Conversion of unresponsiveness to immunotherapy by Fecal Microbiota Transplantation in patients with metastatic melanoma and non-melanoma skin cancer: a randomized phase Ib/IIa trial

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Primary objective:• To investigate the efficacy, defined as clinical benefit (stable disease (SD), partial response (PR), complete response (CR)) at 12 weeks, confirmed on a second scan after 4 weeks, of an FMT-intervention with responder and non-...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Skin neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52200

Source
ToetsingOnline

Brief title
FMT to convert response to immunotherapy

Condition

- Skin neoplasms malignant and unspecified

Synonym
melanoma, skin cancer

Research involving

Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: de AVL Foundation

Intervention

Keyword: Fecal microbiota transplantation, Immunotherapy, Melanoma

Outcome measures

Primary outcome

For the efficacy analysis the primary endpoint will be clinical benefit (SD,

PR, CR) at 12 weeks, confirmed on a second scan after 4 weeks.

Secondary outcome

For the safety analysis the endpoint will be occurrence of toxicity of grade 3

or higher (secondary endpoint).

Study description

Background summary

For patients with advanced stage melanoma, treatment possibilities have changed considerably in the past 10 years. Both targeted therapies for BRAF V600 mutated melanomas, blocking intracellular signaling proteins (mutated BRAF and downstream MEK) in the MAPK pathway, and immunotherapy, blocking inhibitory receptors on activated T cells (CTLA-4 and PD-1), have improved outcomes for these patients with at best five year overall survival rates of 50%. Despite these impressive results, the majority of patients with metastatic melanoma still succumbs to the disease.
For non-melanoma skin cancers, immunotherapy has also become a standard of care treatment in recent years.For patients with locally incurable of metastatic cutaneous squamous cell carcinoma (cSCC) anti-PD-1 checkpoint inhibition with cemiplimab induces objective responses in approximately 50% of patients, with a duration of response exceeding six months in 57% of these patients.5,6 For patients with Merkel cell carcinoma (MCC), a rare and highly aggressive neuroendocrine skin malignancy, response rates of up to 68% have been observed

with anti-PD-(L)1 checkpoint inhibitors (avelumab, pembrolizumab or nivolumab). Nevertheless, for both cSCC and MCC, a significant number of patients either do not respond to ICI therapy or experience a relapse after an initial response. Further approved treatment options, such as targeted therapies, are lacking for these patients.
Ample research of the tumor microenvironment has revealed several escape mechanisms to both targeted therapy and immunotherapy, but so far, novel drugs or novel combination of drugs to overcome these resistance mechanisms, have not been approved and some are in clinical development. However, major breakthroughs are still lacking. Therefore, other mechanisms to improve the anti-tumor immune responses should be explored. One such a mechanism may be incorporated in the gut microbiome. Preclinical data showed that the presence or absence of certain microbial taxa in the gut plays an important role in immune responses, including antitumor immunity.
In a recently published study, investigators analyzed the microbiota taxa in stool samples from metastatic melanoma patients either responding or progressing on anti-PD-1 treatment. The presence of certain taxa was strongly correlated with better outcome (Firmicutes) whereas the presence of Bacteroides species was correlated with worse outcome. Stool transplantation of anti-PD-1 responders and progressors to germ-free mice followed by melanoma transplant and treatment with anti-PD-1 showed that only mice having received FMT from anti-PD-1 responder patients had an anti-PD-1 antitumor response. These data corroborate that the capacity of the murine immune system to response to anti-PD-1 may be influenced by the gut microbiome.
FMT is in itself not a new treatment. FMT has been successfully used to treat patients with multiple recurrent Clostridium difficile infection (rCDIs) of the colon, with cure rates over of 85%. Also in severely immunocompromised patients, FMT appears safe and effective for the treatment of rCDI though extra screening tests are included to prevent transmission of low-pathogenic microorganisms.

In conclusion, manipulation of the gut microbiome by donor fecal microbiota transplantation may influence the immune response in both autoimmune disease and cancer, inducing remission in autoimmune bowel disease or severe and refractory immune-related colitis, whereas augmenting an anticancer immune response in the context of immune checkpoint blockade. Preclinical studies illustrate that both CD4 and CD8 T cell responses are affected by FMT, probably by improving antigen-presentation by dendritic cells. These finding are further supported by several observational (pre)clinical studies, in which feces from R/NR patients was transferred into mice. They found that a favorable gut microbiome was associated with reduced tumor growth, higher density of CD8+ T cell infiltrate, increased number of CD8+ T cells in the gut, higher systemic levels of effector CD4+ and CD8+ T cells, and lower levels of Tregs and myeloid-derived suppressor cells (MDSCs). Furthermore, in clinical studies using FMT to treat ICI-unresponsive patients, complete responses, partial responses and durable stable disease have been observed, with prolonged overall survival. The exact underlying mechanism determining which patients will or

will not respond, and what the optimal FMT composition is, are not completely understood.

Therefore, based on these findings in inflammatory bowel disease and in cancer, we propose to initiate a randomized phase Ib/IIa study investigating the effect (safety and efficacy) of donor FMT on unresponsiveness of metastatic melanoma and non-melanoma skin cancer patients while on immune checkpoint blockade.

Study objective

Primary objective:
• To investigate the efficacy, defined as clinical benefit (stable disease (SD), partial response (PR), complete response (CR)) at 12 weeks, confirmed on a second scan after 4 weeks, of an FMT-intervention with responder and non-responder patients as donors in ICI-refractory metastatic melanoma and non-melanoma skin cancer patients while on immune checkpoint blockade.

Secondary objective:
• To study the safety of FMT with responder and non-responder patients as donor in metastatic melanoma and non-melanoma skin cancer patients.

Study design

This is a randomized double-blind intervention phase Ib/IIa trial in ICI refractory metastatic melanoma and non-melanoma skin cancer patients receiving either FMT of an ICI responding or FMT from an ICI non-responding donor, in combination with ICI.

Intervention

Following randomization, patients will receive vancomycin 250 mg, four times daily for 4 days (day -5 up until day -2), and undergo bowel clearance on day -1 (in total 1L MoviPrep). The FMT, either derived from donor group R or donor group NR, will be performed by a gastroenterologist using esophagogastroduodenoscopy. A total amount of 198mL (containing a total of 60 gram feces) will be used for transplantation. Anti-PD-(L)1 treatment will be continued according to the patient*s regular treatment schedule. Evaluation of safety and response to treatment will be performed.

Intervention tested: FMT, while continuing anti-PD-(L)1 treatment.
Lab testing: baseline, +2 weeks, +6 weeks and +12 weeks after FMT.
Feces sample: baseline, pre-FMT, +2 weeks, +6 weeks, +12 and +16w weeks after FMT.
Tumor biopsies: baseline and +12 weeks after FMT.
CT scans: baseline, +12 and +16 weeks after FMT.

Study burden and risks

Metastatic melanoma patients with disease progression while on first line or adjuvant immunotherapy (IT), especially those without an activating mutation in the BRAF V600 gene, have a dismal prognosis. Currently, there are no approved treatment options, other than single agent ipilimumab in case of progressive disease (PD) on single agent anti-PD-1. For patients with metastatic MCC or cSCC developing progressive disease during ICI treatment, further approved treatment options are lacking at all. Clinical trials are a preferred choice for these patients, of which most are phase I clinical trials.
Here, we propose to initiate a phase Ib/IIa clinical trial combining the transfer of fecal microbiota originating from responder or non-responder metastatic melanoma patients via FMT with immunotherapy (anti-PD-1) in order to revert the IT unresponsive state of the tumor microenvironment during immune checkpoint blockade. Patients that become feces donors will be screened for comorbidities, and assessments of serum and stool samples will be performed for presence of potential pathogens.
Patients with refractory metastatic melanoma or non-melanoma skin cancer while on anti-PD-(L)1 treatment will be informed and asked to participate in this randomized phase Ib/IIa trial. Both reversion of unresponsiveness and safety will be measured. Considering the poor life expectancy, we consider the bowel clearance, treatment with antibiotics, and FMT via oesophagogastroduodenoscopy an acceptable burden. Based on the results from two recently published studies by Baruch et al. and Davar et al. who did not observe any significant side effects, direct toxicity from FMT or the combination with anti-PD-1 seems unlikely. Likewise, serious adverse events are rare in FMT treated patients with multiple, recurrent Clostridium difficile infection (rCDI). Nonetheless, FMT in healthy volunteers may result in systemic inflammatory response syndrome. Apart from FMT, patients will undergo stool sampling, blood sampling and, if feasible, tumor biopsies to measure the changes during this combined treatment. As this is a phase Ib/IIa study we consider this patient population with anti-PD-(L)1 treatment-refractory disease the optimal population to perform this study.

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

- Patients should be 18 years or older
- Patients have pathologically confirmed advanced stage cutaneous melanoma cutaneous squamous cell carcinoma or Merkel cell carcinoma (stage III or IV) requiring systemic treatment with anti-PD-(L)1
- In case of melanoma patients with stage IV disease, only patients with limited disease progression without immediate clinical risks of delaying other treatment options, based on the judgment of the treating physician, are eligible.
- Patients have confirmed disease progression (>=20% increase according to RECIST 1.1 or measurable recurrence under adjuvant treatment) on two consecutive scans with a four week interval while on anti-PD-1 treatment, of which the second scan has to be performed within 3 weeks prior to signing informed consent.
- Patients must have measurable disease per RECIST 1.1 criteria
- Patients have an ECOG performance status of 0-1
- Patients have a life expectancy of >3 months
- Patients have adequate organ function as determined by standard-of-care pre-checkpoint inhibitor infusion lab (including serum ALAT/ASAT less than three times the upper limit of normal (ULN); serum creatinine clearance 50ml/min or higher; total bilirubin less than or equal to 20 micromol/L, except in patients with Gilbert*s Syndrome who must have a total bilirubin less than 50 micromol/L)
- Patients have an LDH level of <2x times ULN
- Patients of both genders must be willing to use a highly effective method of

birth control during treatment
- Patients must be able to understand and sign the Informed Consent document

Exclusion criteria

- Patients with acral, uveal or mucosal melanoma.
- Patients with non-cutaneous squamous cell carcinoma
- Patients who have received systemic treatment for their melanoma or non-melanoma skin cancer other than anti-PD-(L)1 treatment.
- Stage IV melanoma patients with rapid or invasive disease progression necessitating an immediate switch to a proven effective treatment, as judged by the treating physician.
- Patients with autoimmune diseases: patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn*s disease, are excluded from this study (except Hashimoto thyroiditis, vitiligo, history of psoriasis, but no active disease)
- Patients with any grade 3 or 4 immune-related adverse events still requiring active immunosuppressive medication (prednisone <=10mg/day or equivalent are permitted), apart from endocrinopathies that are stable under hormone replacement therapy. Patients who had developed grade 3-4 immune related toxicity, which has reverted to grade I with immunosuppressive drugs and who are off immunosuppression at least two weeks prior to enrollment are eligible (prednisone <=10mg/day or equivalent are permitted.
- Patients with active or symptomatic brain metastasis or LM metastasis (brain metastases treated with radiotherapy, that are inactive and asymptomatic are allowed).
- Patients with an elevated LDH level.
- Patients that have undergone major gastric/esophageal/bowel surgery (like Wipple, subtotal colectomy)
- Severe food allergy (e.g. nuts, shellfish)
- Patients with a swallowing disorder or expected bowel passage problems (ileus, fistulas, perforation).
- Severe dysphagia with incapability of swallowing 1 liter of bowel lavage.
- Patients with a life expectancy of less than three months
- Patients with severe cardiac or pulmonary comorbidities (per judgement of the investigator)
- Women who are pregnant or breastfeeding
- Patients with any active systemic infections, coagulation disorders or other active major medical illnesses
- Patients with other malignancies, except adequately treated and a cancer-related life-expectancy of more than 5 years.
- Patients who received treatment with antibiotics in the three months prior to study enrolment, or patients we are expected to receive systemic antibiotics during the course of this study

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	31-08-2022
Enrollment:	28
Type:	Actual

Ethics review

Approved WMO Date:	24-02-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	05-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-11-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-08-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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
ClinicalTrials.gov	NCT05251389
CCMO	NL78423.031.21