A Phase 1, Open-Label, Dose-Escalation, Safety, Tolerability, and Preliminary Efficacy Study of MCLA-145 in Participants With Advanced or Metastatic Malignancies

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Primary:- To determine the safety, tolerability, and dose-limiting toxicities (DLTs) of MCLA-145 and to determine an MTD and/or the RDE in advanced or metastatic solid tumors or B-cell lymphomas.Secondary:- To explore preliminary antitumor activity...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON54744

Source
ToetsingOnline

Brief title
MCLA-145-CL01 study / M19MCL

Condition

- Other condition
- Lymphomas non-Hodgkin's B-cell

Synonym
Advanced or Metastatic Malignancies

Health condition

melanoma, head and neck squamous cell carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Merus N.V.
Source(s) of monetary or material Support: Incyte Biosciences;International Sàrl

Intervention

Keyword: Advanced Malignancies, MCLA-145, Metastatic Malignancies, Phase 1

Outcome measures

Primary outcome

Primary:

Safety and tolerability will be assessed by monitoring the frequency, duration, and severity of AEs. The RDE will be considered a dose that achieves a functional target engagement of PD-L1 and CD-137 based on PK, pharmacodynamic markers, and early signs of clinical activity.

Secondary outcome

Secondary:

• ORR, defined as the percentage of participants having a CR or PR as the best on-study response, will be determined by investigator assessment per RECIST v1.1 or Lugano Criteria

• DCR, defined as the percentage of participants having a CR, PR, or SD as the best on-study response, will be determined by investigator assessment per RECIST v1.1 or Lugano Criteria

• PFS is defined as the time from date of first dose of MCLA-145 until the earliest date of 1) radiographic PD (determined by investigator assessment per RECIST v 1.1 or Lugano Criteria), or 2) death due to any cause, if occurring

sooner than disease progression.

• DOR is defined as the time from earliest date of CR or PR until 1) the earliest date of radiographic PD (determined by investigator assessment per RECIST v1.1 or Lugano Criteria), or 2) death due to any cause, if occurring sooner than disease progression.

The PK of MCLA-145, including CEOI, Cmax, Tmax, Cmin, t*, AUC0-t, AUC0-inf, CL, and Vdss, will be summarized.

Immunogenicity is defined as the occurrence of specific ADA to MCLA-145.

Study description

Background summary

Open-label, non-randomized, dose-escalation study with expansion cohorts for dose confirmation/safety and preliminary efficacy. MCLA-145 will be administered intravenously as a flat dose over 2 hours every 14 days in 28-day cycles.

MCLA-145 is a drug that is considered an antibody. When a body*s immune system detects something harmful, it can produce antibodies. Antibodies are proteins that fight infection. Monoclonal antibodies are a specific type of antibody made in a laboratory. They can attach to other molecules or cells in your body and affect their function.

MCLA-145 interacts with proteins in your body called CD-137 (4-1BB) and Programmed death-ligand 1 (PD-L1). Your immune system includes a type of white blood cell called T-cells that have the ability to fight cancer. They are often stopped by the cancer cells and this allows the cancer to grow. MCLA-145 is designed to attach to the 4-1BB protein on these T-cells and has the potential to increase the number and enhance the function of your T-cells making them more able to fight your cancer. A mechanism some cancer cells use to hide from your body*s immune system is by taking control of what is called the PD-L1/PD-1 pathway. This pathway normally reduces the amount of

inflammation that the immune system produces. MCLA-145 is designed to block this pathway, allowing the immune system to recognize and attack the cancer cells. By simultaneously interacting with 4-1BB and PD-L1, this interaction may help the body*s immune system fight your cancer.

Study objective

Primary:
- To determine the safety, tolerability, and dose-limiting toxicities (DLTs) of MCLA-145 and to determine an MTD and/or the RDE in advanced or metastatic solid tumors or B-cell lymphomas.

Secondary:
- To explore preliminary antitumor activity of MCLA-145 in participants with advanced or metastatic solid tumors or B-cell lymphomas by assessing ORR, DCR, PFS, and DOR.
- To evaluate the PK of MCLA-145 when given as a single agent in advanced or metastatic solid tumors or B-cell lymphomas.
- To assess the immunogenicity of MCLA-145 when given as a single agent in advanced or metastatic solid tumors or B-cell lymphomas.

Exploratory:
- To evaluate the receptor modulation of MCLA-145 when given as a single agent.
- To characterize the effect of MCLA-145 on tumor and immune cell infiltrate biomarkers as predictive markers of MCLA-145 activity.
- To determine the 1-year OS of MCLA-145.
- To evaluate the clinical activity of MCLA-145 by assessing ORR, DCR, PFS, and DOR by iRECIST (in participants with solid tumors) or RECIL 2017 (in participants with B-cell lymphomas)

Study design

Up to 118 participants will be treated in Part 1 and Part 2, as follows:
• Part 1 will include approximately 38 participants across 10 dose levels (starting dose = 0.4 mg).
• Part 2 will include up to 80 participants in up to 2 dose levels. The dose levels will be determined based on safety, PK, pharmacodynamic activity, and preliminary efficacy in Part 1.
If there are tumor specific expansions, up to 40 participants per histology-specific cohort may be enrolled.

Intervention

This is an open-label, nonrandomized, Phase 1 study to determine the safety, tolerability, and preliminary efficacy of MCLA-145 in adult participants with advanced or metastatic solid tumors or B-cell lymphomas that will be conducted

in 2 parts, as follows:

Part 1:
Dose escalation to determine the MTD and/or RDE of MCLA-145 in participants with any advanced metastatic solid tumors or B-cell lymphomas, regardless of PD-L1 expression. During dose escalation, cohorts of participants will be treated with MCLA-145 until the MTD is reached or a lower recommended dose(s) is established. The dose escalation will be guided by an adaptive BLRM following the escalation with overdose control principle.
* A maximum of 5 participants with a given tumor type may be enrolled across all dose levels in Part 1, unless the medical monitor approves additional enrollment in that tumor type.

Part 2:
Dose expansion to confirm the dose of MCLA-145 through further evaluation of safety, tolerability, PK, preliminary antitumor activity, and functional target engagement.
* Participants with the following advanced or metastatic tumors, regardless of PD-L1 expression, may be enrolled:
* Anti-PD-1 therapy relapsed or refractory melanoma.
* Anti-PD-1 therapy relapsed or refractory HNSCC.
* Anti-PD-1 therapy relapsed or refractory urothelial carcinoma.
* Immunotherapy-naive TNBC.
* Any tumor histology from Part 1 for which preliminary efficacy was observed with MCLA-145.
* Up to 2 confirmatory dose levels may be explored. Confirmatory dose levels will be selected based on PK, antitumor and pharmacodynamic activity including receptor modulation, safety, and tolerability.

Study burden and risks

All medicinal products can have side effects. The side effects in humans are not known. Even if previous animal studies have shown that Study Drug was well-tolerated when tested and did not show any adverse effects related to a specific organ system, the subject may still experience side effects. These may go away after the Study Drug is stopped, but in rare cases they may be serious, long lasting, and/or permanent and may even cause death.

a. Side effects
Study Drug works through the immune system; therefore, possible symptoms or adverse effects that could occur may be immune-related effects such as
• inflammation of the skin or mucosa (e.g., itching, redness, rash)
• inflammation of the lungs (e.g. cough)
• inflammation of the bowels (e.g., diarrhea).
• endocrine (hormone) dysfunction
• liver injury

• fatigue or lack of energy.

Although adverse effects related to immunotherapies are generally mild and reversible, serious immune-related adverse effects do occur.

Reactions to the Study Drug infusion could also occur. Possible reactions include
• nausea
• vomiting
• abdominal pain
• headache
• low blood pressure
• fever
• tremor
• allergic reactions

b. Discomforts related to biopsy, bone marrow biopsy and/or aspirate, Computed Tomography (CT)-scan, Magnetic Resonance Imaging (MRI)-scan, Positron Emission Tomography (PET)/CT scan, Electrocardiogram: for more details see appendix D Informed Consent Form.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Participants with melanoma, head and neck squamous cell carcinoma (HNSCC), urothelial carcinoma, NSCLC, MSI-H/dMMR tumors, or triple negative breast cancer (TNBC)
- Tumor should histologically or cytologically confirmed

See protocol for more detailed criteria.

Exclusion criteria

- The following B-cell neoplasms: Burkitt lymphoma, lymphoblastic leukemia/lymphoma, lymphoplasmacytic lymphoma, chronic lymphocytic leukemia
- Prior therapy containing a 4-1BB agonist or prior therapy with CAR T-cell therapy.

See protocol for more detailed criteria.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	21-04-2022
Enrollment:	10

Type:	Actual

Ethics review

Approved WMO Date:	02-07-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	15-10-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-10-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-11-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-06-2022
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	23-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	27-06-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-07-2024
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
EudraCT	EUCTR2018-004396-13-NL
ClinicalTrials.gov	NCT03922204
CCMO	NL72327.031.20