PHASE II, EXPLORATORY, MULTICENTER, NON RANDOMIZED, SINGLE AGENT COHORT STUDY TO DETERMINE BEST TUMOR RESPONSE WITH TRASTUZUMAB EMTANSINE IN HER2 OVEREXPRESSING SOLID TUMORS

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

Summary

ID

NL-OMON46221

Source
ToetsingOnline

Brief title
KAMELEON

Condition

- Other condition

Synonym
bladder cancer, cholangiocarcinoma, pancreascancer

Health condition

lokaal gevorderde , gemetastaseerde of niet-curatief te behandelen urotheel blaaskanker of alvleesklier/galwegkanker (en mogelijk andere typen tumoren in een later stadium)

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: F. Hoffman- La Roche

Intervention

Keyword: HER2 positive, solid tumor, trastuzumab emtansine

Outcome measures

Primary outcome

BOR (Best overall response rate) as determined by the investigator (using

RECIST 1.1). BOR is defined as the best response recorded from

the first day of study treatment until disease progression/recurrence or death.

Secondary outcome

To evaluate the efficacy of trastuzumab emtansine by investigating Progression

Free Survival (PFS) and Overall Survival (OS).

In addition, the following will be investigated: Incidence and type all adverse

events (AEs) and serious adverse events, Changes in vital signs, Number of

deaths, Cases of drug-induced liver injury, Pneumonitis, Change in LVEF,

Incidence of CHF, concentrations of trastuzumab emtansine in plasma/serum to

determine exposure, Exploratory assessment of immune checkpoint-inhibitors and

infiltrating lymphocytes, HER2 status , and biomarkers that may be associated

with response.

Study description

Background summary

Four HER2-targeted therapies have been approved for HER2-positive breast cancer. Trastuzumab is a humanized monoclonal antibody directed against the extracellular domain of HER2. Trastuzumab is currently approved and it is part of the current standard of care (SOC) in HER2-positive BC for both the early breast cancer (EBC) and the metastatic breast cancer (MBC) setting. There is currently no clinical data on the potential therapeutic effect of trastuzumab emtansine treatment in HER2-positive tumors such as esophageal-, colorectal-, pancreas/cholangio-, prostate and bladder carcinoma.

Study objective

A number of anti-HER2 therapies have proven efficacy, are approved and part of the Standard of Care for HER2-positive BC and GC. In contrary, there is currently no clinical data on the potential therapeutic effect of trastuzumab emtansine treatment in HER2-positive tumors such as esophageal-, colorectal-, pancreas/cholangio-, prostate and bladder carcinoma. This study will investigate if trastuzumab emtanise could improve patient outcomes for patients with urothelial bladder (MUBC)-, pancreas-, and cholangiocancer where cure is no longer possible and where no other treatment options are available anymore. Besides efficacy, the safety is also investigated.

Study design

This is an exploratory, multicenter, non-randomized, Phase II, single agent study designed to evaluate the efficacy of trastuzumab emtansine in patients with MUBC or metastatic pancreas/cholangio cancer, with other tumor types being potentially explored at a later point in time.

Patients who fulfill the inclusion/exclusion criteria will be enrolled in the study. In a safety run-in, the first 6 patients of each cohort will enter Regimen A (2.4 mg/kg qw). Based on tolerability and safety aspects, such as lack of unacceptable toxicities a decision will be made by the iDMC if the cohort is to continue on Regimen A or if the dose switches to Regimen B (3.6 mg/kg q3w). In total at least 32 patients will be recruited for the Regimen that is chosen.

After 13 patients were enrolled in a Cohort, the response will be evaluated. If no partial or complete response is seen, the enrollment is discontinued.

Intervention

Trastuzumab emtansine intravenously (2.4 mg/kg, weekly or 3.6 mg/kg every 3 weeks) described in the study protocol.

Study burden and risks

RISK ASSOCIATED WITH TRASTUZUMAB EMTANSINE

Pulmonary Toxicity
Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or death, have been reported in patients receiving trastuzumab emtansine.

Hepatotoxicity
-Rare cases of severe hepatotoxicity, including death due to drug-induced liver injury and associated hepatic encephalopathy, have been observed in patients treated with trastuzumab emtansine.
-Increases in serum AST and ALT have been observed in all trastuzumab emtansine studies. Grade 1 and 2 events have been observed frequently; Grade 3 and 4 events have been observed less commonly.
-Cases of NRH have been identified from liver biopsies in patients treated with trastuzumab emtansine who presented with signs and symptoms of portal hypertension. NRH is a rare liver condition characterized by widespread benign transformation of hepatic parenchyma into small regenerative nodules.

Left Ventricular Dysfunction
Patients treated with trastuzumab emtansine are at risk of developing left ventricular dysfunction. To date, significant cardiac events, including LVEF of 40%, have been observed infrequently in clinical trials of trastuzumab emtansine.

Infusion-Related Reactions and Hypersensitivity Reactions
Infusion-related reactions (IRRs) and hypersensitivity reactions have been reported with administration of trastuzumab emtansine. IRRs, characterized by one or more of the following symptoms - flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia - have been reported in clinical trials of trastuzumab emtansine. Hypersensitivity reactions, including serious anaphylactic-like reactions, have been observed in clinical trials of trastuzumab emtansine.

Hematologic Toxicity
Thrombocytopenia has been reported in patients in clinical trials of trastuzumab emtansine. The majority of these patients had Grade 1 or 2 events. Cases of bleeding events with a fatal outcome have been observed.
Declines in other hematopoietic lineages, for example, leukopenia, neutropenia, and anemia, were less frequent than that observed for platelets.

Neurotoxicity

Peripheral neuropathy, mainly Grade 1 and predominantly sensory, has been reported in clinical trials of trastuzumab emtansine.

Extravasation
In trastuzumab emtansine clinical studies, reactions secondary to extravasation have been observed. These reactions were usually mild and consisted of erythema, tenderness, skin irritation, pain, or swelling at the infusion site.

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

* Histologically centrally confirmed HER2-positive (IHC3+ in * 30% of tumor cells): locally advanced (unresectable and not treatable with curative intent) or metastatic urothelial bladder cancer or locally advanced (unresectable and not treatable with curative intent) or

metastatic pancreas/cholangio cancer.
* There must be no standard treatment options available for patients with the above HER2 overexpressing tumors and they must have undergone at least one prior platinum-based treatment for locally advanced (unresectable and not treatable with curative intent) inoperable, locally advanced or metastatic tumor. (Note: for pancreatic cancers/cholangiocarcinoma, prior treatments are NOT required to be platinum-based.)
* The patient must have evaluable disease fulfilling all of the following imaging criteria:
o On diagnostic computed tomography scan/magnetic resonance imaging: lesion should be measurable according to RECIST 1.1.
o Target lesion(s) should not have been previously irradiated.
* At least one formalin-fixed paraffin-embedded biopsy of the primary tumor and/or from a metastatic site is required.
* Age * 18 years.
* Eastern Cooperative Oncology Group performance status of 0-2.
* No significant cardiac history and a current LVEF * 50%. LVEF should be determined within 28 days before the start of trastuzumab emtansine treatment.
* Adequate organ function
* Negative serum pregnancy test for women of childbearing potential. For women of childbearing potential and men with partners of childbearing potential, agreement by the patient and/or partner to use a highly effective non-hormonal form of contraception such as surgical sterilization or two effective forms of non-hormonal contraception until 7 months after the last dose of trastuzumab emtansine.
* Signed written informed consent approved by Ethics Committee and obtained prior to any study procedure.
* Life expectancy of at least 12 weeks.

Exclusion criteria

* Patients with previous exposure to HER2-targeted therapies in any setting.
* Patients showing histologically confirmed focal HER2-expression, i.e., <30% of positively stained tumor cells.
* Patients with brain metastasis as the sole site of metastatic disease and are symptomatic or require therapy to control symptoms. NB: Brain metastases are allowed provided they are asymptomatic and/or controlled by previous radiotherapy.
* Current uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg).
* Current unstable angina pectoris.
* History of symptomatic CHF of any New York Heart Association criteria or ventricular arrhythmia that requires treatment.
* History of myocardial infarction within the last 6 months.
* Peripheral neuropathy, Grade * 3.
* Current dyspnea at rest due to complications of advanced malignancy, or other diseases that require continuous oxygen therapy.
* Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound healing disorders; ulcers; or bone fractures).
* History of other malignancy within the last 5 years, except for appropriately treated

carcinoma in situ of the cervix, non-melanoma skin carcinoma, stage I uterine cancer, or other cancers with a similar outcome as those previously mentioned.
* For female patients, current pregnancy and lactation.
* Concurrent, serious, uncontrolled infections or current known infection with human immunodeficiency virus, active hepatitis B and/or hepatitis C.
* Known prior severe hypersensitivity to trastuzumab and trastuzumab emtansine or the excipients of the investigational medicinal product (IMP).
* Clinically significant bleeding within 30 days before enrollment
* Major surgical procedure or significant traumatic injury within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment
* Concurrent participation in any other therapeutic clinical trial.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-03-2017
Enrollment:	23
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Kadcyla
Generic name:	Trastuzumab Emtansine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	16-08-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-11-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-05-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-10-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-11-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-11-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-01-2018

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-03-2018
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	EUCTR2015-001377-40-NL
CCMO	NL58278.042.16