A phase 1, first-in-human, multicenter, open-label, dose-escalation study to characterize the safety and tolerability of MP0317 in patients with relapsed/refractory advanced solid tumors

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Primary Objectives:• To determine the Recommended Dose of Expanion or the MTD for MP0317 as monotherapy in patients with advanced solid tumors (dose-escalation part only)• To characterize the safety and tolerability of MP0317 as monotherapy in...

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

Summary

ID

NL-OMON51895

Source
ToetsingOnline

Brief title
MP0317-CP101

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Solid tumors / cancer

Research involving
Human

Sponsors and support

Primary sponsor: Molecular Partners AG
Source(s) of monetary or material Support: Molecular Partners

Intervention

Keyword: CD40xFAP, DARPin, MP0317, Relapsed/refractory solid tumors

Outcome measures

Primary outcome

• Incidence of dose-limiting toxicities (DLTs)

• Type, incidence and severity of adverse events (AEs) and serious adverse events (SAEs) according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0

• Changes between screening and post-screening laboratory parameters and vital signs

Secondary outcome

Secundary endpoints:

• Serum concentration-time profiles following first and repeated MP0317 infusions

• Determination of PK parameters including (but not limited to) maximum serum concentration (Cmax), time to Cmax (Tmax), minimal serum concentration (Cmin), area under the curve (AUC), total clearance (CL), volume of distribution at steady state (Vss) and half-life (t1/2)

• Overall response rate (ORR) based on best overall response (BOR) of complete response (CR) and partial response (PR) locally assessed using Response

Evaluation Criteria in Solid Tumors (RECIST) v1.1 and iRECIST

• Disease control rate (DCR) of CR, PR or stable disease (SD) lasting 4 or more weeks following the initiation of MP0317

• Duration of response (DOR) of CR or PR based on RECIST v1.1 and iRECIST, time to progression (TTP) following the initiation of MP0317

• Progression-free survival (PFS) based on RECIST v1.1 and iRECIST

• Overall survival (OS)

Exploratory endpoints:

• Changes in frequency and functionality of B cells, dendritic cells (DC), macrophages and T cell subsets in peripheral blood and tissue biopsies

• Assess FAP and CD40 expression and co-localization with MP0317 in tissue biopsies

• Changes in cytokines in serum

• Changes in soluble FAP (sFAP) and soluble CD40 (sCD40) in serum

• Circulating tumor DNA (ctDNA) (safety expansion part only)

• Occurrence of anti-drug antibodies (ADAs)

• Incidence, titer and time-course of ADAs

Study description

Background summary

There is a clear need for a significant improvement to cancer immunotherapy. Introduction of immune checkpoint inhibitors to cancer therapy has demonstrated the potential of enhancing antitumor immunity to improve patient outcome but has also shown that checkpoint inhibition alone is ineffective in many cases.

CD40 agonism has potential to improve cancer immunotherapy but agonist molecules evaluated to-date have had disappointing efficacy due to extratumoral CD40 activation and resultant dose-limiting peripheral immunotoxicities.

In the Sponsor*s opinion, this could be overcome by strict targeting of CD40 agonistic activity to the tumor - as intended with MP0317. MP0317 (FAPxCD40) is a tri-specific FAP-targeting DARPin® molecule designed to combine high potency for CD40 activation with tumor-targeting and tumor-restricted receptor engagement and immune cell activation. By localizing and restricting the agonistic effect of CD40 to the tumor site, MP0317 is expected to limit the risk of potential systemic side effects (such as cytokine release syndrome [CRS]) and to increase the therapeutic window of CD40 activation.

The tumor types selected for the proposed phase 1 monotherapy study represent good benefit/risk potential for clinical study explorations. Firstly, the advanced solid tumor types are known to express medium to high levels of FAP and secondly, study patients with the selected tumor types are those for whom approved therapies have been exhausted or who are ineligible or unable to tolerate other treatments.

Due to the expected markedly higher level of FAP in tumors than in healthy tissues, the FAP-targeted CD40 agonist MP0317 is expected to have a better safety profile, in particular with respect to CRS and liver toxicity, than the untargeted CD40 agonist monoclonal antibodies that are currently in clinical development.

Future clinical development will focus on MP0317 in combination with other treatment modalities (e.g. checkpoint inhibitors, chemotherapy, radiation therapy).

Study objective

Primary Objectives:
• To determine the Recommended Dose of Expanion or the MTD for MP0317 as monotherapy in patients with advanced solid tumors (dose-escalation part only)
• To characterize the safety and tolerability of MP0317 as monotherapy in patients with advanced solid tumors

Secondary Objectives:
• To describe the PK of MP0317 as monotherapy in patients with advanced solid tumors
• To evaluate preliminary antitumor activity of MP0317 as monotherapy in patients with advanced solid tumors
• To evaluate preliminary clinical benefit of MP0317 as monotherapy in patients with advanced solid tumors

Exploraty Objective:

• To evaluate pharmacodynamic effects of MP0317 as monotherapy in peripheral blood and tissue in patients with advanced solid tumors
• To evaluate the immunogenicity of MP0317 as monotherapy in patients with advanced solid tumors

Study design

This is a phase I, first in human, multi-center, open-label, dose-escalation study, followed by a safety expansion part to evaluate the safety, tolerability, PK, pharmacodynamics and preliminary antitumor activity of study medication MP0317 in adult subjects with advanced solid tumors.

The dose-escalation part is designed to determine the recommended dose for expansion (RDE) or maximum tolerated dose (MTD) for MP0317 mono-therapy. The safety expansion part is designed to confirm safety in a larger population. The dose-escalation scheme will use an adaptive study design following a Bayesian Logistic Regression Model (BLRM). A dose-escalation review committee (DERC) will monitor safety and govern all cohort dosing decisions.
The sponsor in consultation with the DERC may advise on the opening of cohorts with alternative dosing schedules (e.g. every week; q1w). Such additional cohorts may be opened concurrently with the initial dosing schedule cohorts, during dose escalation as well as during safety expansion phase.

Once the RDE (or MTD) has been determined, the safety expansion cohort(s) will be opened and up to 15 additional patients will be treated with MP0317 monotherapy at this dose.

The first doses between the first two patients in any cohort must be separated by a minimum of 7 days.

Study treatment will be administered until progressive disease (PD), unacceptable toxicity, withdrawal of consent or other reasons to discontinue treatment occur, whichever comes first. Treatment beyond PD will be allowed as per Immunotherapy Response Evaluation Criteria in Solid Tumors (iRECIST).

Paired (pre and on/post-treatment) tumor and skin biopsies will be mandatory for all subjects.
Biomarkers that may potentially correlate with antitumor activity or immunomodulatory effects of MP0317 may be explored during the study.

Intervention

For each subject, the assigned dose of MP0317 will be based on the available cohort as recommended by the dose escalation review committee (DERC).
For the dose-escalation study part on q3w schedule, the starting dose is 0.03 mg/kg q3w and up to 6 q3w dose levels are planned. A treatment cycle will last

3 weeks (21 days), with DLT evaluation period of 4 weeks after first study drug administration.
The doses to be evaluated on a q1w schedule in the dose-escalation part starts with 0,50 mg/kg q1w and up to 3 q1w dose levels are planned.

The IMP is provided in 10 mL vials at a nomial concentration of 15 mg/mL.
The IV solution stabilizer (IVSS) is supplied in identical vials, but with differently colored flip-off caps.
Both solutions are stored at -20 °C ± 5 °C.

The prepared IMP is administered as IV solution.
The infusion duration should be at least 50 minutes and no longer than 2 hours.
Subjects who receive the IMP will remain under observation for at least 24 hours after their first and secnd IMP administration.
After the third to fifth cycle, subjects should remain under medical supervision for at least 4 hours, and from the sixth cycle onward for at least 1 hour.

Study burden and risks

The study population consists of cancer patients with advanced solid tumors, which have been known to express medium to high levels of FAP and for whom approved therapies have been exhausted or who are ineligible or unable to tolerate other treatments.

Due to the expected markedly higher level of FAP in tumors than in healthy tissues, the FAP-targeted CD40 agonist MP0317 is expected to have a better safety profile, in particular with respect to CRS and liver toxicity, than the untargeted CD40 agonist monoclonal antibodies that are currently in clinical development.

MP0317 will be administered as an IV solution.
The effect of MP0317 on humans is unknown. MP0317 may cause side effects.
Side effects with other similar drugs and therefore, potential risks from MP0317 to patients include:
• Reactions to the infusion (infusion related reactions), occurring during or shortly after the infusion, including hypersensitivity (allergic) reactions.
• Late onset hypersensitivity (allergic) reactions manifesting as rash accompanied by joint or body pain, starting 10-20 days after receiving the drug
• Cytokine release syndrome is a form of systemic inflammatory response to immunotherapy treatment.
• Tumor lysis syndrome
• Liver toxicity
• Autoimmune diseases

Risks related to study procedures:

Blood draws can cause pain, bruising, inflammation and swelling of the vein, bleeding or even an infection at the puncture site.

MUGA: The radioactive agent will stay in the subject's blood for several hours but will not interact with body tissues. The agent is passed out of the body through the urine usually within 24 hours after the test is completed. The radioactive agent used during the MUGA scan is a diagnostic dose.

ECG: Skin reactions to the sticky pads may occur, such as redness, itching or discomfort. Some hair loss may be associated with the glue at the placement sites of the ECG pads.

CT scan: This is normally painless but is performed in a tunnel which may the subject feel uncomfortable, especially if suffering from claustrophobia. If a contrast agent is used for the imaging procedure, allergic reactions and infusion related side effects may be observed.

MRI scan. This is normally painless but is performed in a tunnel which may feel uncomfortable, especially if suffering from claustrophobia. Certain people with metal inside their body cannot have this scan, including those with pacemakers and cardiac defibrillators, joint replacements, heart and vessel coils and others. Pregnant women should not have an MRI during their first trimester unless they absolutely need the test. The first trimester is when the child's organs develop. Subjects also should not receive contrast agent if they have had an allergic reaction to it in the past or if the subject has severe kidney disease.

Tumor biopsy. During and after the tumor biopsy procedure, the subject may have mild pain, bruising and bleeding at the biopsy site. Occasionally these complications are significant.

Skin biopsy. During and after the skin biopsy procedure, the subject may feel a sting transiently. After the procedure, a suture or dressing may be applied to the site of the biopsy.

The following procedures are performed:
- Physical examination - at screening and pre-dose at each cycle;
- Vital signs measurement and pulse oximetry - at screening, 11x at cycle 1, 7x at cycle 2 - 5 and 4x at cycle 6 and further;
- ECG - at screening, 3x at cycle 1 - 2 and 1x at cycle 3 and further;
- Blood draws (local safety lab, including urinalysis, PKs, immunogenicity, biomarkers) - screening, 9x at cycle 1, 5x at cycle 2 - 5 and 2x at cycle 6 and further;
- Pregnancy test (for women of childbearing potential only): at screening and at the pre-dose at each cycle;
- Skin biopsy - 1x at screening, 1x 3 days after screening, 1x at cycle 1 day 5 and 1x at cycle 1 day 8;

- Tumor biopsy - 1x at screening, 1x at cycle 2 day 8 and, optional, 1x at time of progressive disease or response.

The amount of blood drawn during each cycle study arm A:
Cycle 1 148 mL
Cycle 2 124 mL
Cycle 3 71 mL
Cycle 4 89 mL
Cycle 5 65 mL
Cycle 6 25 mL
Cycle 7 and following cycles 28 mL
Follow-up visit 52 mL
If an immune reaction occurs 10 mL

The amount of blood drawn during each cycle study arm B:
Cycle 1 160 mL
Cycle 2 123 mL
Cycle 3 43 mL
Cycle 4 82 mL
Cycle 5 37 mL
Cycle 6 53 mL
Cycle 7 and following cycles 29 mL
Follow-up visit 52 mL
If an immune reaction occurs 10 mL

Contacts

Public
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Scientific
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CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Has an advanced, histologically-proven solid tumor of one of the following types, and for which approved therapies have been exhausted or for which the Investigator considers the patient ineligible or unable to tolerate other treatments:
a. Colorectal cancer
b. Ovarian cancer
c. Endometrial cancer
d. Gastric cancer
e. Pancreatic cancer
f. Anal cancer
g. Cervical cancer
h. Head and neck squamous cell carcinoma (HNSCC)
i. Mesothelioma
j. Prostate cancer
k. Non-small cell lung cancer (NSCLC)
l. Melanoma
m.Urothelial/bladder cancer
n. Microsatellite instability high cancer of any type
o. Cutaneous squamous cell cancer
p. Breast cancer
2. >= 18 years of age on the day of signing informed consent
3. Has signed and dated written informed consent before performing any study procedure, including screening
4. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 1
5. Anticipated life expectancy >= 12 weeks by Investigator judgement
6. Measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
7. Should agree to undergo mandatory paired (pre and on-treatment) tumor biopsies and be considered to have biopsiable disease. The biopsies should be performed as follows:
a. At least 1 tumor lesion >= 20 mm amenable to percutaneous biopsy other than the target lesion(s) used to follow response as defined by RECIST v1.1.

b. For cutaneous or subcutaneous lesions, tumors should be >= 5 mm in diameter amenable to biopsy by excisional or punch biopsies without unacceptable risk of a major procedural complication.
c. For core needle biopsy specimens, at least 3 to 6 cores with an 18-gauge needle should be collected.
d. The on-treatment tumor biopsy should be taken from the same lesion as the pre-treatment biopsy. The biopsied lesion should be large enough to take both biopsies >= 1 cm apart.
8. Should agree to undergo mandatory paired (pre and on-treatment) skin biopsies
9. At least 28 days must have elapsed between any prior major surgery and screening. The following procedures are not considered major:
a. Obtaining the pre-treatment tumor and skin biopsies as per protocol requirements
b. Placement of a port for central venous access
c. Needle, punch or excisional biopsy of a clinically or radiographically detected lesion
10. Laboratory parameters at screening:
a. Hematology:
i. Platelet count >= 100,000 cells/mm3
ii. Absolute neutrophil count >= 1,000 cells/mm3
iii. Hemoglobin >= 9 g/dL
b. Serum creatinine < 1.5 x upper limit of normal (ULN) or creatinine clearance > 50 mL/min on the basis of Cockcroft-Gault glomerular filtration rate estimation
c. Coagulation:
i. International normalized ratio (INR) < 1.5
ii. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) <= 1.5 x ULN unless therapeutically warranted
d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 x ULN
e. Bilirubin normal, except for patients with known familial hyperbilirubinemia (such as Gilbert syndrome); for patients with documented Gilbert*s syndrome (Gilbert-Meulengracht syndrome) total bilirubin <= 3 x ULN is acceptable
f. Albumin > 2.8 g/dL or > 28 g/L, and without albumin transfusion for >= 7 days before screening
11. Is using highly effective contraception, for female of childbearing potential (FCBP) and for men, as follows:
a. Female: Is not pregnant, is not breastfeeding, and one of the following applies:
- Not a FCBP
- A FCBP who agrees and/or whose male partner agrees to follow the contraceptive guidance from screening, during the treatment period, and for at least 3 months after the last study drug administration. A FCBP must have a negative serum pregnancy test result at screening.
b. Male: Agreement to use a highly effective contraception method from

screening, during the treatment period, and for at least 3 months after the last study drug administration and to refrain from donating sperm during this period.

Exclusion criteria

1. Known hypersensitivity to excipients used in the MP0317 formulation
2. Autoimmune diseases, except autoimmune endocrinopathies that are stable with hormone replacement therapy
3. Inflammatory diseases such as arthritis, colitis, liver fibrosis, cirrhosis, interstitial fibrosis or chronic obstructive pulmonary disease (COPD) that may have elevated tissue fibroblast activation protein (FAP) expression unless approved after consultation with the Sponsor.
4. Serious illness or concomitant non-oncological disease considered by the Investigator to be incompatible with participating in the protocol
5. Left ventricular ejection fraction of < 50% on echocardiographic exam or multi-gated acquisition (MUGA) scan at screening
6. History or evidence of clinically significant cardiovascular disease defined as at least one of the following criteria:
a. Evidence of poorly controlled arterial hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg)
b. Myocardial infarction or instable angina pectoris within 6 months before screening
c. Heart failure (New York Heart Association Class III or IV)
d. Any cardiac arrhythmia that is not well controlled
e. QT corrected (QTc) prolongation >= Grade 2 (> 480 ms) at screening measured on 2 separate electrocardiograms (ECG) at least 10 minutes apart
f. Clinically significant valvular heart disease
7. Severe dyspnea, pulmonary dysfunction or need for continuous supportive oxygen inhalation
8. Arterial thromboembolic event, stroke or transient ischemia attack within 12 months before screening
9. Known central CNS metastases that are either untreated or are treated but are associated with clinical symptoms (e.g. headache, convulsions); patients with CNS metastasis that have been treated with radiotherapy and/or surgery are eligible if they are clinically without symptoms for at least 6 weeks before screening; if under treatment with corticosteroids (not exceeding 10 mg/day prednisone or equivalent) and/or anticonvulsive agents, patients must be on a stable dose for at least 14 days before first study drug administration.
10. Active uncontrolled bleeding or a bleeding diathesis
11. Therapy for active infection needs to be completed at least 7 days before first study drug administration
12. Known positivity for human immunodeficiency virus (HIV) or history of HIV (HIV testing is not mandatory)
13. Active hepatitis B (chronic or acute; HBV) defined as having a positive

hepatitis B surface antigen (HBsAg) test at screening. Patients with past or resolved HBV infection (defined as having a negative HBsAg test and a positive hepatitis B core antigen antibody test) are eligible.
14. Active hepatitis C (HCV) infection defined as having a positive HCV antibody test followed by a positive HCV ribonucleic acid (RNA) test at screening. The HCV RNA test will be performed only for patients who have a positive HCV antibody test. Patients who are positive for HCV antibodies are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
15. Serious or non-healing wound, skin ulcer or non-healing bone fracture
16. Abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 6 months before screening
17. Any vaccines within 28 days before first study drug administration
18. An allogenic tissue/solid organ transplant
19. History of another primary malignancy except for:
a. Malignancy treated with curative intent and with no known active disease >= 2 years before screening and of relatively low potential risk for recurrence
b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of residual disease
c. Adequately treated carcinoma in situ without evidence of disease
d. Cancer patients with incidental histologic findings of prostate cancer that, in the opinion of the Investigator, is not deemed to require active therapy (e.g. incidental prostate cancer identified following cystoprostatectomy that is tumor/node/metastasis Stage <= pT2N0) may be eligible, pending discussion and approval by the Sponsor
20. Previous treatment with a DARPin® molecule
21. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study, or it is the follow-up period of an interventional study
22. Use of an investigational agent within 28 days before first study drug administration
23. Any anticancer treatment, including chemotherapy, hormonal therapy or radiotherapy, within 21 days before first study drug administration; however, the following are allowed:
a. Hormonal therapy with gonadotropin-releasing hormone (GnRH) agonists or antagonists
b. Hormone-replacement therapy or oral contraceptives
c. Palliative radiotherapy for bone metastases within 14 days before first study drug administration
24. Continuous corticosteroid use exceeding 10 mg/day prednisone or equivalent
25. Any condition that, in the opinion of the Investigator, would interfere with evaluation of the investigational medicinal product (IMP) or interpretation of the patient*s data
26. Unable or unwilling to comply with all study requirements for clinical visits, examinations, tests and procedures
27. Patient deprived of liberty by a judicial or administrative decision, patient admitted to a social institution or who is under a measure of legal protection, patient hospitalized without consent or who is in an emergency

situation

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):	27-01-2022
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MP0317
Generic name:	MP0317

Ethics review

Approved WMO

Date:	22-06-2021
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	01-09-2021
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	27-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-06-2022
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	EUCTR2020-005516-22-NL
ClinicalTrials.gov	NCT05098405
CCMO	NL75998.031.21