Phase I clinical study combining L19-IL2 with stereotactic ablative body radiotherapy in patients with oligometastatic solid tumor

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To determine the safety and tolerability of L19-IL2 combined with SABR.

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

Summary

ID

NL-OMON44415

Source
ToetsingOnline

Brief title
SABR and L19-IL2

Condition

- Other condition
- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory tract neoplasms

Synonym
oligometastatic, Solid tumors

Health condition

Solide tumoren

Research involving

Human

Sponsors and support

Primary sponsor: MAASTRO clinic
Source(s) of monetary or material Support: Philogen S.p.A.;MAASTRO,Philogen is een biotechnologische firma (keuzemogelijkheid functioneert niet)

Intervention

Keyword: L19-IL2, Oligometastasis, Phase I, SABR

Outcome measures

Primary outcome

Safety and Tolerability of the combination treatment (CTCAE4.03).

Secondary outcome

Progression-free survival, overall survival, local control rate, quality of

life (EORTC QLQ-C30 version 3.0 and QLQ-LC13 questionnaires).

Study description

Background summary

The formation of metastasis is responsible for as much as 90% of cancer-associated mortality. Numerous patients with locoregional disease of a solid tumor initially treated with curative intent develop (oligo)metastases during the course of disease. In both instances, these stage IV patients are generally considered to be incurable and mostly treated palliatively.

Oligometastases, defined as 1-5 sites of active disease on whole body imaging, was coined to refer to isolated sites of metastasis resembling limited tumor metastatic capacity. The implication of this concept is that local cancer treatments are curative in a proportion of patients with metastases (1) and that incorporating local therapy is a conceptually attractive approach (1, 2). In several, but not all, academic centers the standard treatment of patients with oligometastases in good general health is standard systemic therapy followed by surgery or by Stereotactic Ablative Body Radiotherapy (SABR) with radical dose on the macroscopic visible tumors.
The widespread introduction of SABR and of minimally invasive surgery has

fuelled research in treating patients with oligometastases (3-11). Indeed, local control of metastases can be obtained in virtually all parts of the body with a low proportion of patients experiencing severe side effects. In the few prospective studies published to date, approximately 20% of patients remained free of recurrence several years after treatment when all sites of disease were targeted by radiation.
Along with standard anti-cancer therapeutic modalities like chemotherapy and radiotherapy (RT), immunotherapy has recently gained a lot of attention. Angiogenesis is one of the hallmarks of cancer, and therefore, considerable efforts have been made to exploit this unique target for selective drug delivery. One of the appealing targets for both approaches is the splice variant of fibronectin containing extra domain B (EDB), which is abundantly expressed in vascular endothelial cells of a variety of primary tumors as well as metastases , but virtually absent in normal tissues (12-14). Recently, a human recombinant scFv fragment directed against EDB, designated L19, was developed (15) and subsequently combined with the pro-inflammatory interleukin-2 (IL2), resulting in the immunocytokine L19-IL2. L19-IL2 delivers high doses of IL2 to the (metastatic) tumor site(s) exploiting the selective expression of EDB on newly formed blood vessels. Interleukin-2 (IL2) plays an essential role in the activation phases of both specific and natural immune responses. Even though it has no direct cytotoxic effects on cancer cells, it can induce tumor regression by stimulating a potent cell-mediated response (16). In summary, L19-IL2 is an immunocytokine which will stimulate immune response specifically in tumors with angiogenesis and tissue remodeling.

Radiotherapy is a particularly interesting partner for immunotherapy, since it can be harnessed to specifically modify the immunogenicity of the primary tumors and their microenvironment, in the attempt to generate an in situ immunization of the host against a patient*s own cancer. Our overall hypothesis is that three independent therapeutic approaches will synergize to improve dramatically survival in patients with oligometastases of solid tumors.
The three hypotheses pursued are that combining L19-IL2 with SABR will lead to:
* Direct cytotoxic effect of SABR to all detected metastatic lesions;
* Immunogenic cell death induced by radiation creating an abscopal systemic effect of SABR thus eliminating micrometastases;
* Modification of tumor immunogenicity with L19-IL2 treatment (systemic).

Study objective

To determine the safety and tolerability of L19-IL2 combined with SABR.

Study design

This study includes patients who were diagnosed with metastasized cancer as well as patients who have developed metastases in the course of the disease (possibly after surgery of radiation).

(1) Information about the standard treatment will be given by the treating physician.

(2) The study treatment consists of the administration of L19-IL2, which starts one week after completion of the radiotherapy. L19-IL2 will be administered via an intervenous infusion on day 1, 3 and 5 of every cycly of 3 weeks (with a maximum of 6 courses in total). The dose of L19-IL2 will be increased in 3 steps from low dosage to high dosage.

L19-IL2 is administered on day 1, 3 and 5 of every cycle via an intravenous infusion during three hours. A cycle will take 3 weeks and in total, a patient can receive 6 cycles. The total treatment time therefore is 18 weeks maximum. For the L19-IL2 infusion, we advise to take 1000mg of paracetamol to prevent any possible flew-like complaints.

The first group of patients will be administered 15 Mio international units (IU) via infusion. If no dose limiting toxicities occur, the dosis will be increased to 22,5 Mio IU with a new group of patients. The dosage for an individual patient will remain identical during the maximum of 6 cycles.

Intervention

Intravenous treatment with L19-IL2 on day 1, 3 and 5 of every cycle of three weeks. To a maximum of six cycles.

Prior to start of radiation extra examinations:
* Bloodtest
* 18FDG-PET-CT scan (standard)

Prior to start of the intravenous treatment extra examinations:
* Bloodtest
* After 3 cycles of L19-IL2 and three months after the end of the last intravenous treatment every time an 18FDG-PET-CT scan. The data of these scans will probably in the future help selecting patients who benefit from the proposed study treatment.
* If additional consent was given: tissue sampling of the tumour or metastases. This shall prefarably take place before, during and after treatment. This examination will be focussed on the underlying reaction of the tumourtissue to the treatment in the laboratory. Depending on the localisation of the tumour/metastases, the treating physician will offer this examination and discuss with the patient how to approach this in a way the burden for the patient will be minimal.
* If addition consent was given: blood sampling at 5 moments during the study which will be stored at Biobank UM for immunological assessment.

Study burden and risks

Known/potential risks include: fever with chills, fatigue, nausea, vomiting, asthenia, (peripheral) edema, skin rash, hyperhydrosis, chest pain, pruritus, elevated serum creatinine levels and pain at tumor site. Signs of mild capillary leak syndrome and hypotension were found in the dose-limiting dosage level that is subsequently not studied here.

The (potential) benefit found in stage IV melanoma/renal cell carcinoma patients is a prolonged progression-free survival and possibly overall survival. However, these questions will be the subject of the possible subsequent phase II/III clinical studies combining L19-IL2 with SABR.

Furthermore there are the (small) risks of bloodwithdrawal and the intravenous administration. Also, patients will receive a higher level of radiation as a consequence of the extra scans.

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

-Histological or cytological confirmed oligometastatic originating from non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), colorectal cancer (CRC), renal cell carcinima (RCC) and melanoma occurring synchronous (at time of diagnosis) or metachronous (> 6 months after radical treatment for primary tumor; i.e., surgically). A biopsy could be omitted in selected cases if a biopsy is medically contraindicated or unfeasible (e.g. fear of entmetastasis, lesion not accessible). In this case the diagnosis of metastatic disease should be certified using an alternative approach (e.g. imaging,...);
-More diffuse metastasized NSCLC patients, with up to 10 metastasis that received standar of care primary chemotherapy with a platinum doublet for a maximum of 6 cycles are also allowed in case these patients showed at least disease control under this treatment (complete remission, partial respnse or stable disease according to RECIST1.1);
-All oligometastatic tumor sites (including brain) are eligible;
-* 5 metastases, or 4 if the primary tumor is to be treated concomitantly;
-* 3 metastatic lesions confined to one organ;
-* 2 organ systems affected with metastases;
-WHO performance status 0-2;
-Adequate bone marrow: Normal white blood cell count and formula, normal platelet count, no anemia requiring blood transfusion or erythropoietin;
-Adequate hepatic function: total bilirubin * 1.5 x upper limit of normal (ULN) for the institution; ALT, AST, and alkaline phosphatase * 2.5 x ULN for the institution);
-Adequate renal function: MDRD calculated creatinine clearance at least 60 ml/min;
-The patient is capable of complying with study procedures;
-Signed and dated written informed consent;
-Life expectancy of at least 12 weeks;
-For women of childbearing potential, a negative pregnancy test prior to the first dose of study treatment;
-Men and women with reproductive potential must be willing to practice acceptable methods of birth control during the study and for up to 12 weeks after the last dose of study medication.

Exclusion criteria

-Other oligometastatic (hormone-sensitive) solid tumors;
-Previous radiotherapy to an area that would be re-treated by SABR;
-Previous systemic treatment to treat recurrent disease;
-Other active malignancy or malignancy within the last 2 years (with exception of localized skin basal/squamous cell carcinoma, bladder in situ carcinoma);
-History of allergy to intravenously administered proteins/peptides/antibodies;
-HIV infection, active infection, or active hepatitis;
-Chronic use of corticosteroids used in the management of cancer or non-cancer-related illness;

-Acute or sub-acute coronary syndromes within the last year, acute inflammatory heart disease, heart insufficiency or irreversible cardiac arrhythmias;
- Impaired cardiac function defined as left ventricular ejection fraction (LVEF) <50% (or below the studý site's lower limit of normal) as measured by MUGA of echo. (LVEF measurements dating back up to 8 weeks will be acceptable in the absence of incurrent use of potentially cardiotoxic treatment or cardiac medical history);
- Uncontrolled hypertensive disease;
-History or evidence of active autoimmune disease;
-Severe diabetic retinopathy;
-Major trauma including surgery within 4 weeks prior to the first L19-IL2 infusion. Focal biopsies in the tumor are allowed;
-Any underlying medical or psychiatric condition which in the opinion of the investigator will make administration of study drug hazardous or hinder the interpretation of study results (e.g., AE);
-Unstable or serious concurrent uncontrolled medical conditions;
-Pregnancy or breast-feeding.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-12-2015
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	L19-IL2
Generic name:	L19-IL2

Ethics review

Approved WMO Date:	30-12-2014
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	27-05-2015
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	08-07-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-08-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	03-10-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-10-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2014-001955-22-NL
ClinicalTrials.gov	NCT02086721
CCMO	NL49389.068.14