CLINICAL STUDY PROTOCOL AMENDMENT - CONFIDENTIAL

Protocol Number:	OMO-103-01
EudraCT Number:	2020-003802-30
Investigational Product:	OMO-103
Title:	A Phase 1/2 Study to evaluate the Safety, Pharmacokinetics, and Anti-Tumour Activity of the Myc Inhibitor OMO-103 administered intravenously in Patients with Advanced Solid Tumours
Version and Date:	Amendment Final V1.0; 01 September 2021
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Confidentiality Statement:

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SIGNATURE PAGE

Title: A Phase 1/2 Study to evaluate the Safety, Pharmacokinetics, and Anti-Tumour Activity of the Myc Inhibitor OMO-103 administered intravenously in Patients with Advanced Solid Tumours

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Signing of this page of the protocol indicates that the protocol format and content has been agreed and approved by both parties, and that it is agreed that no further changes to the protocol are required at the time of signing.

PROTOCOL AGREEMENT PAGE

I confirm that I have read and that I understand this protocol, the Investigator Brochure, and all other product information provided by Peptomyc S.L. I agree to conduct this study in conformity with this protocol and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the E6 International Council on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP), all applicable laws and regulations, including, without limitation, data privacy laws and regulations, and the regulatory requirements for reporting serious adverse events (SAEs) defined in Section **Error! Reference source not found.** of this protocol.

Principal Investigator

Title and Name: .....

Position: .....

Signature: .....

Date: .....

SYNOPSIS

Study title:	A Phase 1/2 Study to evaluate the Safety, Pharmacokinetics, and Anti-Tumour Activity of the Myc Inhibitor OMO-103 administered intravenously in Patients with Advanced Solid Tumours
Protocol number:	OMO-103-01
Type of study:	Phase 1/2
Sponsor:	Peptomyc S.L.
Coordinating Investigator:	Dr Elena Garralda Oncology Department Vall d'Hebron University Hospital (VHIO) P. Vall d'Hebron 119-129 08035 Barcelona Spain e-mail: egarralda@vhio.net
Study drug:	OMO-103
Dose to be studied:	**Part 1: Dose Escalation:** 5 OMO-103 dose levels planned, including 0.48 mg/kg, 1.44 mg/kg, 2.88 mg/kg, 4.32 mg/kg and 6.48 mg/kg. **Part 2: Dose Expansion:** OMO-103 at the RP2D found in the previous part of the study.
Dosage form:	OMO-103 solution for infusion presented in vials.
Route:	In both study parts, OMO-103 will be administered IV as a 30-45 min infusion once weekly.
Study centres:	Planned: Up to 15 centres in up to 5 countries
Study objectives:	**Primary (Part 1: Dose Escalation):** • To evaluate the safety and tolerability of OMO-103 in adult patients with advanced solid tumours. **Secondary (Part 1: Dose Escalation):** • To establish and confirm the RP2D and dosing regimen of OMO-103 for further development. • To characterise the PK of OMO-103. • To evaluate preliminary anti-tumour activity in the dose escalation part. • To assess the development of human ADA to OMO-103. **Primary (Part 2: Dose Expansion):** • To assess the preliminary anti-tumour activity of OMO-103 monotherapy as measured by ORR according to standard criteria (RECIST v1.1 [Eisenhauer 2009]).

	Secondary (Part 2: Dose Expansion): • To confirm the RP2D and dosing regimen of OMO-103 for further development. • To assess the type, incidence, severity, timing, seriousness, and relatedness of AEs and laboratory abnormalities. • To characterise the PK of OMO-103. • To assess other efficacy parameters in patients with advanced solid tumours including DCR, PFS, OS, TTP, TTR and DOR by RECIST v1.1. • To assess the development of human ADA to OMO-103. **Exploratory (Both Parts 1 and 2):** • Evaluation of biomarkers. • Myc expression levels.
Study design:	This study is an open label, two-part, FIH Phase 1/2 dose-finding study designed to determine the safety, tolerability, PK, PD and proof-of-concept of OMO-103 in patients with advanced solid tumours. The study consists of two parts: • **Part 1**: Dose escalation in patients with advanced solid tumours, including 5 OMO-103 dose levels. Approximately 11 to 24 patients in total will be enrolled in Part 1, covering 5 dose levels with the primary objective of determining the safety and tolerability of OMO-103 and defining an appropriate dose for further evaluation in Part 2. The study will start with an accelerated-titration dose-escalation scheme enrolling one evaluable patient per cohort for the first 2 dose levels followed by a classic 3+3 design. • **Part 2**: Dose expansion where at least 3 parallel groups of patients with advanced NSCLC, TNBC and CRC will be treated at the RP2D of OMO-103 to further characterise the safety, tolerability, PK, PD and anti-tumour activity of OMO-103. Approximately 18 patients will be enrolled in each of the 3 parallel groups of patients (NSCLC, TNBC, CRC) in Part 2. Note: If an objective response is observed in a tumour group within Part 1, or a long period without disease progression is observed (in Part 1), additional tumour groups may be added in this Phase 1/2 study for further assessment.
Diagnosis and main criteria for inclusion:	Male or female patients, 18 years of age or older who sign the informed consent document, are willing and able to comply with the study protocol and have:

Part 1 (Dose Escalation):

Histologically or cytologically proven advanced solid tumour for which there is no curative therapy and has progressed on SOC treatment or is intolerant to or has no available SOC or SOC unacceptable.

Part 2 (Dose Expansion):

Histologically or cytologically proven advanced NSCLC whose tumours are KRAS-mutated and where the disease has progressed after a chemotherapy and immunotherapy regimen (at least two prior lines of standard therapy), advanced TNBC where the disease has progressed after having received at least one line of prior systemic treatment for advanced disease and advanced CRC whose tumours are RAS mutated and where the disease has progressed after at least two prior lines of standard therapy.

Parts 1 and 2:

- Patient must have measurable disease as per RECIST v1.1 criteria and documented by CT and/or MRI. NOTE: Lesions to be used as measurable disease for the purpose of response assessment must either:
  a. not reside in a field that has been subjected to prior radiotherapy, or
  b. have demonstrated clear evidence of radiographic progression since the completion of prior radiotherapy and prior to study enrolment.
- Tumour biopsy (either from the primary tumour or from metastases) during Screening and during Treatment should be obtained from the patients. Discussion needed with Sponsor if considered not feasible. In Part 1, biopsy obtained only from the 3rd dose level onwards.

  Note: In case a patient has had a tumour biopsy in the previous 6 months and a paraffin block is available, a new biopsy does not need to be done at Screening.
- For each patient undergoing pre- and on-treatment biopsies, the identified lesion to be biopsied should not have been previously irradiated and should not be the only lesion being utilised as a measurable-disease target lesion for objective response assessment. Patients must have tumour lesions that can be accessed for biopsy with acceptable clinical risk in the judgement of the Investigator.
- Documented progression on or following the last line of therapy.
- ECOG performance status up to 1.

	• Life expectancy of ≥12 weeks. • Resolution of all acute, reversible toxic effects of prior therapy or surgical procedure to Grade ≤1 (except alopecia and peripheral neuropathy to Grade ≤2). • Adequate organ function as defined by the following criteria: Haematological: a. Neutrophils ≥1,000μL b. Platelets ≥100,000/μL c. Haemoglobin ≥9 g/dL Renal: a. Creatinine Clearance (calculated via Cockcroft-Gault Equation) ≥40 mL/min Hepatic: a. Serum total bilirubin ≤1.5 ULN or b. Direct bilirubin ≤ULN for patients with total bilirubin >1.5 ULN c. AST/ SGOT and ALT/ SGPT ≤2.5 ULN or ≤5 ULN if liver metastases Coagulation: a. INR ≤1.5 b. aPTT ≤1.5 ULN Chemistry: a. Albumin >25 g/L • If not postmenopausal or surgically sterile, female patients must be willing to practice at least one highly effective methods of birth control (defined as having a low failure rate) for at least a menstrual cycle before and for 4 months after last study drug administration. • Male patients and their sexual partners must use an appropriate contraceptive from Screening for 4 months after last study drug administration.
Total sample size:	In total, about 78 eligible patients will be enrolled.
Number of planned visits:	Part 1: Dose Escalation • **Screening period**: 28 days to 1 day prior 1st dose • **Treatment period**: - Cycle 1 (DLT period): C1D1, C1D2, C1D3, C1D4, C1D5, (Days 3 to 5 only from dose level 3 onwards for PK evaluation), C1D8, C1D15, C1D16 or C1D17 (Day 16 or Day 17 for biopsy and only from dose level 3 onwards) - Cycle 2: C2D1, C2D8, C2D15

	- Cycle 3*: C3D1, C3D2, C3D3, C3D4, C3D5, (Days 3 to 5 only from dose level 3 onwards for PK evaluation), C3D8, C3D15 *NOTE: Assumed 3 cycles but these are unlimited. The planned visits of other cycles will occur on D1, D8 and D15, except for every 3 cycles from Cycle 3 (i.e., Cycle 6, Cycle 9, etc. as PD biomarkers for target validation will be sampled on D1, as well as on D2 during these cycles). - EOT visit • **Follow-up period**: 1-Month Follow-up visit <u>Part 2: Dose Expansion</u> • **Screening period:** 28 days to 1 day prior 1st dose • **Treatment period:** - Cycle 1: C1D1, C1D2, C1D8, C1D15 - Cycle 2: C2D1, C2D8, C2D15, C2D16 or C2D17 (Day 16 or Day 17 for biopsy) - Cycle 3: C3D1, C3D2, C3D8, C3D15, - Cycle 4: C4D1, C4D8, C4D15, - Cycle 5: C5D1, C5D8, C5D15, - Cycle 6*: C6D1, C6D2, C6D8, C6D15, *NOTE: Assumed 6 cycles but these are unlimited. The planned visits of all other cycles will occur on D1, D8 and D15, except for every 3 cycles from Cycle 3 (i.e., Cycle 6, Cycle 9, etc. as PD biomarkers for target validation will be sampled on D1, as well as on D2 during these cycles). - EOT visit • **Follow-up period:** 6-Month Follow-up period, including monthly visits if feasible. Telephone visits may be allowed if considered appropriate, e.g., hospice patients
Safety parameters:	Physical examinations; vital signs assessments; ECOG performance status; laboratory analyses; autoimmunity; 12-Lead ECG; reported AEs.
Efficacy parameters:	Tumour response: • ORR (primary efficacy endpoint); • DCR; PFS; OS; TTP; TTR; DOR (secondary efficacy endpoints) (only Part 2).
Pharmacokinetic parameters:	PK parameters of OMO-103: AUC; C_{min}; C_{max}; t_{max}; $t_{1/2}$.
PD parameters:	Circulating human ADA to OMO-103; Ki67 and CC3 by IHC; Immune infiltration by IHC (CD3, CD4/CD8, PD-1/ PD-L1) and others to be determined; Multiplex assay from biopsies (e.g., MYC-

	expression levels); Cytokines and other PD biomarkers for the purpose of an optional genetic analysis and for target validation; PBMC and immune characterisation blood samples only during Part 2 (Dose Expansion).
Statistical methods:	Sample Size The sample size is determined based on clinical rather than statistical considerations. For the dose escalation part, up to 24 patients are anticipated to be recruited. The number of patients in this study is consistent with Phase 1 dose finding studies. In Part 2, at least 3 parallel groups of patients with advanced NSCLC, TNBC and CRC will be treated. Approximately 18 patients will be enrolled in each group in Part 2. General Considerations In general, all data will be summarised using appropriate descriptive statistics by per dose cohort and for the expansion groups where applicable. Summary tabulations will be presented that display the number of patients (N), number of observations, mean, SD, median, minimum, and maximum for continuous variables, and the number and percent (of non-missing values) per category for categorical data by absolute and relative frequencies. Unless indicated otherwise, summary statistics will be reported for observed data only. Missing data will not be imputed. If a baseline value is missing, no change from baseline will be calculated. Baseline is defined as the last assessment before the start of IMP administration. Safety data will be reviewed continuously and integrated with PK and PD data at the end of dose escalation in order to determine the dose to be administered during the dose expansion part of the study. The same data will be integrated at the conclusion of the study in order to determine the RP2D to be used in future trials of OMO-103. Interim Analysis An interim analysis is planned at the end of Part 1 (Dose Escalation) to provide an overview of available study results at that stage. Note: This interim analysis will not replace the role of the SMC and will not affect dose escalation rules, nor the decision to proceed to Part 2 (Dose Expansion). Another interim analysis is planned in the dose expansion part. After half of the patients in all groups (i.e., 9 patients per group) have been included and treated for 3 cycles, efficacy and safety will be analysed. If no response (as per RECIST v1.1) is seen during the interim analysis in at least one patient regardless of group, or for safety reasons, recruitment could be stopped (or the dose reduced) following discussion between the Investigator, the SMC and the Sponsor.

	If there are no safety concerns and a response is seen, the study will continue until 18 patients have been recruited in each group.