Study of pembrolizumab combined with ataluren in Patients with metastatic pMMR and dMMR colorectal cancer adenocarcinomas or metastatic dMMR endometrial carcinoma: the ATAPEMBRO study.

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This study has been transitioned to CTIS with ID 2023-509457-31-00 check the CTIS register for the current data. To determine the immune-related progression free survival (irPFS) rate at 21 weeks and objective response rate (irORR) at 30 weeks in...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON55845

Source
ToetsingOnline

Brief title
ATAPEMBRO

Condition

- Metastases

Synonym
advanced cancer of the colon, metastastic colon cancer

Research involving

Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: een grant van MSD,Merck Sharp & Dohme (MSD),PTC therapeutics

Intervention

Keyword: Immunotherapy, read-though translation

Outcome measures

Primary outcome

The endpoints are similar to the endpoints in the MK-3475-016 trial, with minor adaptations to accommodate the new Q3W treatment regimen. Also, for ethical reasons dMMR patients can be included after 1 metastatic treatment line (instead of 2 metastatic or non-metastatic chemotherapy lines required in the MK-3475-016 trial). Taking the caveats of cross-trial comparisons into account, the close analogy to the MK-3475-016 study facilitates case-matched cross-trial comparisons of the results of both studies. This way, we will be able to estimate whether further exploration of this combination is warranted.

Secondary outcome

To determine the overall survival of patients with pMMR CRC, dMMR mCRC, dMMR EC, , dMMR SBC, dMMR SC treated with pembrolizumab combined with ataluren.

To estimate irPFS and PFS in patients with pMMR CRC, dMMR mCRC, dMMR EC, dMMR SBC, dMMR SC treated with pembrolizumab combined with ataluren at 30 weeks using irRC and RECIST

To estimate best overall response rate and disease control rate in patients with pMMR CRC, dMMR mCRC and dMMR EC treated with pembrolizumab combined with

ataluren.

To assess safety and characterize toxicities of pembrolizumab combined with

ataluren in patients with pMMR CRC, dMMR mCRC and dMMR EC.

To compare the outcomes of abovementioned primary and secondary study

objectives with a series of case-matched controls treated within the

MK-3475-016 study.

Study description

Background summary

In the MK-3475-016 study2 8 out of 13 dMMR mCRC patients responded to immune checkpoint inhibition treatment with pembrolizumab. This unexpectedly high response rate identified dMMR CRC as a highly immunogenic tumour. Part of the responses that were induced in the above mentioned trial may have been directed against neo-antigens originating from neo-ORFs. Since out-of-frame translation almost always encounters a premature termination codon (PTC), it leads to a truncated gene product with a short out-of-frame C-terminal tail that usually is no more than approximately 20 amino acids (aa) long. The short length of the neo-ORF*s makes it unlikely to contain a stretch of approximately 10 consecutive aa*s that can bind MHC-1 or MHC-2. In dMMR mCRC and dMMR EC patients the relatively large amount of frame-shifted coding microsatellites (cMS) may yield sufficient neo-epitopes for tumor rejection. However, in pMMR CRC frame shift mutations are scarce. This may partly explain the lack of immunogenicity of pMMR CRC compared to dMMR CRC and dMMR EC. the same is the case for dMMR SBC and dMMR SC
PTC Therapeutics nonsense mutation readthrough research has been focused on its application of small molecules to identified nonsense mutations as they have key roles in several congenital conditions. Recently, ataluren has shown clinical activity in patients suffering from nonsense mutation Duchenne Muscular Dysptrophy (nmDMD) by restoring expression of the mutant dystrophin gene carrying a nonsense mutation resulting in truncation. Based on this observation, we hypothesize that in CRC patients read through translation induced by ataluren may result in an approximate doubling of the neo-epitopes derived from neo-ORF*s. Thereby it might increase the immunogenicity of these tumors (Fig1). Based on analyses on the TCGA dataset we have no reason to believe that nonsense mediated decay (NMD) significantly impacts the expression level of frameshifted neo-antigens in colorectal cancer tissue. In short, we hypothesize a potential synergistic effect between immune checkpoint inhibition

and ataluren-enabled read-through translation.

Study objective

This study has been transitioned to CTIS with ID 2023-509457-31-00 check the CTIS register for the current data.

To determine the immune-related progression free survival (irPFS) rate at 21 weeks and objective response rate (irORR) at 30 weeks in patients with pMMR CRC, dMMR mCRC, dMMR EC , dMMR SBC, dMMR SC treated with pembrolizumab combined with ataluren using immune related response criteria (irRC)

Study design

In the phase-1 part of the study 2-4 groups of 3 patients each are treated with pembrolizumab 200mg i.v. q3w but with increasing ataluren doses (i.e. group1 25%, group2 50% and group3 100% of 10-10-20mg/kg). These can be either pMMR mCRC, dMMR mCRC, dMMR EC patients , dMMR SBC, dMMR SC . The reported toxicity in phase-1 will be used to define the maximum tolerated dose (MTD) of the combination, that will determine the ataluren dose in phase-2.
In the phase-2 part of the study a dMMR group (cohort A, 20 patients either CRC, EC, SC, SBC) and a pMMR group (cohort B, 15 CRC patients) will be treated with pembrolizumab 200mg i.v. q3w combined with ataluren t.i.d. at the MTD defined in phase-1.

Intervention

Systemic treatment with Pembrolizumab anti-PD1 monoclonal antibodies by 3-weekly infusions, combined with oral ataluren taken three times daily every day.

Study burden and risks

Patients will be at risk for the auto-immune side effects that may be the result of anti-PD1 treatment. Additionally, patients will be at risk for the side effects that may result from ataluren treatment. Both drugs have a relatively mild toxicity profile compared to alternative systemic treatment options, i.e. second line chemotherapy regimens. Moreover, in dMMR patients the response rates that have been described with anti-PD1 monotherapy rival those of chemotherapy regimens, but importantly the response duration after anti-PD1 treatement is longer on average. Moreover, anti-PD1 therapy is not available as a standard treatment option.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Metastatic or irresectable locally advanced mismatch repair proficient or deficient colorectal carcinoma or mismatch repair deficient endometrial carcinoma or mismatch repair deficient stomach carcinoma or mismatch repair deficient small bowel carcinoma carcinoma
- Have received or refused at least one chemotherapy treatment for metastatic disease
- Life expectancy greater than 3 months
- Normal organ and marrow function (as defined in protocol)
- Be willing and able to provide metastasis tissue pre and post treatment by core or excissional biopsy.

Exclusion criteria

- (Partner is) currently pregnant or breastfeeding or is planning to become pregnant or nurture a child during the duration of the trial and a designated period thereafter.
- Prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti OX-40, anti-CD40 or anti-CTLA-4.
- Active central nervous system metastsasis or carcinomateus meningitis
- (History of) auto-immune disease
- Immunodeficiency or use of immunosuppressing drugs.
- Active infection
- Uncontrolled intercurrent disease (for example hearth failure)
- (History of) active Tuberculosis
- HIV, Hep A, Hep B.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-08-2019
Enrollment:	47
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Keytruda
Generic name:	Pembrolizumab
Registration:	Yes - NL outside intended use

Product type:	Medicine
Brand name:	Translarna
Generic name:	Ataluren
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-02-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-02-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-09-2021
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
EU-CTR	CTIS2023-509457-31-00
EudraCT	EUCTR2017-004752-34-NL
CCMO	NL64152.018.18