Treatment of cancer with Immune Checkpoint Inhibition therapy boosted by High-Intensity Focused Ultrasound Histotripsy; the iFOCUS study.

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Primary objective: to determine 1) the safety, tolerability and feasibility of a single-session of HIFU-HT treatment with ICI (IV anti-PD-1; nivolumab + anti-CTLA-4; ipilimumab).Secondary objective: to evaluate clinical, radiological and...

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

Summary

ID

NL-OMON56837

Source
ToetsingOnline

Brief title
iFOCUS

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
cancer, malignancy

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: via Vrienden van UMC Utrecht

Intervention

Keyword: High-Intensity Focused Ultrasound, Immune checkpoint inhibition, Malignancy

Outcome measures

Primary outcome

Safety 1. Incidence and severity of adverse events (related to HIFU-HT or the

combination of HIFU-HT and ICI.) Adverse events will be assessed up to three

months after the last ICI administration.

Tolerability

1. PROMS questionnaires:

• Customized HIFU-HT-tolerability questionnaire.

• EuroQol Group EQ-5D.

• Utrecht symptom diary immunotherapy (USD-I).

2. Discontinuation rate due to adverse events.

Feasibility

1. The number of technically effective HIFU-HT procedures.

2. The percentage screening failures.

3. Time burden of the study procedures.

Secondary outcome

Radiological response

1. Local response of HIFU-HT treated tumor with a MRI directly and 12 weeks

after HIFU-HT

2. Systemic response using RECIST 1.1 as assessed by CT-scan every 12 weeks (or

using PERCIST as assessed by PET-CT if not RECIST measurable)

Immunologic response

1. Analysis of immunological parameters in peripheral blood samples (plasma and

peripheral blood mononuclear cells (PBMCs)

2. Analysis of immune infiltrates in tumor biopsies taken at baseline and 7

days after HIFU-HT

Clinical response

1. Explorative analysis to assess progression-free survival and overall

survival while taking into consideration the heterogeneous patient population

in this basket design.

Study description

Background summary

Immune Checkpoint Inhibition (ICI) has led to remarkable advances in cancer therapy, leading to improved clinical outcomes (1,2). Cytotoxic T-lymphocyte-associated antigen 4 (anti-CTLA-4) antibody and programmed cell death-1 antibody (anti-PD-1) are the two most frequently used types of ICI. Their combination has also frequently been investigated (3,4) and is part of standard clinical practice for an increasing number of cancer types. In several tumor types, combining CTLA4- and PD1- inhibition has been proven to improve response rates as compared to PD1-inhibition alone (5-7) However until now, ICI only benefits a small percentage of patients with cancer, and can be associated with severe adverse effects (8). Despite leading to very durable responses and

at times even cure for patients with metastatic immunogenic (*hot*) tumors, response rates for *cold* tumors to ICI have been disappointing. Many cancer types exert this **cold** biological environment, meaning that they are either non-immunogenic, or poorly immunogenic, and in these cases, ICI has shown limited success.

High-intensity focused ultrasound histotripsy (HIFU-HT) is a high-intensity focused ultrasound method that can be used to mechanically fractionate tissue. As opposed to thermal ablation using HIFU, which involves sonication at the same location over an extended period of time resulting in the generation of heat, histotripsy is a mainly mechanical technique using short high-power ultrasound pulses. The rapid oscillation between high amplitude negative and positive peak pressures, leads to the formation and collapsing of microbubbles, thus creating mechanical forces that lead to tissue damage and destruction (9). In addition to its ablative use, there is growing evidence that the immunological effects of histotripsy can enhance the efficacy of immune checkpoint inhibitors.

In preclinical studies, it was shown that HIFU-HT can lead to the release of tumor-associated antigens and damage-associated molecular patterns (DAMPs) for activation of dendritic cells in the sentinel node(s), causing a sudden sterile local inflammation (10). In preclinical murine studies, a reduction in tumor growth was observed after treatment with histotripsy. However, in many of these mice, tumor growth reduction was a temporal effect and mice developed progressive disease after a period of time (11-14). Although HIFU-HT alone triggered immunological effects in these studies, this appeared insufficient to sustain a long-lasting systemic response.

In collaboration with the Children's National Medical Center in Washington our research group has studied the combination of HIFU-HT with ICI (α-CTLA4 and α-PD-1) and found a significantly improved effect of ICI in a previous immunotherapy-refractory neuroblastoma murine model. In this study, combination treatment resulted in improved overall response, long-lasting survival for the majority of the mice (61%) and a memory effect that prohibited new tumors to grow after re-inoculation with tumor cells (15). Combination of histotripsy and ICI resulted in significant improved survival compared to mice that were treated with histotripsy alone. These findings corroborate with other preclinical studies that found an improved effect of immune checkpoint inhibitors after HIFU-HT treatment (11,16,17). Histotripsy may thus have the potential to convert a *cold* non-immunogenic tumor into a *hot* immune responsive tumor.

An increasing number of clinical studies have been initiated in recent years exploring the use of histotripsy in human patients. These early studies have focused primarily on the ablative effect of histotripsy, although there is rising attention for the potential immunological effects of histotripsy. Histotripsy has been studied as an application in patients with benign prostatic hyperplasia (BPH) and patients with liver tumors in multicenter trials in both Europe and the United States (18-20). To date, the combination of HIFU-HT and ICI has not been investigated in human patients.

The iFOCUS study is therefore the first clinical study that will assess the

safety and tolerability of HIFU-HT combined with anti-CTLA4 and anti-PD-1 in patients. In this study, patients with advanced cancer that have progressed on regular treatment will be treated.

Study objective

Primary objective: to determine 1) the safety, tolerability and feasibility of a single-session of HIFU-HT treatment with ICI (IV anti-PD-1; nivolumab + anti-CTLA-4; ipilimumab).
Secondary objective: to evaluate clinical, radiological and immunological responses of a single-session of HIFU-HT during treatment with ICI (IV anti-PD-1 + anti-CTLA-4).

Study design

Single-arm phase 1 clinical trial consisting of two phases:
• Phase 1 cohort 1: Six patients will be treated with the combination of HIFU-HT and ICI.
• A safety stop is planned between phase 1 cohort 1 and phase 1 cohort 2. If no additional safety concerns arise in this safety stop and if the funding for phase 1 cohort 2 is guarantueed, the study proceeds to phase 1 cohort 2. The preliminary results of phase 1 cohort 1, toghether with the documents containing agreements concerning additional funding, will be submitted as a substantial amendment for review by the MERC NedMec; phase 1 cohort 2 will only be started after approval by the MERC.
• Phase 1 cohort 2: Eighteen patients will be treated with the combination of HIFU-HT and ICI.

Intervention

The study treatment consists of intravenous administration 4 cycles qw3 of the combination of nivolumab and ipilumumab, followed by nivolumab qw4. This first administration of the medication occurs 1 week before HIFU-HT treatment. On day 8, patients undergo single-session HIFU-HT treatment. Additional study procedures will include (DCE) MRI immediately after HIFU and after 12 weeks, and follow-up visits with blood sampling and PROMS. Tumor biopsy will be taken from the treated lesion 7 days after HIFU-HT treatment. Every three months, response will be evaluated with CT of thorax and abdomen. Adverse events will be followed up to 3 months after the last ICI administration.

Study burden and risks

Possible benefits of study treatment include an increased chance of tumor response, even possibly eradicating the treated tumor, as well as other metastases. Since the patients in the study population have progressed on regular treatment, the risks associated with study participation are considered

proportional to the possible benefit.
Risks associated with HIFU-HT: Although HIFU has been extensively and successfully used in patients for thermal ablation of whole tumors, the total number of patients treated with HIFU-HT for mechanical tissue destruction is limited yet increasing. No serious adverse events apart from one case of urinary retention were reported from the trials to date (18-20). Risks of HIFU-HT treatment in our trial are mitigated by real-time image-guided feedback with thermometry. As the aim of the HIFU-HT treatment is not complete ablation of the tumor but rather partial ablation, adjacent critical structures can be more easily avoided in treatment planning.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Histologically confirmed metastatic or unresectable cancer that progressed under regular treatment options
2. Age >= 18 years.
3. Has signed and dated written informed consent before performing any study procedure, including screening.
4. Anticipated life expectancy >= 12 weeks by Investigator judgement.
5. At least one tumor lesion (primary tumor or metastasis) which is amenable to application of high intensity focused ultrasound histotripsy (determined by a radiologist with HIFU-expertise).
• The lesion must have a distance of <=30 mm to the skin.
• At least part of the lesion must have a distance of >=10 mm to the skin and other vulnerable structures (e.g. large blood vessels). This part should be sufficient to be able to select at least one HT focus in an area of solid tumor.
• If the target lesion contains cystic or necrotic regions: the solid component should be >=10 mm in diameter, sufficient to be able to select at least one HIFU-HT focus in an area of solid tumor.
6. Sonication will be performed on tumors that have not previously directly been treated with radiation therapy or surgery unless they showed significant mass regrowth.
7. Measurable disease (at least one lesion besides the HIFU-HT treated lesion) on CT according to RECIST V 1.1 criteria or on PET-CT according to PERCIST criteria as assessed by investigator and local radiology review.
8. Performance status of 0 or 1 on the WHO Performance Scale.
9. Screening laboratory values must meet the following criteria:
• WBC >= 2.0x109/L,
• Neutrophils >=1.5x109/L
• Platelets >=100 x109/L
• Hemoglobin >=5.5 mmol/L
• Serum creatinine <=1.5 x upper limit of normal (ULN) or calculated creatinine clearance >=60 mL/minute (<=Grade 1)
• Aspartate aminotransferase (AST) <=2.5 x ULN; alanine aminotransferase (ALT) <=2.5 x ULN; AST/ALT <5 x ULN if liver involvement
• Serum bilirubin <=1.5 x ULN or direct bilirubin <=ULN for subjects with total bilirubin levels >1.5xULN, except in subjects with Gilbert*s Syndrome
10. Patients must agree to use an adequate method of contraception for the course of the study through 120 days after the last dose of study medication.
11. Patients must be willing to undergo tumor biopsy.

Exclusion criteria

1. Presence of known central nervous system, meningeal, or epidural metastatic

disease. However, subjects with known brain metastases are allowed if the brain metastases are stable for >=4 weeks before the first dose of study treatment. Stable is defined as neurological symptoms not present or resolved to baseline, no radiologic evidence of progression, and steroid requirement of prednisone <=10 mg/day or equivalent.
2. Patients currently participating and receiving study therapy or patients who participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks prior to the first dose of the study treatment.
3. Prior chemotherapy, targeted small molecule therapy or monoclonal antibodies within 4 weeks prior to the first dose of the study treatment.
4. Prior radiotherapy within 8 weeks prior to the first dose of the study treatment. The patient will be excluded from the study if the only targetable lesion has directly been treated with radiation therapy in the past with an exception for lesions that showed massive regrowth.
5. Prior surgery or ablative therapy within 4 weeks prior to the first dose of the study treatment. The patient will be excluded from the study if the only targetable lesion has directly been treated with ablative therapy in the past.
6. Ongoing adverse events > Grade 1 due to a previously administered therapy. Subjects with <= Grade 2 neuropathy, vitiligo, thyroid disorders, hypocortisolism or alopecia of any grade are an exception to this criterion and may qualify for the study.
7. History of other malignancies, except adequately treated and a cancer-related life-expectancy of more than 5 years.
8. Concurrent medical condition requiring the use of immunosuppressive medications, or immunosuppressive doses of systemic or absorbable topical corticosteroids; exceeding prednisolone 10 mg or equivalent.
9. Active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, high-dose corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
10. Active infection requiring systemic therapy.
11. History of (non-infectious) pneumonitis that required steroids or current pneumonitis.
12. Known history of active Tuberculosis.
13. Receipt of a live vaccine within 4 weeks prior to the first dose of the study treatment.
14. Hypersensitivity to any of the study drugs or their excipients.
15. Contra-indications to MR imaging (e.g. certain pacemakers). Contra-indications to gadolinium-based contrast agents are not an exclusion criterion, as a different brand of gadolinium can be used or if necessary the MRI can be performed without contrast.
16. Pregnancy or lactation.
17. Any other medical or social condition that, in the opinion of the Principal Investigator, might put the subject at risk of harm during the study or might

adversely affect the interpretation of the study data.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-07-2024
Enrollment:	24
Type:	Actual

Medical products/devices used

Generic name:	Sonalleve V2;MR-HIFU (Histotripsy configuration)
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	21-06-2024
Application type:	First submission
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
CCMO	NL85300.041.23