An Open-Label, Dose Escalation, Phase 1, First-in-Human Study of TAK-164, an Antibody-Drug Conjugate, in Patients with Advanced Gastrointestinal Cancers Expressing Guanylyl Cyclase C

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Primary Objective:* To evaluate the safety of TAK-164 and to determine the MTD and/or RP2D.Part C (imaging substudy) secondary objectives are:* To determine the biodistribution of 89Zr-TAK-164 in patients with mCRC and/or metastatic gastric...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON48866

Source
ToetsingOnline

Brief title
Research of TAK-164 in patients with gastrointestinal cancers

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
gastrointestinal cancers; gastrointestinal cancers

Research involving
Human

Sponsors and support

Primary sponsor: Millenium Pharmaceuticals
Source(s) of monetary or material Support: Milennium Pharmaceuticals (the sponsor)

Intervention

Keyword: First-in-Human, Gastrointestinal cancers, Open-Label, TAK-164

Outcome measures

Primary outcome

Primary endpoints for this study are:

* Number of patients with a DLT.

* Percentage of patients with adverse events (AEs).

* Percentage of patients with Grade 3 or above AEs.

* Percentage of patients with drug-related AEs.

* Percentage of patients with drug-related Grade 3 or above AEs.

* Percentage of patients with serious adverse events.

* Percentage of patients with AEs leading to discontinuation.

* Percentage of participants who meet the markedly abnormal criteria for safety

laboratory tests at least once postdose.

* Percentage of participants who meet the markedly abnormal criteria for vital

sign measurements at least once postdose.

* MTD and/or an alternate RP2D of TAK-164.

Secondary outcome

Secondary endpoints for this study are:

* TAK-164 PK parameters: Cmax, tmax, and AUClast during Cycle 1 Day 1 and Cycle

2 Day 1. In addition, observed concentration at the end of a dosing interval

(Ctrough) may be reported for other dosing days during which a single predose

PK sample is collected.

* ORR as assessed per modified RECIST version 1.1.

* DCR.

* DOR.

* PFS.

* Antidrug antibody (ADA) in serum.

Imaging-specific secondary endpoints (Part C only):

* Qualitative and quantitative (in terms of standardized uptake value [SUV])

determination of patient-level biodistribution of 89Zr-TAK-164 at all

89Zr-TAK-164 imaging time points.

* Qualitative and quantitative (SUV) determination of 89Zr-TAK-164 uptake in

tumor lesions identified with CT/18F-FDG-PET at all 89Zr imaging time points.

Study description

Background summary

Scientific Background
Antibody-directed cancer chemotherapy in the form of antibody-drug conjugates (ADCs) can improve therapeutic indices, with the potential to enhance efficacy and decrease systemic toxicity. After the ADC is internalized by the target tumor cell and shuttled to the lysosomal compartment, enzymatic cleavage of the chemical linker releases the cytotoxic drug [4]. In an effort to further exploit ADC technology to improve treatment of gastrointestinal (GI) malignancies, Takeda Pharmaceuticals Inc (Takeda) has developed TAK-164, a new ADC which targets guanylyl cyclase C (GCC) and consists of a human monoclonal antibody (mAb) specifically targeting GCC, a potent cytotoxic agent, and a linker. Prior and ongoing clinical studies evaluating an ADC-based therapy with another cytotoxic agent, monomethylauristatin E have shown promising results

[5]. The mechanism of action of TAK-164 should result in potent target-dependent eradication of GCC-expressing tumor cells.

Disease Under Treatment

TAK-164 is being developed to be a standard of care in the metastatic and adjuvant setting for patients with GI cancers that express GCC.

The expression of GCC is maintained throughout the spectrum of adenoma and carcinoma in the colorectum [6,7]. Also, GCC expression has been observed in lymph nodes harboring metastatic cells and is being studied as a potential marker for more accurate staging of this disease [8]. In addition to colorectal carcinoma (CRC), other GI malignancies have been found expressing GCC, such as gastric, esophageal, small intestine, and pancreatic carcinomas.

Study Drug

TAK-164, a novel ADC consists of a mAb that specifically targets GCC, linked to a cytotoxic DNA-damaging agent by a peptide linker. TAK-164 is designed to internalize into tumor cells and to release the cytotoxic agent, which binds to DNA, resulting in DNA damage due to alkylation, ultimately leading to apoptosis-driven cell death.

GCC is expressed throughout the GI tract and plays an important role in maintaining fluid ion homeostasis and genomic integrity in intestinal cells. GCC binds to the endogenous ligands, guanylin and uroguanylin, as well as to the heat-stable enterotoxin [45,46]. In normal epithelial cells, GCC is localized on the apical side of intestinal epithelium. This anatomically distinct location is accessible from the luminal side, but not from the vascular compartment due to the presence of the epithelial tight junctions [47]. The anatomically distinct apical localization is altered in malignant intestinal cells in which normal tissue architecture and tight junctions are disrupted. Therefore, a systemic intravenous (IV) administration of TAK-164 targeting GCC should affect both primary and metastatic GI carcinoma without affecting normal epithelia (where GCC would not be accessible to the drug). By accessing malignant cells but not normal GI cells due to GCC localization and tight junctions, TAK-164 is expected to have improved treatment efficacy while minimizing toxicity of the treatment.

In a broad range of GI cancer cells expressing GCC, TAK-164 has demonstrated antitumor activity at picomolar range. Based on preclinical studies, TAK-164 is expected to have a manageable safety profile (as described in Section 4.6) when administered IV to patients.

Preclinical studies have been completed to refine the flexibility of the dose and schedule of TAK-164 that could be adopted in the clinical setting to support administration of single-agent TAK-164 as part of this study, as well as a subsequent combination study. Several pharmacodynamic biomarkers have been found to be modulated in response to single-agent TAK-164, as shown by nonclinical studies. These include gamma-H2AX and Chk1. Robust and long-lasting increases in both of these markers are observed in human tumor xenografts. The

increases are sustained for longer than 24 hours in response to various doses of TAK-164.
Studies which evaluated a range of response across a spectrum of tumor xenografts as well as baseline variability of GCC expression in human tumors have suggested that a majority of tumor models that responded to TAK-164 treatment generally had a GCC H-score of higher or equal to 100.

Study objective

Primary Objective:
* To evaluate the safety of TAK-164 and to determine the MTD and/or RP2D.

Part C (imaging substudy) secondary objectives are:
* To determine the biodistribution of 89Zr-TAK-164 in patients with mCRC and/or metastatic gastric carcinomas.
* To determine the tumor targeting of 89Zr-TAK-164.
* To determine dosimetry of 89Zr-TAK-164.

Study design

This is a multicenter, nonrandomized, open-label, phase 1 study of TAK-164 in patients with advanced guanylyl cyclase C (GCC)-positive gastrointestinal (GI) cancer for whom standard treatment is no longer effective or for whom there is no available standard therapy. This study will be the first to administer TAK-164 to humans. For the dose escalation portion of the study (Part A), the patient population will consist of adults, aged 18 years or older, with any various GI malignancies expressing GCC for whom standard treatment is no longer effective or for whom there
is no available standard therapy. Maximum tolerated dose (MTD) and/ or recommended phase 2 dose (RP2D) will be estimated in Part A. In the expanded cohort (Part B), patients with colorectal carcinoma (CRC) and gastric carcinoma will be enrolled at RP2D. In the expanded cohort (part
C-imaging substudy), patients with CRC and gastric carcinoma will be enrolled at the recommended imaging dose (RID).

This study is designed to determine safety, tolerability, and pharmacokinetics (PK) and to determine an MTD and/or RP2D of TAK-164 that may be safely administered to patients with advanced GCC-positive GI cancer. The study may also help define a therapeutic window of TAK-164 based on pharmacodynamics and systemic exposures achieved over the evaluated dose range. It is anticipated that approximately 100 patients could be enrolled, including the escalation phase (Part A), the expansion phase (Part B), and the imaging substudy (Part C).

Once enrolled in the study, patients will receive TAK-164 treatment intravenously (IV) on Day 1 of each 21-day treatment cycle or every 3 weeks (Q3W).

Imaging Substudy (Part C, To Be Conducted in The Netherlands Only)
Up to 25 patients with GCC-expressing metastatic colorectal carcinoma (mCRC) and/or gastric carcinoma at up to 2 investigational sites in the Netherlands will be enrolled to determine the in vivo biodistribution and tumor targeting of zirconium 89 (89Zr)-TAK-164 by positron emission tomography (PET) imaging. In addition, the relationship of 89Zr-TAK-164 tumor targeting with 18-fluorodeoxyglucose (18F-FDG)-PET*determined response and RECIST version 1.1 response, and the relationship of 89Zr uptake with GCC expression, in tumor tissues and other biomarkers will be investigated. Based on emerging data from the dose escalation phase (part A) and in agreement between the site investigator and sponsor, part C will be triggered at a dose that is considered safe and having treatment potential (RID).

Initially, approximately 6 patients (including 3 dosimetry patients) will be enrolled for dosimetry and imaging optimization (DIO). This DIO subgroup will receive only 89Zr-TAK-164 (mass dose <50% of the RID) 14 days before to the first regularly scheduled study dose at Cycle 1 Day 1 and a second 89Zr-TAK-164 administration on Cycle 1 Day 1 in combination with unlabeled TAK-164 at a maximum mass dose of 100% of the
RID. Imaging will be performed 1 hour after end of infusion (EOI) of the first 89Zr-TAK-164 administration for dosimetry in the first 3 patients and for all patients at 2 time points between Day 2 and Day 7 after EOI. Imaging time points and mass dose of TAK-164 can be adjusted to optimize imaging conditions. Up to 19 additional patients will be enrolled into Part C to receive a single dose of 89Zr-TAK-164 at Cycle 1 Day 1 in addition to unlabeled TAK-164 as determined for optimal imaging. Once the RP2D of TAK-164 is determined, part C patients who have received TAK-164 at an RID lower than the RP2D of TAK-164 may dose-escalate to the RP2D in the absence of PD or unacceptable treatment-related toxicity at the investigator*s discretion and with the sponsor*s approval. If the full RID/RP2D is not administered at Cycle 1 Day 1, the differential will be provided after the second image acquisition. Part C patients will continue treatment with the RID/RP2D of TAK-164 at Cycle 2 Day 1 and beyond.

Intervention

TAK-164 will be given as an infusion in the vein; the administration could last up to 90 minutes.
The patient will receive the study drug on day 1 of each treatment cycle. Each treatment cycle is 21 days. For the first treatment cycle the dose may be split into multiple infusions over the first week. This is to optimize the scanning procedure to detect the study drug in the body. If the dose the patient received is lower than what is later considered the recommended dose, the dose may be increased on recommendation of the treating physician and with approval of Takeda. The patient can have up to 12 treatment cycles or more if the doctor thinks it is beneficial. The patient will be asked to stay at the hospital for around 8 hours after the first administration and for 2 hours during the

subsequent cycles, as a consequence, per site standard of care and depending on assessment timing, 1 to 2 overnight stays might be required.

The first group participating in this study will receive a low dose of study drug 14 days prior to the first treatment cycle.

The following group (up to 19 additional patients) will start with the first treatment cycle and a dose that may be split into multiple infusions over the first week. For every subsequent treatment cycle, everyone will receive a single dose of study medication on day 1.

Study burden and risks

There is limited experience with TAK-164 in humans and therefore the benefits and risks are not yet known. During the study there is a risk that the patient may have discomfort and side effects from the study drug and from the study procedures. Discomfort and side effects may vary from person to person. Everyone taking part in the study will be watched carefully for side effects, however, doctors do not know all the side effects that may happen. There is always the possibility that an unknown risk or side effect may occur. These may be mild or very severe, and in some cases may be very serious, long-lasting, delayed, or may never go away. There is also a risk of death.

The study doctor may give the patient medications to help lessen some of the possible discomfort and side effects. If a severe reaction to TAK-164 occurs, the study doctor may stop the study drug.

The study doctor or health care provider will inform the patient of some foods and other drugs that the patient may not consume during the trial as they may interfere with TAK-164.
TAK-164 has been administered to a limited number of humans in the current clinical trial. Not all of the clinical benefits and risks have been determined

Potential side effects based on the clinical study
Liver Injury, including liver failure:
* Treatment with TAK-164 has resulted in liver injury in some patients, sometimes requiring hospitalization and resulting in liver failure. Liver injury is identified by elevations in liver blood test results. Abnormally high levels of liver blood test results can mean that your liver is not functioning properly. Symptoms associated with poor liver function can include fatigue and jaundice (yellowing of the skin and eyes). Although liver injury can be mild and reversible, it can also be serious or life threatening and lead to liver failure and death.
* In the current clinical trial, one patient treated with TAK-164 developed severe liver failure requiring hospitalization. Another patient whose cancer had spread to the liver also developed liver failure and passed away due to progression of their cancer.

* Liver blood tests are done to monitor the health of the liver and this monitoring will be done at various time points throughout the entire duration of your participation in the study. Some abnormal liver tests indicate possible liver damage. If you have abnormal liver tests, your study doctor may request you to have additional follow up and testing.
* Patients with abnormal liver blood tests may or may not have clinical symptoms. It is very important that you contact your study doctor immediately if you do experience symptoms such as nausea (a strong urge to vomit), vomiting, pain in the upper part of your stomach, loss of appetite, fatigue (feeling tired), fever, rash, dark coloration of your urine, or yellowing of the skin or eyes. Depending on your liver test results and symptoms, if any, your study doctor may ask you to stop taking the study drug.
* It is always important that any time you start taking any new medication, including all over-the-counter medicines such as vitamins, herbal preparations or natural remedies, you bring this to the attention of your study doctor. This will help your study doctor have the most complete information while evaluating abnormal liver blood test results.

Potential side effects based on animal studies:
Based on animal studies with TAK-164, it may be possible to predict some of the discomforts and side effects. Animal studies do not always predict what happens in humans. We do not know if these side effects will occur in patients taking TAK-164.
* Decrease in the number of white blood cell count which may increase the risk of infection and may be associated with fever
* Decrease in the number of red blood cells, which may make the patient feel tired or lose energy; have pale skin; or experience shortness of breath and/or a faster heart rate.
* Decrease in the number of platelets (a type of blood cell), which could increase the chance of bruising and bleeding (eg. nosebleeds, bleeding from gums).
* Skin sores and scabbing at injection sites which may persist even after stopping TAK-164.
* Bleeding at blood collection sites which may persist even after stopping TAK-164.
* Generalized bruising which may persist even after stopping TAK-164.
* Darkening of the skin sometimes with sores and scabbing, present on the face, arms legs or all over the body, which may persist even after stopping TAK-164.
* Diarrhea.
* Inability to become pregnant, or to impregnate a female partner.
* Changes in salivary and tear glands, leading to painful red eyes.

Potential side effects based on other drugs in the same class
* Any drug can cause an allergic reaction. Symptoms of an allergic reaction may include shortness of breath, wheezing, dizziness, fainting, skin rash, hives, itching lip or face swelling, throat tightness and swallowing difficulties. Allergic reactions may require treatment with medications. If a severe allergic

reaction does not respond to treatment, it may result in death. It may happen in the course of the first infusion or later on after repeated doses.
* Your body may make a protein against TAK-164 that can reduce the activity of the drug.
* TAK-164 may be a risk to an unborn child or breast-feeding baby.

Risks or inconveniences from study procedures
Blood Samples:
Drawing blood may cause pain, bruising or infection at the site where the needle enters the body. It is also possible that the patient may feel lightheaded or faint.

MRI or CT scans:
During the study, the patient will have MRI or CT scans more frequent as he/she would have them if he/she were not in a clinical trial. There are some side effects or risks associated with these scans. Some people cannot have an MRI because they have some type of metal in their body. Often people who have an MRI scan experience feelings of claustrophobia (fear of being confined in any space). The scan may be uncomfortable because the patient has to stay still. Most people experience no unusual side effects or complications from the contrast dye used in these procedures. However, as with any medical procedure, some risk is involved such as allergic type reaction with itching and/or hives, swelling of eyes and lips, sneezing, or difficulty breathing. Some patients may feel uncomfortable during the CT scan because they are surrounded by moving technical equipment. The patient will be exposed to a small amount of radiation from CT scans. The number of tests required as part of the study is representative of standard of care for this disease. Fatal complications are rare with this procedure.

PET-scan:
The scan is painless but can be uncomfortable because the patient has to stay still for around 30 minutes. Some patients may also feel uncomfortable during the PET scan because they are surrounded by moving technical equipment. The PET scan involves radioactive tracers. Most people experience no unusual side effects or complications from the tracer used in these procedures. However, as with any medical procedure, some risk is involved such as allergic type reaction with itching and/or hives, swelling of eyes and lips, sneezing, or difficulty breathing.

Radiation Risks:
CT scan/MRI scan and PET involves using X-rays and radioactive markers. The radiation used during the study may lead to damage to the patient's health. However, this risk is small. We nevertheless advise the patients not to participate in another scientific study involving exposure to radiation in the near future. Examinations or procedures involving radiation for medical reasons are not a problem.

Tumor Biopsy Risks:
There are several procedures the study doctor may use to get the tumor biopsy. The study doctor will discuss the risks of anesthesia and the procedure involved with getting a biopsy of the patient's specific type of cancer. Tissue biopsies have the potential to lead to local discomfort, pain, bleeding and infection. In some cases, complications from a biopsy could be severe.

Study drug administration risk:
Skin lesions with ulceration (sores) or necrosis (tissue death) are a potential risk and are presumed associated with accidental or inadvertent leakage of injection fluid.

ECG Risks:
There is a small risk that redness or swelling could develop from the ECG electrodes (pads) that will be placed on the skin.

Contacts

Public
Millenium Pharmaceuticals

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US
Scientific
Millenium Pharmaceuticals

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MA 02139 Cambridge
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

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

Inclusion criteria

* Histologically or cytologically confirmed measurable advanced and/or metastatic solid GI tumor that expresses GCC protein (H-score *10), for which standard treatment is no longer effective or for whom there is no available standard therapy. For the escalation part of the study (part A), GI malignancies include, but are not limited to, mCRC, gastric carcinoma, esophageal carcinoma, small intestine cancer, and pancreatic cancer. The expansion part of the study (part B) is limited to patients with CRC expressing a high-level GCC (H-score *150) and gastric carcinoma expressing GCC (H-score *10). Part C includes patients with CRC and gastric carcinoma expressing GCC (H-score *10).
* The expansion part of the study (part B) will be limited to patients with 2 or 3 prior lines of systemic
standard of care therapy.
* Voluntary written consent must be obtained from the patient prior to enrollment in the study with the understanding that consent may be withdrawn by the patient at any time without consequences on receiving future medical care.
* Male or female patients 18 years or older.
* Adequate bone marrow function, defined as an absolute neutrophil count of *1.5 × 109/L, platelet count *100 × 109/L, and hemoglobin *9 g/dL. Receiving transfusions or hematopoietic growth factors to meet enrollment criteria are not allowed within 14 days preceding the first dose of study drug.
* Adequate hepatic function with:
* Total bilirubin *1.5 * upper limit of normal (ULN).
* Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) must be *2.5 * ULN (AST and ALT may be elevated up to 3 * ULN if the elevation can be reasonably ascribed to the presence of metastatic disease in liver).
* Serum albumin *3.0 g/dL.
* Adequate renal function as defined by creatinine clearance *60 mL/min.
* Eastern Cooperative Oncology Group performance score of 0 or 1.
* Life expectancy of at least 12 weeks.
* Completion of prior chemotherapy, biologic therapy, immunotherapy, or radiation therapy at least 4 weeks prior to enrollment.
* Resolution of all toxic effects of prior treatments (except alopecia) to Grade *1 by National Cancer Institute
Common Terminology Criteria for Adverse Events, version 5.
* A portion of patients should have tumors amendable for serial biopsy and a willingness to provide consent for pharmacodynamic assessment.

Additionally, for part C (imaging substudy), patients must fulfill the following criteria:

* At least 1 extrahepatic metastatic lesion *2 cm in the longest diameter.

Exclusion criteria

* Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the screening period, or male or female patients of reproductive potential who are not employing an effective method of birth control.
* Serious preexisting medical or psychiatric conditions that, in the opinion of the investigator, would preclude participation in the study.
* Chronic or active infection requiring systemic therapy, as well as a history of symptomatic viral infection which has not been fully cured (eg, HIV or viral hepatitis B or C).
* Symptomatic central nervous system (CNS) malignancy or metastasis. Screening of asymptomatic patients without history of CNS metastases is not required.
* History of congestive heart failure with New York Heart Association class greater than 2 (Class 1 and 2 are eligible), unstable angina (within 3 months prior to study enrollment), recent myocardial infarction (within 6 months of study enrollment), transient ischemic attacks, stroke, arterial or venous vascular disease, or clinically significant symptomatic arrhythmia despite anti-arrhythmic therapy.
* Corrected QT by Fridericia method interval >470 msec.
* Treatment with anticancer chemotherapy or biologic therapy or with an experimental anticancer agent within 28 days of the initial dose of study drug.
* Patient has a history of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in TAK-164 or 89Zr-TAK-164 formulation.
* Patient has concurrent alcohol abuse or a history of drug-induced liver injury (DILI).

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):	03-12-2019
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	89Zr-TAK-164
Generic name:	89Zr-TAK-164
Product type:	Medicine
Brand name:	TAK-164
Generic name:	TAK-164

Ethics review

Approved WMO Date:	07-01-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-06-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	08-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2018-002214-12-NL
ClinicalTrials.gov	NCT03449030
CCMO	NL66658.029.18