EORTC ILOC study: Phase II of immunotherapy plus local tumor ablation (RFA or stereotactic radiotherapy) in patients with colorectal cancer liver metastases

Published: 17-05-2018
Last updated: 12-04-2024

The primary objective of this proof of concept study will be to investigate whether the combined use of local tumor ablation/radiation plus immunomodulating drugs may induce a significant immune response in patient with incurable liver metastases...

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

Summary

ID

NL-OMON55697

Source
ToetsingOnline

Brief title
ILOC

Condition

- Metastases

Synonym
liver metastases - liver tumor

Research involving
Human

Sponsors and support

Primary sponsor: European Organisation for Research in Treatment of Cancer (EORTC)
Source(s) of monetary or material Support: Astra Zeneca,EORTC

Intervention

Keyword: colorectal liver metastases, immunotherapy, local tumor ablation

Outcome measures

Primary outcome

*1 year (maximum) after the start of study treatment of the last enrolled

patient

Primary endpoint: Best overall immune response rate of lesions not treated by

ablation/radiotherapy including the extrahepatic lesions according to iRECIST

(with response confirmation).

Secondary outcome

*Best overall immune response (best overall immune response, iBOR)

rate of liver lesions not treated with local therapy according to iRECIST

(with response confirmation)

*Best overall response rate of lesions not treated by

ablation/radiotherapy including or not the extrahepatic lesions

according to RECIST v1.1 (with response confirmation)

*Response duration according to iRECIST and to RECIST v1.1

*Stable disease duration according to iRECIST and to RECIST v1.1

(At the same time as primary endpoint)

*Progression free survival according to iRECIST and RECIST v1.1

*Overall survival

Study description

Background summary

Basic research has shown that local tumor ablation or stereotactic radiotherapy has a immune stimulating effect especially when combined with immunotherapy. There is seems a clear rationale to evaluate whether the combined use of local tumor ablation/radiation plus immunomodulating drugs may induce a significant immune response in patient with metastatic CRC. In this setting local ablation/radiation will be used to trigger the immune response by antigen release and DC loading, while immunomodulating agents are used to boost the immune response and counteract negative regulatory effects.

Study objective

The primary objective of this proof of concept study will be to investigate whether the combined use of local tumor ablation/radiation plus immunomodulating drugs may induce a significant immune response in patient with incurable liver metastases from colorectal cancer (CRC) (+/- limited extrahepatic disease) being stable or in partial respons after a course of first - or second line therapy.
The primary objective of the study is to show an overall response rate of lesions not treated by ablation/radiotherapy including the extrahepatic lesions (according to iRECIST criteria) higher than 10%. With the continuation of first line systemic treatment, no further responses are expected.

Secondary objectives are:
*To establish the feasibility and safety of the combined treatment modalities;
*To study the impact of the local technique (RFA/Radiotherapy) on the results;
*To investigate biomarkers to predict response to the combined

treatment.

Study design

This is a single-arm, open-label, multi-center early phase II study (proof of concept study) investigating whether the combined use of local tumor ablation/radiation plus immunomodulating drugs may induce a significant immune response in patient with metastatic CRC.

After verification of eligibility criteria, patients will be enrolled and will receive treatment with durvalumab and tremelimumab plus local tumor ablation/stereotactic radiotherapy of selected liver lesions, followed by maintenance treatment with durvalumab.

Intervention

The therapeutic interventions being tested in this study are both local therapy (RFA or SBRT), combined immunotherapy (tremelimumab 75 mg and durvalumab 1500 mg for 4 cycles), then maintenance therapy with durvalumab 1500 mg every 4 weeks up to week 48.
There should be a maximum 42 days between

Study burden and risks

BURDEN

The burden of the patient mainly consists of extra local treatment of one or more liver metastases by radiofrequency ablation (1 -2 days admission) or stereotactic radiotherapy (3 doses). In addition there is an extra MRI scan and some additional hospital visits adding up to an extra 8 hours above normal treatment.

RISC IMMUNOTHERAPY

To date, approximately more than 800 patients have been treated with durvalumab and tremelimumab. Like all drugs, these can cause mild or serious side effects;

Very common side effects (>10%):
* Diarrhea
* Rash/dry itchy skin
* Liver problems:

Common side effects (>1% to *10%)
* Inflammation in the lungs (pneumonitis):
* Low thyroid (Hypothyroidism):
* High thyroid (Hyperthyroidism):

* Kidney problems:
* Nervous system problems: Symptoms can include unusual weakness of legs, arms, or face, numbness or tingling in hands or feet.
* Infusion Related Reactions:
* Inflammation of the intestine (colitis).

Side effects relating to radiofrequency ablation (RFA)
Complications are rare, but no procedure is completely free of risk. If you are planned to undergo ablation, your doctor will review with you a list of possible complications, which may include:
* Pain, discomfort at ablation site
* Bruising or bleeding on the site of puncture or on the liver
* Infection at ablation site
* Lung collapse upon insertion of the probe (when the procedure involves involves accidentally the lung, liver, or upper kidney)

RISK RADIOTHERAPY

Generally, radiotherapy is well tolerated. Side effect may be
* liver dysfunction
* general side effects like fatigue, pain or discomfort, itchiness and skin irritation
* intestinal irritation with can cause diarrhea, painful bowel movements and blood in the stool
* gastric irritation with can cause nausea and vomiting
* increase in liver enzymes without symptoms

RISK RADIOFREQUENCY ABALTION

Radiofrequency ablation is a safe procedure, side effect however may occur being
* Pain, discomfort at ablation site
* Bruising or bleeding on the site of puncture or on the liver
* Infection at ablation site
* Lung collapse
* Liver abscess (small, localized collection of pus within a cavity left by the destroyed tissue)
* Collection of bile fluid (biloma)

Contacts

Public
European Organisation for Research in Treatment of Cancer (EORTC)

Avenue E Mournier 83/11 Brussel
Brussel 1200
BE
Scientific
European Organisation for Research in Treatment of Cancer (EORTC)

Avenue E Mournier 83/11 Brussel
Brussel 1200
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

*Histologically confirmed CRC
*Patients with CRC liver metastases, with/without extrahepatic disease,in which curative treatment is not possible by resection and or local ablation/radiotherapy
** 18 years of age at time of study entry
*WHO performance status 0 to 1
*Body weight >30kg Measurable disease according to RECIST 1.1
*Stable disease or partial remission by RECIST 1.1 criteria after at least 3 months systemic therapy for CRC. Patients are eligible following first - or - second line treatment. Note: if patient receives maintenance treatment after the first line treatment, she/he remains eligible for this study
*Complete responders or partial responders with a 80% or more decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions following last systemic treatment, taking as reference sum of diameters from baseline scan prior to initiation of systemic therapy are

excluded as well as patients with almost complete cystic degeneration of liver metastases. Note: the interval between last dose of systemic treatment to the first dose of the study drugs must be of maximum 8 weeks (in case bevacizumab was administered as part of the systemic treatment, a min 21days wash out period is required from last administration to planned local ablative treatment initiation)
*Liver metastases amenable to ablation or stereotactic radiotherapy (SBRT) at completion of systemic therapy
*For SBRT: allowing a total ablated volume of at least 25 cm3 &a maximum of 40 cm3 with a max of 2lesions treated with SBRT
*For RFA: allowing a total ablated volume of at least 25 cm3 &amaximum advised volume of 120 cm3
*At least 2measurable liver metastases, or at least 1measurable liver metastasis and 1 measurable extrahepatic lesion should remain untreated by ablation or SBRT to allow response monitoring according to RECIST 1.1 & iRECIST
*Limited extra hepatic disease is allowed, including up to 2extra hepatic metastatic sites,either lung, abdominal, pelvis, bone, or localized lymph node metastases. Each is counted separately as 1site. 2abdominal lesions will be counted as 1extra-hepatic site; 1lung & 1abdominal lesion will be counted as 2sites. Individual extrahepatic lesions should be * 5 cm
*Availability of tumor sample for biomarkers testing (MSI, PDL-1, etc) (archival tissue from primary tumor)
*Adequate normal organ &marrow function before initial systemic treatment as well as baseline as defined below:
*Absolute neutrophil count (ANC) * 1.5 x 109/L (> 1500 per mm3)
*Platelet count * 100 x 109/L (>100,000 per mm3)
*Serum bilirubin * 1.5 x institutional upper limit of normal (ULN). This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in absence of hemolysis or hepatic pathology), who will be allowed only in consultation with physician
*AST (SGOT)/ALT (SGPT) * 5 x institutional upper limit of normal
*Creatinine * 1.5 x institutional ULN or measured or calculated creatinine clearance >40 mL/min by the Cockcroft-Gault formula
*Hemoglobin * 9.0 g/dL at baseline
*PLEASE SEE THE PROTOCOL FOR FURTHER INCLUSION CRITERIA

Exclusion criteria

*Patients with known brain metastases or history of leptomeningeal carcinomatosis
* Hilar liver lesions close to central bile ducts to be treated by RFA
* Prior treatment:
*History of radiation therapy of the liver, upper abdomen or lower thorax
*History of radioembolization of the liver

*Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of durvalumab and tremelimumab.
*Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab, a CTLA-4 including tremelimumab or other checkpoint inhibitors or other immune therapy during the last 12 months
*Any unresolved toxicity NCI CTCAE v 4.0 Grade *2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
*Patients with Grade *2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
*Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the Study Physician.
*Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab and tremelimumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid, or steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)
*Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab
*Active or prior documented autoimmune or inflammatory disorders (including inflammatory pulmonary disorders, interstitial lung disease, inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]).
*History of allogeneic organ transplant
*History of hypersensitivity to durvalumab, tremelimumab or any excipient
*Uncontrolled intercurrent illness including, but not limited to:
*Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
*Active peptic ulcer disease or gastritis
*Liver cirrhosis CHILD B+, C
*Active bleeding diatheses
*History of primary immunodeficiency
* Cardiac disorders:
* Symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia
*Mean QT interval corrected for heart rate (QTc) *470 ms calculated from 3 electrocardiograms (ECGs) using Frediricia's Correction

*Female patients who are pregnant or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy.
*Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
Important note: All eligibility criteria must be adhered to, in case of deviation discussion with Headquarters and study coordinator is mandatory.

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):	28-05-2019
Enrollment:	13
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	IMFINZI
Generic name:	Durvalumab
Product type:	Medicine
Brand name:	Tremelimumab
Generic name:	Tremelimumab

Ethics review

Approved WMO Date:	17-05-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	11-01-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	23-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-07-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-08-2021
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2017-001375-22-NL
CCMO	NL64627.031.18