Deep phenotyping of the gut immune system during Immune Checkpoint Inhibitor therapy (DEFENCE)

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To define the immunohistopathological changes induced in the colon lamina propria by ICI therapy.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON55053

Source
ToetsingOnline

Brief title
The gut immune system during immunotherapy

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: gut immune system, immune checkpoint inhibitor, immunotherapy

Outcome measures

Primary outcome

To define the difference in number of CD8+ T cells in the gut mucosa between pre-treatment biopsies and biopsies at 6-8 weeks after starting ICI therapy between responders and non-responders.

Secondary outcome

To determine the difference in number of CD8+ T cell subpopulations (naïve, memory, effector/cytotoxic) between pre-treatment biopsies and biopsies at 6-8 weeks after starting ICI therapybetween responders and non-responders to ICI therapy.

To determine differences in CD4+ T cell counts between pre-treatment biopsies and biopsies at 6-8 weeks after starting ICI therapy between responders and non-responders to ICI therapy.

To determine the difference in CD68+ macrophage to mucosal tissue ratio between pre-treatment biopsies and biopsies at 6-8 weeks after starting ICI therapy between responders and non-responders to ICI therapy.

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Study description

Background summary

Activation of the immune system by Immune checkpoint inhibitors (ICIs) results in long lasting anti-tumour activity in many patients with various cancer types. However, the majority of patients do not benefit from ICI treatment. There is an unmet need to better understand the determinants of ICI tumour response and to develop novel therapeutic strategies to enhance this response. Patients responding to ICIs have been shown to have higher peripheral and tumour-infiltrating CD8+ T cells than non-responders at baseline and during ICI therapy. The cytotoxic, tumour-directed effect of CD8+ T cells is affected by interactions with other immune cells including CD4+ T cells and macrophages. The gut is the largest barrier between the body and the outside world. The gut wall is a crucial immune organ, hosting over 70% of our immune cells. ICI therapy affects the gut, as evidenced by: (1) a per-treatment increase of faecal calprotectin - indicating intestinal immune activation, (2) shifts in immune cell subtypes including CD8+ T cells due to ICI therapy. CTLA-4 and PD-1, the targets of ICI, are expressed by immune cells in the gut wall, and moreover, have been shown to play an important role in the regulation of the gut wall immune system. Furthermore, recent gut microbiome studies indicate that the tumour response to ICI can be modified by gut-directed interventions. Surprisingly, the gut wall has hardly drawn attention in the context of ICI therapy. The effects of ICIs on the gut immune system are not fully understood. We hypothesise that the gut immune system reflects relevant immune changes taking place in the tumour due to ICI therapy. More specifically, we hypothesize that in line with what has been reported within the tumour microenvironment, ICI leads to an increase in CD8+ T cells in the lamina propria and responders have higher CD8+ T cell counts than non-responders.

Study objective

To define the immunohistopathological changes induced in the colon lamina propria by ICI therapy.

Study design

This project is an exploratory study aiming to gain insight in gut immune system phenotypes before and after ICI therapy. After informed consent is obtained, sigmoidoscopies limited to the sigmoid and rectum will be performed. Eight biopsies will be taken at both locations at baseline and 6-8 weeks after initiation of ICI therapy. The immune cell infiltrates in these biopsies will be analysed by immunohistochemistry (IHC), RNA sequencing and flowcytometry. The design of the present study is based on ongoing as well as completed successful studies (e.g. GEID study and VISION study) at the Department of

Gastroenterology and Hepatology of the UMCG. Both sample acquisition as well as analyses will be done according to standardised procedures of the Department of Gastroenterology and Hepatology, Medical Oncology and Pathology.

Intervention

Sigmoidoscopies
Bowel preparation will be limited to 2 x 0.5 L PLEINVUE (oral solution) the day before the endoscopy. The endoscope will be inserted up to upper border of the descending colon. After white light endoscopic observation, biopsies will be taken from the following areas: descending colon, sigmoid colon and rectum. Per location, five biopsies will be taken. Biopsies will only be taken if judged safe by the gastroenterologist. In order to minimise discomfort, patients may undergo the procedure under sedation if desired. In case patients are sedated with propofol, the vitals will be monitored by an employee of anaesthesiology department (standard clinical care).

Peripheral Blood
Ten millilitres of peripheral blood will be collected using 368589 - 16x100 mm 10.0 mL BD Vacutainer® Plus Plastic whole blood tube, K2EDTA 18.0 mg. Peripheral blood will be used to measure gut-specific inflammatory markers before and during ICI therapy.

Study burden and risks

By taking part in this trial, patients can help to increase knowledge on the effects of ICI therapy on the gut wall immune cell composition and to identify new targets to improve ICI therapy. Patients will not directly benefit from participating in this study.
Sigmoidoscopies with gut wall biopsies will be performed at baseline and at 6-8 weeks after starting ICI therapy. In addition to the sigmoidoscopy, blood will be drawn at both timepoints. Thus, patients will be required to make 2 visits outside of their routine care to the hospital. The sigmoidoscopies are minimally invasive and take about 15 minutes.
Patients may experience some degree of discomfort. No anaesthesia nor sedation will be required. However, patients may be sedated during the procedure if desired. The risks are limited and include temporary complaints such as mild abdominal pain and bloating. The risk of severe complications such as intestinal perforation or haemorrhage is <1%. The preparation for the sigmoidoscopy is limited to bowel preparation with PLEINVUE. This study causes no delay of starting ICI therapy.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

•18 years or older
•Written informed consent
•Evaluable according to iRECIST v1.1
•Indication for treatment with anti-PD-1 ICI or a combination of anti-PD-1 and anti-CTLA-4 ICI
for locally advanced or metastatic cancer for which no curative local treatment is available.
• Informed consent to participate in Oncolifes Immunotherapy or POINTING

Exclusion criteria

•Concomitant, chronic or infectious illness in the past 6 months causing moderate to severe colitis
•Use of a medication in the past 6 months with a known elevated risk of developing moderate to severe colitis (such as mycophenolate mofetil)

•Gastrointestinal resection
•Ileostomy or colostomy
•Abdominal radiotherapy in the past 6 months
•Pregnancy

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-10-2021
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO Date:	10-09-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-01-2022
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
ClinicalTrials.gov	NCT04600180
CCMO	NL75124.042.20