or pericardial effusion (CTCAE Grade >= 2)
- Left Ventricular Ejection Fraction (LVEF) < 50% (as measured at screening by echocardiogram).

- History of anaphylactic reactions to monoclonal antibody therapy
- History of Myelodysplastic syndrome (MDS)/treatment-related acute myeloid leukemia (t-AML) or with features suggestive of MDS/AML
- Infections of CTCAE (Common Terminology Criteria for Adverse Events) version 5.0 Grade 2 not responding to therapy or active clinically serious infections of CTCAE Grade >2; known human immunodeficiency virus (HIV) infection; active hepatitis B virus (HBV) or hepatitis C virus (HCV)infection requiring treatment. Patients with chronic HBV or HCV infection are eligible at the investigator*s discretion provided that the disease is stable and sufficiently controlled under treatment
- Known brain, spinal or meningeal metastases

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):	03-01-2019
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	non radio active equivilant antibody
Product type:	Medicine
Brand name:	N/A
Generic name:	thorium-227 labeled antibody-chelator conjugate
Product type:	Medicine
Brand name:	N/A

Generic name:	Zr-89-MSLN imaging agent

Ethics review

Approved WMO Date:	10-01-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-04-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-11-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-06-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-10-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-01-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	05-03-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-04-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-04-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-06-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-06-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-10-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-01-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-02-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-02-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2017-004052-29-NL
ClinicalTrials.gov	NCT03507452
CCMO	NL64302.042.17

Study results

Results posted: 16-02-2023

First publication
01-01-1900

URL result
Type
ext
Naam
clinicaltrials.bayer.com
URL
Type
ext
Naam
clinicaltrials.gov
URL