Dendritic Cells loaded with allogeneic tumor lysate (MesoPher) in combination with a CD40 agonist (Mitazalimab) in metastatic pancreatic disease (REACtiVe-2 Trial)

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To investigate safety and tolerability as well as the induced immune response upon MesoPher/mitazalimab combination therapy in metastasized pancreatic disease after (modified) FOLFIRINOX.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Exocrine pancreas conditions
Study type	Interventional

Summary

ID

NL-OMON52234

Source
ToetsingOnline

Brief title
REACtiVe-2

Condition

- Exocrine pancreas conditions
- Gastrointestinal neoplasms malignant and unspecified

Synonym
metastasized pancreatic cancer, metastasized pancreatic ductal adenocarcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,Alligator Bioscience AB,Amphera B.V.,TKI-PPP allowance call

Intervention

Keyword: CD40 agonist, Dendritic cell, Immunotherapy, Pancreatic cancer

Outcome measures

Primary outcome

The main study endpoint is dose-limiting toxicities of MesoPher/mitazalimab

combination therapy.

Secondary outcome

Secondary endpoints are the radiographical response rate according to

RECIST/iRECIST and systemic immune responses induced by the combination

therapy.

Study description

Background summary

Pancreatic cancer is expected to be the second leading cause of cancer-related death in 2020. Pancreatic cancer is known as an immunological cold tumor. It is thought that the characteristic desmoplastic stroma of established pancreatic adenocarcinomas acts as a physical as well as an immunosuppressive barrier leading to exclusion of T cells. The use of CD40 agonists (such as mitazalimab, also known as JNJ-64457107 and ADC-1013) may convert pancreatic adenocarcinomas into immunological hot tumors by T-cell-dependent and T-cell-independent mechanisms. Targeting the desmoplastic stroma, thereby making the tumor more permeable for T-cell infiltration, is seen as one of the assisting mechanisms. Furthermore, the immunological coldness of pancreatic cancers infers that tumor-reactive T-cell responses are absent or weak at best. Dendritic cell therapy introduces tumor-specific T cells and in combination with a CD40 agonist, may lead to synergistic anti-tumor responses which could be beneficial

for pancreatic cancer patients.

Study objective

To investigate safety and tolerability as well as the induced immune response upon MesoPher/mitazalimab combination therapy in metastasized pancreatic disease after (modified) FOLFIRINOX.

Study design

Open-label, single-center, phase I dose finding study using a mTPI dose-escalation design.

Intervention

Leukapheresis is performed after which monocytes are used for differentiation to dendritic cells. Autologous dendritic cells pulsed with an allogeneic tumor lysate (MesoPher) will be administered intra-dermally and intravenously 3 times every 2 weeks. Booster vaccinations are given after 3 and 6 months. On the same day after administration of MesoPher a CD40 agonist (mitazalimab) will be administered intravenously.

Study burden and risks

Patients have to undergo additional outpatient clinic visits for this study and additional invasive procedures specifically for this trial, e.g. intravenous catheter placement and tumor metastasis biopsies. Although these are invasive procedures, associated risks are limited. Intravenous access is necessary during every visit, i.e. for leukapheresis, for drawing blood samples and for the administration of study medication. Leukapheresis is a standard procedure and will be performed according to our institutional guidelines. Leukapheresis demonstrates a limited risk for transient thrombocytopenia and leukopenia. Previous clinical studies have shown that injection with tumor lysate-pulsed dendritic cells (MesoPher) was well tolerated without major systemic toxicity, with the exception of low-grade flu-like symptoms (REACtiVE Trial, NL67169.000.18; DENIM/MM04: NCT03610360; MM03 NL44330.000.14 / NCT02395679). Also, intravenous injection of mitazalimab up to 1200 µg/kg was well tolerated with manageable side effects. There are currently no trials investigating this combination therapy. Combining two immunomodulatory drugs increases the risk for toxicity. The objective of this phase I study is to investigate safety and tolerability of administrating MesoPher/mitazalimab combination therapy in metastatic pancreatic cancer patients. Patients may have potential beneficial anti-tumor responses following study medication.

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

• Metastatic pancreatic cancer as defined by the presence of radiologically suspect metastatic lesions.
• Inclusion <= 4 weeks after stopping FOLFIRINOX chemotherapy.
• No more than 1 line of chemotherapy for metastatic disease is allowed. Prior FOLFIRINOX for locally advanced disease if given within 1 year before screening will be counted as first-line treatment. Any FOLFIRINOX given in the curative intent setting if more than a year before screening will not be considered first line therapy.
• An accessible metastasistic lesion for histological tissue collection.

• Patients must be at least 18 years old and must be able to give written informed consent.
• WHO performance status 0-1.
• Patients must have normal organ function and adequate bone marrow reserve: absolute neutrophil count > 1.0 x 109/l, platelet count > 100 x 109/l, and Hb > 6.0 mmol/l (as determined during screening). Transfusion in the 2 weeks preceding screening is not allowed.
• Laboratory tests: ASAT/ALAT <5xULN (upper limit of normal), bilirubine <1.5xULN, Creatinine value <1.5xULN, Lactate dehydrogenase value <= ULN and albumin value >= LLN (lower limit of normal).
• Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test just prior to the first study drug administration on Day 1, and must be willing to use an effective contraceptive method (intrauterine devices, hormonal contraceptives, contraceptive pill, implants, transdermal patches, hormonal vaginal devices, infusions with prolonged release) or true abstinence (when this is in line with the preferred and usual lifestyle)* during the study and for at least 12 months after the last study drug administration.
*True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (such as calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
• Men must be willing to use an effective contraceptive method (e.g. condom, vasectomy) during the study and for at least 12 months after the last study drug administration.
• Ability to return to the hospital for adequate follow-up as required by this protocol.
• Written informed consent according to ICH-GCP.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

• Medical or psychological impediment to probable compliance with the protocol.
• Abdominal ascites.
• Current or previous use of a CD40 antibody and/or anti-tumor vaccinations.
• Current use of steroids (or other immunosuppressive agents). Patients must have had 6 weeks of discontinuation and must stop any such treatment during the time of the study. Prophylactic usage of dexamethasone during chemotherapy is excluded from this 6 weeks interval.
• Prior malignancy except adequately treated basal cell or squamous cell skin cancer, superficial or in-situ cancer of the bladder or other cancer for which the patient has undergone curative intent treatment and has been disease-free for two years.

• Serious concomitant disease, or active infections.
• History of autoimmune disease, organ allografts or active acute or chronic infection, including but not limited to HIV and viral hepatitis.
• Serious intercurrent chronic or acute illness such as pulmonary disease (asthma or COPD), cardiac disease (NYHA class III or IV), hepatic disease or other illness considered by the study coordinator to constitute an unwarranted high risk for the investigational treatment.
• Known allergy to shell fish (may contain keyhole limpet hemocyanin (KLH)).
• Pregnant or lactating women.
• Inadequate vein access to perform leukapheresis.
• Concomitant participation in another clinical intervention trial (except participation in a biobank study).
• An organic brain syndrome or other significant psychiatric abnormality which would compromise the ability to give informed consent, and preclude participation in the full protocol and follow-up.

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):	30-08-2021
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous
Product type:	Medicine
Brand name:	mitazalimab
Generic name:	agonistic, human IgG1 monoclonal antibody, targeting CD40

Ethics review

Approved WMO Date:	11-03-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-07-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-06-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-09-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	10-01-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-04-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 27591
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2021-000289-13-NL
CCMO	NL76592.000.21
OMON	NL-OMON27591