A modular, multi-arm, multi-part, first time in patient study to evaluate the safety and tolerability of OMO-1, alone and in combination with anti-cancer treatments, in patients with locally advanced, unresectable or metastatic solid malignancies

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Core:Core Primary Objective:* To investigate the safety and tolerability of OMO-1 when given orally to patients with locally advanced, unresectable or metastatic solid malignancies, alone or in combination with anti-cancer treatments, and define the...

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

Summary

ID

NL-OMON48960

Source
ToetsingOnline

Brief title
OMO1.01.02

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym

Cancer, Malignancy

Research involving
Human

Sponsors and support

Primary sponsor: OCTIMET Oncology NV
Source(s) of monetary or material Support: Octimet Oncology NV

Intervention

Keyword: OMO-1, OMO1.01.02, solid malignancies

Outcome measures

Primary outcome

Module 1:

* Objective response rate (ORR) by RECIST 1.1 - the proportion of patients with a confirmed* reduction in tumour burden of a predefined amount (this will include short lived responses).

* Time to response.

* Percentage change in tumour size: Percentage change in tumour size will be determined for patients with measurable disease at baseline and is derived at each visit by the percentage change from baseline in the sum of the diameters of target lesions (TLs). The best percentage change in tumour size will be the patient*s value representing the largest decrease (or smallest increase) from baseline in tumour size.

* Clinical benefit rate.

* Overall survival.

* Durable response rate (DRR) - a partial (PR)** or complete response (CR)+ lasting a specific length of time.

* Durability of response (DoR) - the time from documentation of tumour response to disease progression.

* Assessment of stabilisation of disease, using waterfall plots. DRR will be combined with SD to produce a disease control rate (DCR).

* Progression free survival (PFS) will be assessed, where applicable, but is unlikely to be mature enough to enable it to be used in decision making at the time of Proof of Concept (PoC). This and other *regulatory endpoints* will be formally explored in the Phase 2/3 studies.

* TTP

*CR or PR may be claimed only if the criteria for each are met at a subsequent time point (generally 4 weeks later).

**At least a 30% decrease in the sum of diameters of TLs.

+Disappearance of all TLs.

Secondary outcome

Pharmacokinetic (PK) parameters: Module 1: Parameters such as the following may be assessed:

* Maximum concentration (Cmax)

* Trough concentration (Ctrough)

* Area under the curve (time zero to infinity) (AUC*)

* Area under the curve (time to last measurable concentration) (AUC0-last)

* Apparent volume of distribution (Vd)

* Clearance

* Elimination half-life (t*)

* Time at which the Cmax is observed (Tmax)

Module 2: Parameters such as those listed above for Module 1 may be assessed for both OMO-1 and any combination EGFR-TKI.

Pharmacodynamic (PDc) parameters: Parameters such as the following may be assessed:

* Plasma Kynurenine/tryptophan ratio
* Blood neutrophil-to-lymphocyte ratio (NLR)/platelet-to-lymphocyte ratio (PLR)/systemic immune inflammation (SIII) (derived from haematology results)
* MET amp/mut cftDNA (for all MET+ patients) (Module 1 only)
* MET amp cftDNA (Module 2 only)
* EGFR amp/mut cftDNA (Module 2 only)
* HGF plasma
* Creatinine serum
* Blood Immunophenotyping including cMET (+cMET)
* ShedMET plasma
* % Phospho MET positive tumour cells
* % Phospho EGFR positive tumour cells (Module 2 only)
* Phenotypic proliferation biomarkers (e.g. Ki67)
* Phenotypic Apoptosis biomarker (e.g. cleaved caspase)
* % pERK positive tumour cells
* % pAKT positive tumour cells
* % pGAB2 positive tumour cells
* TILs
* Immune oncology biomarker panel (e.g. Nanostring Pan Cancer Immune Panel)

Safety parameters: Module 1 and Module 2: Physical examination and

ophthalmological examination, vital signs; 12-lead electrocardiogram (ECG);

pregnancy test; haematology; coagulation; clinical chemistry; serum renal

markers; urinalysis; urine renal markers; tumour markers; ECOG performance

status; DLT; adverse events (AEs).

Study description

Background summary

This study is the first study of OMO-1 in patients with solid tumour cancer. It is sponsored by OCTIMET Oncology NV, a biotechnology company, developing drugs to treat cancer.
The purpose of this study is to find out the tolerability, safety and potential benefits of OMO-1 in patients who have solid tumour cancer. It will help to get more knowledge about how OMO-1 affects the human body, and which dose is able to treat cancer and has an acceptable side effect profile
The study drug is called OMO-1. It is a small chemical that stops the activity of the MET receptor tyrosine kinase, a protein that causes tumour growth which is present in solid tumour cancer.
The MET gene has been shown to be responsible for some hereditary types of cancer. In addition, inappropriate MET activation has been shown in most types of solid tumours, often correlating with poor prognosis (Maulik 2002; Peruzzi 2006). The role of MET signalling in cancer stem cells is also a field of increasing interest since it is known that the MET pathway has been found to play a crucial role in the field of stem cell biology. In addition, it has recently been proposed that invasive growth, such as that regulated by MET, is a characteristic feature of stem cells as well as progenitor cells and may be usurped by cancer stem cells (Boccaccio 2006). We assume that MET inhibition may be a route to targeting cancer stem cells thereby offering a potential for cure.

Study objective

Core:
Core Primary Objective:
* To investigate the safety and tolerability of OMO-1 when given orally to patients with locally advanced, unresectable or metastatic solid malignancies, alone or in combination with anti-cancer treatments, and define the doses and schedules for further clinical evaluation
Core Secondary Objectives:
* To characterise the PK and pharmacodynamics (PDc) of OMO 1, following a

single dose and/or at steady state after multiple dosing, when given orally alone or in combination with anti-cancer treatments.
* To assess the preliminary efficacy of OMO-1 by Response Evaluation Criteria In Solid Tumours (RECIST) 1.1. locally*.
*Note: Scans will also be collected for potential future central review.
Core Exploratory Objectives:
* To explore the relationship between dose and PK, efficacy, safety, and/or blood borne and tissue biomarkers.
* To collect and store an optional pre-dose plasma and serum sample and/or analyse blood or tissue including patient specific archival tumour tissue, if available, for potential future exploratory research into factors that may influence the development of agents to treat human disease and/or response to OMO 1 (where response is defined broadly to include efficacy, tolerability or safety). This may include the analysis of tumour specific and circulating biomarkers, such as tumour deoxyribonucleic acid (DNA), messenger ribonucleic acid (mRNA), proteins or metabolites. In the event that additional tumour molecular profiling is required to understand further any response to OMO 1, a sample of the most recent tumour biopsy for additional research may be requested.
* To collect and store pharmacogenetics (PGx) samples, for potential future exploratory research into factors that may influence the development of agents to treat human disease and/or response to OMO 1 (where response is defined broadly to include efficacy, tolerability or safety).
* To collect and store plasma circulating free tumour DNA (cftDNA) for future exploratory research into genes/genetic variation that may influence response (i.e., distribution, safety, tolerability and efficacy) to OMO 1 treatment.
* To investigate predictive markers and acquired resistance to OMO-1 that may be observed in tumour or cftDNA from patients treated with OMO-1.
* To investigate the per-patient concordance between potential patient selection biomarkers (and/or other molecular aberrations) and PDc biomarkers as determined either by OCTIMET Oncology NV or local test methods, in comparison to potential patient selection biomarkers and PDc biomarkers levels obtained by central laboratory tests.
In addition to the core objectives, module specific objectives include:
Module 1:
Primary Objectives:
* Parts A and B: To assess the safety and tolerability of OMO-1 when given alone in patients with locally advanced, unresectable or metastatic solid malignancies.
* Part B: To assess the preliminary efficacy of OMO-1 given orally as a single agent in patients with selected locally advanced, unresectable or metastatic solid malignancies.
Secondary Objectives:
* Part A: To determine the recommended dose and schedule of OMO-1 to take forward into Part B of the study module.
* Part A: To determine the dose(s) and schedule(s) of OMO-1 with which to begin to explore dose escalation of OMO-1 in combination with anti-cancer agents in

further study modules.
* Part B: To refine the choice of tumour indications for controlled Phase 2 trial(s).
Exploratory Objectives:
* To assess the effects of modulation of mesenchymal-epithelial transition (MET)/organic cation transporter 2 (OCT 2) pathways signalling in surrogate and/or tumour tissue, including but not limited to hepatocyte growth factor (HGF) protein levels, phosphorylated MET (pMET), shedMET, total MET (tMET), phosphorylated extracellular regulated kinase (pERK), phosphorylated GAB2 (pGAB2), immune-phenotype, tumour infiltrating lymphocyte (TIL) population.
* To assess the effects of dual modulation of OCT 2 and MET, including but not limited to the measurement of the plasma levels of tryptophan and kynurenine and serum creatinine.
* To measure tumour cell response biomarkers, including but not restricted to markers of cell proliferation and apoptosis.
Module 2
Primary Objectives:
* Parts A and B: To assess the safety and tolerability of OMO-1 when given in combination with a small molecule EGFR-TKI in patients who have MET amplified tumours and whose disease is progressing on current EGFR TKI treatment.
* Part B: To assess the preliminary evidence of efficacy activity of OMO-1 when given in combination with a small molecule EGFR-TKI in patients who have MET amplified tumours and whose disease is progressing on current EGFR TKI treatment.
Secondary Objective:
* Part A: To determine the recommended dose and schedule of OMO-1 to take forward into Part B of the study module.
Exploratory Objectives:
* To assess the effects of modulation of MET pathway signalling in surrogate and/or tumour tissue, including but not limited to HGF protein levels, pMET, pERK, pGAB2, immune-phenotype, TIL population.
* To measure tumour cell response biomarkers, including but not restricted to markers of cell proliferation and apoptosis.

Study design

This is a modular, first time in patient, open-label, multicentre study of OMO-1, administered orally, alone and in combination with anti-cancer treatments, in patients with locally advanced, unresectable or metastatic solid malignancies.
The study will consist of a number of study modules * the first of which is Module 1. Module 2 follows subsequent to the initiation of Module 1.
Study modules will consist of a Part A (dose finding) and an optional Part B (cohort expansion). The option to start Part B and add further modules will be the decision of the SRC, based on emerging preclinical anti-tumour data and, safety and tolerability information from the study as a whole.
The initial dosing schedule and/or sequence of OMO-1 in each module may be

subsequently changed between patient cohorts in response to emerging safety, PK and PDc findings. The maximum tolerated dose (MTD) of OMO-1 for individual modules may therefore differ based on the emerging safety profile for each combination.
Once a MBAD of OMO-1 for a module has been identified from Part A of that module, the SRC may decide to commence Part B. The optional Part B will include approximately 30 patients and a maximum of 40 patients in specific patient groups to explore preliminary efficacy or the effect of food or particular drug combinations on drug PK. Single arm cohorts would provide reasonable estimation of safety and efficacy against a well-defined background knowledge of the class effect of cMET inhibitors.
For all modules, Parts A or B may be expanded by additional paired biopsy sub-groups (sequential biopsy cohorts) of up to 12 additional patients at doses (at or above the MBAD) that have been confirmed to be tolerated. These patients will have mandatory serial biopsies to assess the tumour for relevant PDc biomarkers, and to explore further the tolerability, safety and PK activity at these doses.
In all combination modules, the dose of each combination agent investigated will not exceed their current recommended dose. The starting dose of OMO-1 in combination modules will be one dose level below the recommended Phase 2 dose (RP2D) in Module 1 (monotherapy). For cohorts in which OMO-1 is dosed in combination with cytotoxic chemotherapy, dosing of OMO-1 will discontinue once the course of chemotherapy has been completed.
Module 1:
Module 1 will consist of Part A which will assess the safety and tolerability of multiple ascending doses of OMO-1 given as monotherapy in patients with locally advanced, unresectable or metastatic malignancy, providing a starting dose(s) and schedule(s) for the initiation of further modules. An optional Part B will assess preliminary signs of monotherapy efficacy activity of OMO-1. If eligible (e.g. having disease measurable according to RECIST 1.1), these patients will be included within the clinical response assessment for Part A.
Dose-escalation within Part A will commence at a dose level (Cohort 1) of 100 mg BD taken with food; with 4-5 hours between the OMO-1 doses on a single day, apart from on PK sampling days when there must be 4 hours between OMO-1 doses. Cohorts of patients will be recruited in a 3+3 design. A normal treatment cycle will consist of 21 days (3 weeks). Subsequent indicative cohort dose levels are 200 mg (Cohort 2), 400 mg (Cohort 3), 600 mg (Cohort 4*s dose level was changed from 600 mg BD to 250 mg BD based on SRC recommendation following review of data) and 350 mg BD (Cohort 5); doses and schedules are subject to SRC recommendations based upon emerging PK, tolerability and PDc data. Additional PK samples will be collected in Part A (including the sequential biopsy cohorts) at specific time points in all of patients who are admitted overnight on Cycle 1 Day 1 (C1D1). Treatment with OMO-1 will continue until stopping criteria are met.
Initially patients will be recruited irrespective of the MET status of their tumour. Once a MBAD of OMO-1 has been achieved in Module 1, the following will occur:

* Patients will continue to be recruited into the dose escalation cohorts of Part A, irrespective of the MET status of their tumour.
* Parallel sequential biopsy cohorts of patients, who have confirmed MET amplified or mutated tumours, may be recruited into Part A at doses that have been confirmed to be tolerated. Sequential tumour biopsies will be mandated to further explore drug-on-target effects within the tumour, and to explore further the tolerability, safety and PK activity at these doses.
* Part B may be initiated in parallel at doses that have been confirmed to be tolerated.
* Subsequent modules may be initiated in parallel (following substantial amendment approval).

In the optional Part B, patients will be recruited into cohort expansions of OMO-1 monotherapy as confirmed by the SRC. Treatment will continue until individual stopping criteria are met. Cohort expansions of specific patient groups, may include, but not be restricted to:
* Any patient with MET amplified/mutated tumours.
* Locally advanced or metastatic MET amplified/mutated non-small cell lung cancer (NSCLC) (squamous and non-squamous).
* Locally advanced or metastatic MET amplified/mutated squamous cell carcinoma of the head and neck (SCCHN).
* Locally advanced or metastatic MET amplified/mutated gastric carcinoma.
* Locally advanced or metastatic MET overexpressing/amplified/mutated papillary renal cell carcinoma (PRCC).
* Locally advanced or metastatic MET amplified/mutated gastro-oesophageal junction (GEJ) carcinoma.

Cohorts of other tumour types or specific phenotypic/genotypic subtypes of tumours may be expanded depending upon emerging data.
The expected duration of the trial (Module 1) for each patient is 18 weeks (6 cycles). The clinical cut-off for Module 1 is 3 months following the recruitment of the last patient or the last patient last visit, whichever is sooner. All patients still receiving treatment at that time will continue to receive OMO-1 until the stopping criteria are met. Data collection may be reduced after the clinical cut-off date. The specific changes will be based on a review of the data summarized at that time. All patients still receiving treatment at the time of end of study will continue to receive OMO-1 based on clinical benefit and until the stopping criteria are met.
Module 2:
Module 2 will consist of 2 parts: Part A will assess the safety and tolerability of OMO-1 when given orally in combination with a small patients who have MET amplified tumours and whose disease is progressing on current EGFR-TKI treatment. The optional Part B will assess preliminary signs of efficacy activity of OMO-1 when given orally in combination with a small molecule EGFR-TKI. If eligible (e.g. having disease measurable according to RECIST 1.1), these patients will be included within the clinical response assessment in Part A.
* Part A: Dose finding: Dose escalation of OMO-1 given in combination with a small molecule EGFR-TKI.

* Part B: Optional cohort expansion: OMO-1 given in combination with a small molecule EGFR-TKI.
Combination therapy cohorts in Parts A or B may be expanded by additional sequential biopsy cohorts at doses that have been confirmed to be tolerated. Sequential tumour biopsies will further explore drug-on-target effects within the tumour, and to explore further the tolerability, safety and PK activity at these doses. The option to start Part B and to include sequential biopsy cohorts will be the decision of the SRC.
For Parts A and B, the primary endpoint is an assessment of the safety and tolerability of OMO-1 when given orally in combination with a small molecule EGFR-TKI.
Part A (dose finding):
1. Dose escalation: OMO-1 given in combination with a small molecule EGFR-TKI (gefitinib/erlotinib, afatinib and osimertinib). OMO-1 administered from a dose (as defined by the SRC) which will be at or above the monotherapy MBAD (defined from Module 1 Part A);
For Part A: Dose escalation:
Patients will be treated with OMO-1 in combination with a small molecule EGFR-TKI. Patients will be treated in 3 parallel treatment cohorts (OMO-1 + gefitinib/erlotinib, afatinib or osimertinib).
Dose escalation within Part A will commence at an OMO-1 dose and schedule sequence defined by the SRC, depending upon data generated from Module 1 Part A of the study; OMO-1 dose levels will not be weight-adjusted and doses and schedules are subject to SRC recommendations based upon emerging safety, PK, tolerability and PDc data
A normal combination treatment cycle will consist of 21 days (3 weeks). Safety will be monitored on an ongoing basis; dose-limiting toxicities (DLTs) will be assessed during C1 of the combination therapy. Patients will be recruited in a 3+3 design to a planned OMO-1 dose level within a combination therapy.
Once a MTD/maximum feasible dose (MFD) dose of OMO-1 in combination with a small molecule EGFR-TKI has been identified, the SRC may decide to commence Part B of Module 2.
Part B: Cohort expansion:
The initiation of the cohort expansion with the recommended dose and schedule of OMO-1 in combination with a small molecule EGFR-TKI will be based on an adequate safety and tolerability profile of the combination from Part A of Module 2. Part B will consist of cohort expansions in which patients will be followed for objective response rate (ORR) and duration of response (DoR). The SRC will define the recommended dose(s) and schedule(s) for OMO-1 to be explored in Part B from Part A of Module 2.
The expected duration of the trial (Module 2) for each patient is 18 weeks (6 cycles). The clinical cut-off for Module 2 is 3 months following the recruitment of the last patient or the last patient last visit, whichever is sooner. The EGFR-TKI will be administered as per the relevant package insert. All patients still receiving treatment at that time will continue to receive study treatment until the stopping criteria for either study treatment are met. Data collection may be reduced after the clinical cut-off date. The specific

changes will be based on a review of the data summarized at that time. All patients still receiving treatment at the time of end of study will continue to receive study treatment based on clinical benefit and until the stopping criteria for either study treatment are met.

Intervention

Module 1:
Starting dose of 100 mg twice daily (BD) taken with food; with 4 5 hours between the OMO-1 doses on a single day, apart from on pharmacokinetic (PK) sampling days when there must be 4 hours between OMO 1 doses.
Doses and schedules for the subsequent cohorts will be defined by the safety review committee (SRC).
Module 2:
* Dose finding: OMO-1 given in combination with a small molecule EGFR TKI (gefitinib/erlotinib, afatinib and osimertinib). OMO 1 administered at the monotherapy recommended Phase 2 dose (RP2D; defined from Module 1 Part A). Doses and schedules for the subsequent cohorts will be defined by the SRC).
The dosage and administration of the EGFR-TKIs as per the package insert for the relevant EGRF TKI, or recognised dose reduction in the case of afatinib.

Study burden and risks

As with all medicines, there is a risk that OMO-1 may cause unwanted effects (side-effects).
OMO-1 has generally been relatively well tolerated in a recent healthy volunteer clinical study.
Laboratory Tests
Laboratory tests performed could be uncomfortable or painful but are necessary to monitor the patient's health status.
Biopsy
Whenever a biopsy is done, there is a risk of bleeding (haemorrhage) during the procedure. The study doctor will monitor the amount of bleeding. In rare cases, the bleeding can be major.
Risk of MRI (magnetic resonance imaging)
MRI looks at the internal organs by using a large magnet, radio waves and computer equipment to produce pictures, or images, of the human body. During a MRI, the patient will lie on their back motionless in a big machine. This may produce anxiety. At certain times during the scan, loud tapping noises can be heard. The MRI scan does not cause any pain and does not expose the patient to X-ray radiation.
Risk of CT scan
A CT scan is a commonly used diagnostic procedure. The test exposes the patient to a small dose of radiation. All radiation is cumulative over their lifetime.
The radiation risk in this study has been assessed as insignificant, taken in the context of their current condition.

Pregnancy avoidance
Patients must ensure they avoid pregnancy by undergoing highly effective contraceptive methods.

The safety and welfare of the patients has been considered and will continue to be paramount during the course of the research study. Safety of the participants in the study will be monitored by qualified and appropriately trained clinical staff, including nurses, physiologists and research physicians.

It is not known for certain that you will have any clinical benefit by taking part in the study. The chances of success with experimental treatments are low (it is possible that no benefit results from treatment with OMO-1). However, the information we get from this study may help us to treat future patients with locally advanced, unresectable or metastatic solid tumours.

Contacts

Public
OCTIMET Oncology NV

Turnhoutseweg 30
Beerse 2340
BE
Scientific
OCTIMET Oncology NV

Turnhoutseweg 30
Beerse 2340
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

Core:
* Aged at least 18 years.
* Provision of signed and dated, written informed consent.
* Histological or cytological confirmation of locally advanced, unresectable or metastatic solid malignancy
* Performance status: Eastern Co-operative Oncology Group (ECOG) *1 and life expectancy *3 months.
* Patients must have recovered from toxicities of prior therapies (i.e. CTCAE Grade *1).
* Ability to swallow and retain oral medication.
* Adequate organ functions.
* Not receiving other cancer therapy, or other investigational product, apart from the combination agent(s) described in the relevant combination module(s).
* No radiotherapy for the primary tumour within 1 week from screening visit.
* Not receiving medications predominantly metabolized by CYP2B6. Washout period for medications predominantly metabolized by CYP2B6, apart for tamoxifen, is 7 days prior to the first dose of study treatment. Washout period for tamoxifen is 2 months prior to the first dose of study treatment
* Not receiving cannabinoid substances and St. John's Wort. Washout period for cannabinoid substances and St. John's Wort is 5 and 7 days respectively prior to the first dose of study treatment.
* Not receiving medication that are known to have potent aldehyde oxidase (AO) inhibitory activity. Washout period for medications that are known to have potent AO inhibitory activity is 7 days prior to the first dose of study treatment.
* No prior splenectomy.
* No current or history of uveitis.
* No known uncontrolled inter-current illness including ongoing or active infections, symptomatic congestive heart failure, conditions that could adversely be affected by hypertension or tachycardia, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
* No history or clinical evidence of neoplastic central nervous system (CNS) involvement if not stable for 9 weeks prior to the first dose of study treatment.
Note: Patients with glioblastomas are allowed if their symptoms are stable.
* No current or history of, any seizure or seizure disorder. This includes receiving, or having received, seizure threshold-raising medication for

the treatment of epilepsy.
In addition to the main core eligibility criteria, module specific eligibility criteria include:
Module 1:
Patient recruited into the sequential biopsy cohorts of Part A:
* At least 1 lesion suitable for biopsy.
* Tumours that are MET gene amplified and/or mutated.
(MET gene amplified and/or mutated status defined in the laboratory manual).
* No prior therapy with a selective MET inhibitor.
Patients recruited into Part B cohorts:
* Tumours that are MET gene amplified and/or mutated.
(MET gene amplified and/or mutated status defined in the laboratory manual).
* At least one lesion, not previously irradiated, that can be accurately measured at baseline.
* No prior therapy with a selective MET inhibitor.
* No co-incident malignancy that would impact on survival.
* No metastasis limited to the bone only.
Module 2:
Patient recruited into both Part A and Part B:
* Tumours that are EGFR gene mutant that are currently progressing on treatment with a small molecule EGFR-TKI (gefitinib, erlotinib, afatinib or osimertinib administered as per the relevant medication package insert, or recognised dose reduction in the case of afatinib). Enrolment must be restricted to patients that are resistant to all relevant EGFR TKI therapy according to their tumour mutated status.
* Received the EGFR-TKI as monotherapy for at least 12 weeks.
* Tolerated current dose of EGFR-TKI for at least 12 weeks.
* Tumours that are MET gene amplified
(MET gene amplified status defined in the laboratory manual).
* No prior therapy with a selective MET inhibitor.
* No prior EGFR-TKI treatment of >2 lines.
* No past medical history of interstitial lung disease (ILD), druginduced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD.
* No significant gastrointestinal disorders with diarrhoea as a major symptom, mal-absorption, or Common Terminology Criteria for Adverse Events (CTCAE) Grade >2 diarrhoea of any aetiology.
In addition to the above inclusion criteria, additional criteria for patients recruited into Part B:
* At least one lesion, not previously irradiated, that can be accurately measured at baseline.
* No co-incident malignancy that would impact on survival.
* No metastasis limited to the bone only.

Exclusion criteria

1. Patients receiving other cancer therapy, or other investigational product, apart from the combination agent(s) described in the relevant combination module(s).
Note:
Bisphosphonates and granulocyte-colony stimulating factor (GCSF) are acceptable.
Immunotherapy's such as mAbs, interferons and cytokines should not be taken other than the combination therapy agent. Immunosuppressant's such as cyclosporine, rapamycin, tacrolimus, rituximab, alemtuzumab, natalizumab etc, should not be taken other than the combination therapy agent.
Hormone replacement therapy (HRT) and stable treatment of >6 months with luteinizing hormone releasing hormone (LHRH) analogues are acceptable.
During the study period, patients using HRT and bisphosphonates should maintain a constant dose and should not change existing regimen. However, if a change in HRT is indicated, e.g. due to intolerable adverse effects, the regimen may be modified but change should be minimized thereafter.
Washout period for cytotoxic drugs and other mAbs is 21 days prior to the first dose of study treatment. Washout period for approved molecular targeted non-cytotoxic drugs is 5 half-lives prior to the first dose of study treatment.
2. Patients who have received radiotherapy for the primary tumour within 1 week from screening visit.
3. Patients receiving medications predominantly metabolized by CYP2B6 (refer to Section 12.1 for more information).
Washout period for medications predominantly metabolized by CYP2B6, apart for tamoxifen, is 7 days prior to the first dose of study treatment. Washout period for tamoxifen is 2 months prior to the first dose of study treatment.
4. Patients receiving cannabinoid substances.
Washout period for cannabinoid substances is 5 days prior to the first dose of study treatment.
5. Patients receiving St. John's Wort.
Washout period for St. John's Wort is 7 days prior to the first dose of study treatment.
6. Patients receiving medications that are known to have potent AO inhibitory activity (refer to Section 12.1 for more information).
Washout period for medications that are known to have potent AO inhibitory activity is 7 days prior to the first dose of study treatment.
7. Patients with prior splenectomy.
8. Patients testing positive for human immunodeficiency virus (HIV) infection, hepatitis B based on findings of persistent hepatitis B virus surface antigen (HBsAg) or other serology test, hepatitis C virus (HCV)

or Epstein-Barr Virus (EBV) infection.
9. Patients with current, or a history of, uveitis.
10. Patients with any known uncontrolled inter-current illness including ongoing or active infections, symptomatic congestive heart failure, conditions that could adversely be affected by hypertension or tachycardia, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
11. Patients with a history or clinical evidence of neoplastic central nervous system (CNS) involvement if not stable for 9 weeks prior to the first dose of study treatment.
Note: Patients with glioblastomas are allowed if their symptoms are stable.
12. Patients with major and/or planned surgery within 12 weeks of the first dose of study treatment.
13. Patients with any known severe allergies (e.g., anaphylaxis) to any active or inactive ingredients in OMO 1.
14. Patients with nephrolithiasis;
15. Patients with current, or a history of any seizure or seizure disorder. This includes receiving, or having received, seizure thresholdraising
medication for the treatment of epilepsy.
In addition, the following are criteria for exclusion from the optional exploratory genetic research:
16. Patients with previous allogenic bone marrow transplant.
17. Patients with non-leukocyte depleted whole blood transfusion

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):	10-11-2017
Enrollment:	18

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	OMO-1
Generic name:	OMO-1

Ethics review

Approved WMO Date:	19-10-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-11-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-01-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-06-2018
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-06-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2017-000878-11-NL
ClinicalTrials.gov	NCT03138083
CCMO	NL62803.056.17