CLINICAL STUDY REPORT

1 TITLE PAGE

Study Title:	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
Investigational Product:	OMO-1
Indication Studied:	Locally advanced, unresectable or metastatic solid malignancies
Study Design:	Multi-arm, multi-part, Open-label, first time in patient study, to study OMO-1 alone and in combination with anti-cancer treatments for 18 weeks in patients with locally advanced, unresectable or metastatic solid malignancies
Name of Sponsor:	OCTIMET Oncology NV
Protocol Number:	OMO1.01.02
Development Phase:	Phase 2
Studied Period:	First Patient Screened: 08 August 2017 First Patient Enrolled: 23 August 2017 *Date of Early Termination of Recruitment: 09 December 2019* Last Patient Last Contact: 25 May 2020
Co-ordinating Investigator:	Martijn Lolkema, MD PhD, Medical Oncologist ErasmusMC, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands
Sponsor Signatory:	Glen Clack, MB BS MD FFPM, Chief Medical Officer OCTIMET Oncology NV Tel: +44 (0) 7765898619 E-mail: glen.clack@OCTIMET.com
GCP Compliance:	This study and the archiving of essential documents were performed in compliance with Good Clinical Practice (GCP).
Version and Date of the Report:	CSR Final V1.0, 25 August 2020

Prepared by: Simbec Orion, 7 Bath Road, Slough, Berkshire, SL1 3UA, UK

SIGNATURE PAGE

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

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

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2 SYNOPSIS

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Title of Study: 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.

Co-ordinating Investigator:

Period 1 (from start of study to 21 July 2019): Sarah Blagden, PhD FRCP, Associate Professor of Experimental Oncology

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Period 2 (from 22 July 2019 to end of study): Martijn Lolkema, MD PhD, Medical Oncologist

ErasmusMC, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

Study Centres:

United Kingdom (4), Belgium (1), France (3), Netherlands (2), United States (1). Additional sites in US (2) and Taiwan (3) were set up but these eventually were not initiated to recruit patients due to the early termination of the study.

Study Period:	**Phase of Development:**
First Patient First Visit: 08 August 2017 *Date of Early Termination of Recruitment: 09 December 2019* Last Patient Last Contact: 25 May 2020	I/II

Core Study: The following aspects of the study applied to both Modules

Core Objectives:

<u>Core Primary Objective of the study was:</u>

- To investigate the safety and tolerability of OMO-1 when given orally to patients with

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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 were:

- To characterise the pharmacokinetics (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 (i.e., [epidermal growth factor receptor (EGFR)-tyrosine kinases inhibitor (TKI)]).
- To assess the preliminary efficacy of OMO-1 by response evaluation criteria in solid tumours (RECIST) 1.1. locally*.

*__Note:__ Scans were also collected for central review.

Objectives Module 1 specific (OMO-1 as monotherapy)

In addition to the core objectives, module specific objectives included:

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 (i.e., EGFR-TKI) in further study modules.
- Part B: To refine the choice of tumour indications for controlled Phase 2 trial(s).

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Objectives Module 2 specific (OMO-1 in Combination with EGFR-TKI)

In addition to the core objectives, module specific objectives included:

Primary objective:

- 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 N-methyl-N0-nitronitrosoguanidine induced gene (MET) amplified tumours and whose disease was 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.

Methodology:

This was a modular, first time in patient, open-label, multicentre study of OMO-1 (a highly potent, selective oral inhibitor of MET kinase and organic cation transporter 2 [OCT2]), administered orally, alone and in combination with anti-cancer treatments (i.e., EGFR-TKI), in patients with locally advanced, unresectable or metastatic solid malignancies. All patients also had the choice of participating in the optional genetics research part (pharmacogenetics [PGx] sample) of this study.

The study started with Module 1.

Module 1 consisted of Part A (dose escalation/finding), which assessed the safety and tolerability of multiple ascending doses of OMO-1 given as monotherapy in unselected patients with locally advanced, unresectable or metastatic malignancy, providing a starting dose(s) and schedule(s) for the initiation of Part B (cohort expansions) of Module 1, and also the initiation of Module 2 (EGFR TKI combination; only one patient was recruited into this module before study recruitment was closed). The option to start Part B and add further modules was the decision of the Safety Review Committee (SRC), based on the preclinical anti-tumour data and, safety and tolerability information from the study as a whole.

Dose-escalation within Part A commenced at a dose level (Cohort 1) of 100 mg twice daily

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(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 were 4 hours between OMO-1 doses. Cohorts of patients were recruited in a 3+3 design. A normal treatment cycle consisted of 21 days (3 weeks). Subsequent cohort dose levels were 200 mg BD (Cohort 2), 400 mg BD (Cohort 3), 250 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 were subjected to SRC's recommendations based upon emerging PK, safety, tolerability and PDc data. Additional PK samples were collected in Part A at specific time points in all patients who were admitted overnight on Cycle 1 Day 1 (C1D1). Treatment with OMO-1 was continued until stopping criteria were met. Once a minimally biologically active dose (MBAD) of OMO-1 was identified from Part A (defined at 100mg BD), the SRC made the decision to commence the following:

- Patients continued to be recruited into the dose escalation cohorts of Part A, irrespective of the MET status of their tumour.
- Initiation of parallel sequential biopsy cohorts of patients, who had confirmed MET amplified or mutated tumours. These patients had mandatory serial biopsies to assess the tumour for relevant PDc biomarkers, and to also further explore the tolerability, safety and PK activity at these doses.
- Part B was initiated, at doses that had been confirmed to be tolerated. The the recommended Phase 2 dose (RP2D) was set at 250mg BD.

Patients with MET pathway aberrations who were enrolled into Part A were actually analysed in Part B in expansion cohorts of OMO-1 monotherapy as confirmed by the SRC.

Treatment continued until individual stopping criteria were met. Cohort expansions of specific patient groups included:

- Cohort 1 (MET EXON 14 mutated non-small cell lung cancer [NSCLC] patients, N=10);
- Cohort 2 (MET amplified or mutated basket patients, N=5).

Module 2 opened following the conclusion of Module 1 Part A. The Module was planned to consist of a Part A (dose finding) and an optional Part B (cohort expansion). Only one patient was enrolled in this Module. The dose of the EGFR-TKI combination agent investigated, in

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this case gefitinib, did not exceed the current recommended dose. The starting dose of OMO-1 was one dose level below RP2D in Module 1 (monotherapy).

On 09 December 2019, recruitment in the study (Module 1 Part B and Module 2) was prematurely closed due to a strategic decision, not due to either a safety concern or lack of efficacy.

Criteria for Evaluation:

Efficacy Parameters:

- Percentage change in tumour size: Percentage change in tumour size was determined for patients with measurable disease at baseline and was 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 was the patient's value representing the largest decrease (or smallest increase) from baseline in tumour size;
- Clinical benefit rate.

PK Parameters:

- Maximum concentration (C_{max});
- Trough concentration (C_{trough});
- Area under the curve (time zero to infinity) (AUC_{∞});
- Area under the curve (time to last measurable concentration) ($AUC_{0\text{-}last}$);
- Elimination half-life ($t_{½}$);
- Time at which the C_{max} was observed (T_{max}).

PDc parameters:

The following parameters were assessed:

- Serum creatinine;
- (Phospo) MET expression in paired biopsies.

Safety parameters:

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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; Eastern Co-operative Oncology Group (ECOG) performance status; dose-limiting toxicity (DLT); adverse events (AEs).

Number of Patients Enrolled (Planned and Actual):

Planned:

- Module 1- Part A 50 patients; Part B approximately 30 patients in each cohort expansion; and additional 12 patients for Biopsy cohorts for Part A or B.
- Module 2- Part A 50 patients; Part B approximately 30 patients in each cohort expansion; and additional 12 patients for Biopsy cohorts for Part A or B.

Actual:

- Module 1- Part A- 24 patients; Part B- 15 patients; Biopsy cohorts- included in Part B expansion Cohorts 1 or 2.
- Module 2- Part A- 1 patient; Part B- 0 (Never started).

Test Product, Dose and Mode of Administration, Batch Number:

OMO-1:

Module 1 (Monotherapy): Starting dose of 100 mg BD taken with food in Part A; with 4 to 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. A normal treatment cycle consisted of 21 days (3 weeks). Subsequent cohort dose levels were 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 were subjected to SRC recommendations based upon emerging PK, tolerability and PDc data.

The RP2D for Part B was set at 250mg BD.

Module 2 (Combination with EGFR-TKI): OMO-1 was to be given in combination with a small molecule EGFR-TKI tablet (gefitinib, erlotinib, afatinib and osimertinib); only one patient was recruited and received gefitinib. The OMO-1 starting dose and schedule were the decision of the SRC based on emerging safety and tolerability data; however, the starting dose

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of OMO-1 in combination modules were to be one dose level below the RP2D in Module 1 (monotherapy). The starting dose for OMO-1 in Module 2 was 200 mg BD.

Batch numbers were as follows:

Batch	Strength	Original Expiry Date	Expiry Extension
1172	100 mg	28 November 17	28 September 18
1173	200 mg	27 November 17	27 September 18
1184	50 mg	September 2018	Not applicable
1183	100 mg	September 2018	May 2019
1185	200 mg	September 2018	Not applicable
1271	50 mg	March 2022	October 2020*
1272	100 mg	March 2022	October 2020*
1420	50 mg	October 2020	Not applicable
1421	100mg	October 2020	Not applicable

*The expiry date of Batches 1271 and 1272 were reduced due to the expiry date of the packaging bottle cap.

Duration of Treatment:

The expected treatment duration of the Module 1 and Module 2 for each patient was 18 weeks (6 cycles). Patients were to continue treatment until disease progression or until apparent safety issues arose.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Not applicable.

Statistical Methods:

The statistical methods for this study, summarised below, were described in a detailed statistical analysis plan (SAP), which was finalised prior to database lock.

Only descriptive statistics were applied, and no inferential statistics were used.

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Summary – Conclusions:

- Overall, multiple BD dosing of OMO-1 in patients with locally advanced, unresectable or metastatic malignancy and patients with MET pathway aberrations was associated with a favourable safety profile.
- No dose-limiting toxicities were observed at any OMO-1 dose level tested.
- In Module 1, Part A, the extent of exposure was highest in Cohorts 1 (100 mg BD) and 2 (200 mg BD), with an apparent reduction in the extent of exposure in the higher dose cohorts. In Module 1, Part B, the extent of exposure was much higher for MET EXON 14 mutated NSCLC patients (MET/EXON, Cohort 1) than for other basket patients with MET aberrations (Cohort 2).
- In Module 1, Part A, the most common drug-related treatment-emergent adverse events (TEAEs) by preferred term (PT) were vomiting, fatigue, increased blood creatinine, nausea and headache. Most drug-related TEAEs were generally recorded in similar proportions of patients across treatment cohorts. More than half of the drug-related serious adverse events (SAEs) were recorded for 2 patients in the highest dose cohort (Cohort 3; 400 mg BD). Fatigue, vomiting and nausea were the most common TEAEs leading to Investigational Medicinal Product (IMP) discontinuation. The vast majority of TEAEs leading to IMP discontinuation (16/18 TEAEs [88.9%]) were recorded for patients in the 3 highest dose cohorts. With the exception of the majority of TEAEs leading to IMP discontinuation being recorded at the higher dose levels, there were no apparent dose-dependent trends in TEAEs recorded across all 5 cohorts.
- In Module 1, Part B, the most common drug-related TEAEs by PT were nausea and increased blood creatinine. All 10 events of increased blood creatinine were reported in Cohort 1 (MET EXON 14 mutated NSCLC patients). With the exception of increased blood creatinine, most drug-related TEAEs were generally recorded in similar proportions of patients across both cohorts. There were no apparent trends in severe TEAEs, SAEs or TEAEs leading to withdrawal recorded across the two dose expansion cohorts in Module 1, Part B.
- No DLTs were reported.
- In Module 1, Part A, no patients died. In Module 1, Part B, 3 patients died following

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treatment discontinuation due to disease progression. No deaths were considered related to IMP.

- In Module 1, Part A and Part B, there was an increase in serum creatinine, which could indicate up to 50% drop in glomerular filtration rate (GFR). However, in Module 1 Part A, there were no notable trends in the serum cystatin C levels, which is another marker of GFR. In Module 1 Part B, there was an increase in serum cystatin C levels that could reflect some loss of GFR. The most common drug related TEAEs by PT included vomiting, nausea and increased blood creatinine. This suggests that if there were true renal function changes, they were from pre-renal azotemia in most cases.
- In both Module 1, Part A and Part B, there were no notable trends in changes in vital signs, physical examinations, 12-lead ECG or ECOG performance score recorded over time or by dose.

Date of the Report:

25 August 2020

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
ALT	Alanine Transaminase
AM	Arithmetic Mean
ASCO	American Society of Clinical Oncology
AST	Aspartate Transaminase
AUC	Area under the Curve
AUC_{∞}	Area under the Curve (Time Zero to Infinity)
$AUC_{0\text{-last}}$	Area under the Curve (Time to last Measurable Concentration)
BD	Twice Daily
BMI	Body Mass Index
C	Cycle (Treatment Cycle)
cftDNA	Cell-free Circulating Tumor DNA
CI	Confidence Interval
C_{max}	Maximum Concentration
C_{trough}	Trough Concentration
CRF	Case Report Form
CTCAE	(National Cancer Institute) Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
CV	Coefficient of Variation
D	Day (Treatment Day)
DLT	Dose-limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
eCRF	Electronic Case Report Form
EE	Exploratory Efficacy Analysis Set
EGFR	Epidermal Growth Factor Receptor
FFPE	Formalin-Fixed Paraffin-Embedded

GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
Geo Mean	Geometric Mean
HDPE	High Density Poly Ethene
IB	Investigator's Brochure
ICH	International Council on Harmonization
IMP	Investigational Medicinal Product
KIM-1	Kidney Injury Molecule-1
mAb	Monoclonal Antibody
MBAD	Minimum Biologically Active Dose
MET	N-methyl-N0-nitronitrosoguanidine induced gene
NGS	Next Generation Sequencing
NSCLC	Non-small Cell Lung Cancer
OCT2	Organic Cation Transporter 2
OLED	Optimum Long Term Exposure Dose
PDc	Pharmacodynamic(s)
PGx	Pharmacogenetic(s)
PK	Pharmacokinetic(s)
PP	Per Protocol
PT	Preferred Term
RECIST	Response Evaluation Criteria In Solid Tumours
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
SRC	Safety Review Committee
$t_{½}$	Elimination Half-life
TEAE	Treatment-emergent Adverse Event

TKI	Tyrosine Kinases Inhibitor
TL	Target Lesion
T_{max}	Time at which the C_{max} was Observed
TP	Tumour Protein
ULN	Upper Limit of Normal

8 STUDY OBJECTIVES

The following objectives applied to all modules of the study:

Core Primary Objective of the study was:

- 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 were:

- To characterise the pharmacokinetics (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 (i.e., [epidermal growth factor receptor (EGFR)-tyrosine kinases inhibitor (TKI)]).
- To assess the preliminary efficacy of OMO-1 by response evaluation criteria in solid tumours (RECIST) 1.1. locally*.

  ***Note:** Scans were also collected for central review. The data from this central review is reported in Appendix 16.1.4.

In addition to the core objectives, module specific objectives included:

Module 1 specific:

The primary objectives of the Module 1:

- 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.

The secondary objectives of the Module 1:

- 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 (i.e., EGFR-TKI) in further study modules.
- Part B: To refine the choice of tumour indications for controlled Phase 2 trial(s).

Module 2 specific:

The primary objective of the Module 2:

- 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 N-methyl-N0-nitronitrosoguanidine induced gene (MET) amplified tumours and whose disease was progressing on current EGFR-TKI treatment.

The secondary objective of the Module 2:

- Part A: To determine the recommended dose and schedule of OMO-1 to take forward into Part B of the study module.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan - Description

This was a modular, first time in patient, open-label, multicentre study of OMO-1 (a highly potent, selective oral inhibitor of MET kinase and organic cation transporter 2 [OCT2]), administered orally, alone and in combination with anti-cancer treatments, in patients with locally advanced, unresectable or metastatic solid malignancies.

All patients recruited into this study had the choice of participating in the optional genetics research part (pharmacogenetics [PGx] sample) of the study.

The study started with Module 1, which consisted of:

- Part A (dose escalation/finding), which assessed the safety, tolerability and PK of multiple ascending doses of OMO-1 given as monotherapy in unselected patients with locally advanced, unresectable or metastatic malignancy.
- Part B (cohort expansions) assessed the anti-tumour activity of OMO-1 in patients with tumours with MET pathway aberrations. In some of these patients, the within tumour PDc effects of OMO-1 were also assessed using paired biopsies.

Dose-escalation within Part A commenced at a dose level (Cohort 1) 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 PK sampling days when there were 4 hours between OMO-1 doses. Cohorts of patients were recruited in a 3+3 design. A normal treatment cycle consisted of 21 days (3 weeks). Subsequent cohort dose levels were 200 mg BD (Cohort 2), 400 mg BD (Cohort 3), 250 mg (Cohort 4's dose level was changed from 600 mg BD to 250 mg BD based on Safety Review Committee (SRC) recommendation following review of data) and 350 mg BD (Cohort 5); doses and schedules were subjected to SRC's recommendations based upon emerging PK, safety, tolerability and PDc data. Additional PK samples were collected in Part A at specific time points in all patients who were admitted overnight on Cycle 1 Day 1 (C1D1). Treatment with OMO-1 was continued until stopping criteria were met. Once a minimally biologically active dose (MBAD) of OMO-1 was identified from Part A (defined at 100mg BD), the SRC made the decision to commence the following:

- Patients continued to be recruited into the dose escalation cohorts of Part A, irrespective of the MET status of their tumour.
- Initiation of parallel sequential biopsy cohorts of patients, who had confirmed MET amplified or mutated tumours.
- Part B was initiated, at doses that had been confirmed to be tolerated.

- Module 2 was initiated following completion of dose escalation (following substantial amendment approval); only 1 patient was recruited to this module before study recruitment was closed.

Part A provided the starting dose(s) and schedule(s) for the initiation of Part B, being the RP2D of 250mg BD. The option to start Part B and add further modules was the decision of the SRC, based on the preclinical anti-tumour data and, safety and tolerability information from the study as a whole.

Patients with MET pathway aberrations who were enrolled into Part A were actually analysed in Part B in expansion cohorts of OMO-1 monotherapy as confirmed by the SRC. Treatment continued until individual stopping criteria were met. Cohort expansions of specific patient groups included:

- Cohort 1 (MET EXON 14 mutated non-small cell lung cancer [NSCLC] patients, N=10);
- Cohort 2 (MET amplified or mutated basket patients, N=5).

Module 2 opened following the conclusion of Module 1 Part A, which provided the starting dose and schedule of OMO-1 for the initiation of Module 2. The Module was planned to consist of a Part A (dose finding) and an optional Part B (cohort expansion). Only one patient was recruited in this Module and dosed with gefitinib. The dose of the EGFR-TKI combination agent investigated did not exceed the current recommended dose. The starting dose of OMO-1 was 200mg BD, one dose level below the recommended Phase 2 dose (RP2D) in Module 1 (monotherapy).

On 09 December 2019, recruitment in the study (Module 1 Part B and Module 2) was prematurely closed due to a strategic decision, not due to either a safety concern or lack of efficacy.

The study protocol and amendments are provided in Appendix 16.1.1 and a sample electronic case report form (eCRF) is provided in Appendix 16.1.2.

9.2 Treatments

9.2.1 Treatments Administered

9.2.1.1 Treatments Administered: Module 1

Dose Escalation

The OMO-1 starting dose and schedule for Module 1 Part A was 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 were 4 hours between OMO-1 doses. A normal treatment cycle consisted of 21 days (3 weeks).

On site/hospital visit days, the patient was instructed not to take their first OMO-1 dose of the day prior to the visit and the first dose was taken as per instruction from the Investigator in order to allow for pre-dose assessments where applicable.

Doses and schedules for the subsequent cohorts were defined by the SRC. Treatment with OMO-1 continued until stopping criteria were met.

The dose escalation scheme did not exceed doubling of the dose, in principle.

Dose Escalation Rules [Module 1, Part A]

The starting dose was 100 mg BD (Cohort 1) taken with food.

A minimum of three patients were assigned sequentially to each planned dose level (see Table 9-1).

For each dose level, at least 2 days elapsed between treatment of the first patient enrolled in a cohort and administration of the first OMO-1 to further patients in that cohort. The staggering interval was subjected to SRC recommendation based upon emerging PK data.

Subsequent cohort dose levels were 200 mg BD (Cohort 2), 400 mg BD (Cohort 3), 250 mg BD (Cohort 4) and 350 mg BD (Cohort 5). The dose and schedule were subjected to SRC recommendation.

For all cohorts, once the third patient in a cohort had been observed for a minimum of 21 days of multiple dosing (i.e. completed one cycle of therapy), all available safety and tolerability data, and any PK and biomarker data available at that time were reviewed by the SRC prior to the enrolment of subsequent patients at the next higher dose level.

The dose of OMO-1 was to be escalated until the occurrence, in any of the first three patients recruited to a given cohort, of either:

- A dose-limiting toxicity (DLT) [no DLTs were observed], or
- Other safety or tolerability findings warranting, in the view of the SRC, expansion of that dose cohort.

At that point, additional patients were recruited to that dose level.

If the SRC concluded that there were no safety or tolerability concerns at that dose level, or in previous cohorts where patients had been dosed for multiple cycles, dose escalation proceeded.

If significant safety or tolerability concerns were observed at any dose level (i.e., adverse events not in keeping with expected long term dosing in ≥2/6 patients), dose escalation stopped, and that dose was determined to have had exceeded the optimum long term exposure dose (OLED) [no dose limiting toxicities were observed in this study, therefore a maximum tolerated dose was not defined]. A lower, intermediate dose was to be considered in order to better define the OLED. Three additional patients were to be recruited into this lower intermediate dose level, to confirm that the incidence of safety or tolerability finding did not exceed 1 out of 6 patients. That dose level defined the RP2D.

Table 9-1 Module 1 Part A: OMO-1 Dose Escalation

Cohort	Dose Level	Minimum Number of Patients	Schedule
1	100 mg	3	100 mg BD with food
2	200 mg	3	200 mg BD with food
3	400 mg	3	400 mg BD with food
4	250 mg[#]	3	250 mg BD with food[#]
5	350 mg	3	350 mg BD with food

BD=Twice daily
[#]Dose level of Cohort 4 changed from planned 600 mg BD to 250 mg BD based on SRC recommendation following review of data.

Module 1 Sequential Biopsy Cohorts

Once the MBAD had been defined, two parallel cohorts (sequential biopsy cohorts) were recruited including patients who have MET amplified or mutated tumours, at doses that had been confirmed to be tolerated, being 200mg BD and 250mg BD. Sequential tumour biopsies were mandated.

MET selected patients were actually reported in Module 1, Part B, with additional sequential biopsies (see Section 9.5.2).

Module 1, Part B: Cohort Expansion

The dose and schedule of OMO-1 administered in Part B were determined by the SRC at 250mg BD.

9.2.1.2 Treatments Administered: Module 2

OMO-1 was given in combination with the first generation EGFR-TKI gefitinib, to the one patient recruited into Module 2.

Following entry in the study the dose of EGFR-TKI was not modified.

The preparation, dosage and administration of the EGFR-TKI used for the purposes of Module 2 of this study took place as per the package insert for the relevant EGFR-TKI.

Patient continued with the current EGFR-TKI treatment dose and schedule. The administration of the EGFR-TKI was to take place at the same time every day.

Patient EGFR-TKI intake was monitored via a patient diary.

9.2.2 Identity of Investigational Product

OMO-1 were supplied as an oral capsule with a dosage of 50 mg, 100 mg or 200 mg. OMO-1 was packaged into high density poly ethene (HDPE) plastic bottles. OMO-1 was packed as

single strength bottles. Each OMO-1 bottle was labelled according to local regulatory requirements.

OMO-1 was stored in a secure, temperature-controlled location between 15˚C and 25˚C (or between 59°F and 77°F) with daily minimum/maximum temperature recording. OMO-1 was dispensed only by the Investigator or by a member of staff specifically authorised by the Investigator, or by a pharmacist, as appropriate.

9.3 Efficacy and Safety Variables

Efficacy, safety, PK and PDc measurements and assessments are outlined in the Flowchart of Schedule of Evaluations for Module 1 Part A, Module 1 Part B, and Module 2 Part A in the study protocol in Appendix 16.1.1.

9.3.1.1 Efficacy Parameters

- Percentage change in tumour size: Percentage change in tumour size was determined for patients with measurable disease at baseline and was 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 was the patient's value representing the largest decrease (or smallest increase) from baseline in tumour size.
- Clinical benefit rate.

9.3.1.2 Pharmacokinetic Parameters:

Parameters such as the following were assessed:

- Maximum concentration (C_{max});
- Trough concentration (C_{trough});
- Area under the curve (time zero to infinity) (AUC_{∞});
- Area under the curve (time to last measurable concentration) ($AUC_{0\text{-}last}$);
- Elimination half-life ($t_{½}$);
- Time at which the C_{max} was observed (T_{max}).

9.3.1.3 Pharmacodynamic parameters:

The following parameter was assessed to assist in assessing the OCT2 activity of OMO-1 (Arya & Yang et al, 2014; Chu et al, 2016; Ciarimboli et al, 2012):

- Serum creatinine;
- (Phospo) MET expression in paired biopsies.

Serum creatinine is also used as an indirect clinical measure of glomerular filtration rate; therefore, this parameter also appears in the safety parameter section.

9.3.1.4 Safety parameters:

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; Eastern Co-operative Oncology Group (ECOG) performance status; DLT; adverse events (AEs).

9.4 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.4.1 Statistical and Analytical Plans

This section presents statistical methods used in the analyses as described in the Statistical Analysis Plan (SAP) Final Version 1.0 dated 05 May 2020 (refer to Appendix 16.1.3).

All statistical analyses were performed using SAS 9.3 or higher.

All summary tables and listings were produced separately for Module 1 Part A/B. Module 2 Part A was only listed. All statistical methods were based on the International Council on Harmonization (ICH E9).

For Module 1 Part A: dose escalation, data were summarised by each of the five cohort dose groups. A total column showing all patients was included for baseline and safety summaries. Where appropriate, data were also summarised by visit with summaries for each visit attended as scheduled and an additional summary for final (last scheduled visit or early withdrawal).

For Module 1 Part B: MET-selected patients, data were summarised by MET/EXON patients Cohort (MET EXON 14 mutated NSCLC patients) or other MET amplified or mutated basket patients Cohort (other MET mutations/amplifications). Where appropriate, data were also summarised by visit with summaries for each visit attended as scheduled.

In summary and analysis tables of continuous variables, standard descriptive statistics (N, mean, standard deviation [SD], median, minimum and maximum) were presented. 95% confidence interval (CI) and, if applicable standard error (SE) were presented in the statistical analysis outputs as appropriate. For PK summaries, arithmetic mean (AM), geometric mean (Geo Mean) and coefficient of variation (of AM) (%CV) were used to summarise the data. The minimum and maximum statistics were presented in summary tables to the same number of significant figures as the original data. The mean/AM, median, Geo Mean, CI, SD and SE were presented to one more significant than the original data.

9.4.1.1 Analysis Sets

Safety Set: The Safety set was defined as those patients who received at least one dose, complete or incomplete, of OMO-1. The safety set was used for all efficacy and safety analyses.

DLT Analysis Set: The DLT analysis set was defined as those patients who took part in the dose-escalation. Patients who took part in the paired biopsy cohort were excluded from this set as they received doses of OMO-1 that had already been defined as tolerated.

PK Set: The PK set was defined as all patients who received OMO-1 with reportable OMO-1 plasma concentrations and no important AEs or protocol deviations that could have impacted PK. The PK set was used for all PK summaries.

Exploratory Efficacy Analysis Set: The Exploratory Efficacy analysis set (EE) consisted of patients with measurable disease at baseline. This set was used for presentation of the waterfall plot and the corresponding table.

9.5 Changes in the Conduct of the Study or Planned Analyses

9.5.1 Changes to the Protocol

On 09 December 2019, recruitment in the study (Module 1 Part B and Module 2) was prematurely closed due to a strategic decision, not due to either a safety concern or lack of efficacy.

Due to the ongoing worldwide COVID-19 situation during the final data cleaning period, assessments on the impact of the study conduct by COVID-19 were performed. The main impact was that some queries and source data verification could not be resolved/completed; however, an impact assessment was completed which concluded the impact on data integrity was limited. The impact assessments and COVID-19 study plan are included in Appendix 16.1.4.

Substantial amendments were made to the protocol during the course of the study. Details of the changes made in the amendment are summarised below (Appendix 16.1.1).

The study was initiated under Protocol Version 2.0 (dated 17 May 2017).

Protocol Version 3.0 (dated 09 January 2018) was updated as follows:

- Preliminary data (safety) included from the Module 1 Part A Dose Escalation provided, based on Cohort 1 – 100 mg and Cohort 2 – 200 mg recruitment as of 12 December 2017.
- Text updated regarding the dose escalation scheme in line with the current status of the study
- Update of OMO-1 with a small molecule EGFR inhibitor or a monoclonal EGFR antibody.
- Text updated to clarify that further information and instruction on the biobank samples will be provided in a separate laboratory manual. Text also updated for consistency with other relevant text in protocol.

- Inclusion criterion #3 updated to clarify that a multidisciplinary meeting would be used to confirm that a patient's solid malignancy was no longer appropriate for further conventional treatment.
- Inclusion criterion #7 to include creatinine clearance ≥50 mL/min estimated by the Cockcroft-Gault formula.
- Inclusion criteria #8 and #9 and potential risks text updated to introduce uniformity within protocol and provide further clarity on contraceptive text. Adequate contraception to be used for the duration of the study and for 6 months following last dose of OMO-1). Negative pregnancy test required prior to start of dosing with OMO-1.
- Exclusion criterion #1 updated for clarification and to confirm that washout for cytotoxic drugs and other monoclonal antibodies (mAbs) is now 21 days prior to first dose of OMO-1.
- Exclusion criterion #2 updated to clarify exclusion radiotherapy treatment (within 1 week from screening visit).
- Exclusion criterion #7 updated to clarify serology testing for exclusion.
- Exclusion criterion #10 updated to clarify that patients with glioblastomas are allowed if their symptoms are stable.
- Exclusion criterion #12 updated to include permanent drainage for patients with pleural effusions and/or ascites.
- New exclusion criteria added excluding patients with current, or a history of, epileptic seizures or seizures induced by intermittent light stimulation. This includes receiving, or having received, seizure threshold-raising medication for the treatment of epilepsy. Added upon request by the French competent authority.
- Text updated to clarify that this includes withdrawal from active or intended treatment with OMO-1. Reasons for when OMO-1 treatment must be discontinued updated to include clinical evidence of disease progression. Confirmed disease progression clarified by the inclusion of reference to RECIST 1.1.
- Additional updates made to provide further clarification concerning withdrawal of treatment.
- Further guidance added on telephone follow-up of patients to confirm withdrawal of treatment.
- Text updated to remove specific reference to calorie intake of solid and/or liquid constituents consumed with intake of OMO-1, based on SRC recommendations.
- Clarification for potential potent inhibitors of aldehyde oxidase.
- Serious adverse event (SAE) definition and reporting details updated.

- Text added to clarify that unexpected urgent surgery should not be delayed due to OMO-1 administration.
- Text added to clarify that during on site/hospital visit days, patient should be instructed to not take the first OMO-1 dose of the day prior to the visit.
- Text updated to clarify that in the event of study discontinuation, all patients still receiving treatment at that time will continue to receive OMO-1 until the stopping criteria are met.
- Text update to include virology testing at screening, as per regulators recommendation in view of exclusion criterion #7.
- Vital signs assessment updated to include additional blood pressure measurements 1 hour post dose on Day 1 (and 6 hours post dose on C1D1) added upon request of the French competent authority.
- Pregnancy tests now performed on Day 1 of Cycle≥2 and at end of treatment
- Oxygen saturation included as an additional assessment. Added upon request by the French competent authority.
- Creatinine added as a clinical chemistry parameter
- PDc sampling timepoints updated to include predose C≥3D1.
- Exploratory objective and PDc endpoints updated to provide further clarification and to incorporate the update of PDc parameters.

Protocol Addendum #2 (France; dated 24 May 2018) was updated as follows:

- To add precautions for use with cytochrome P450 (CYP)2C8 and 2B6 inducers/inhibitors as well as with substrates of CYP3A4, 2C8, 2C9 and 2C19.

Protocol Version 4.0 (dated 28 May 2018) was updated as follows:

- Protocol updated with the introduction of combination therapy of OMO-1 with approved therapeutic interventions: Module 2 will evaluate the safety, tolerability and preliminary efficacy of OMO-1 in combination with small molecule EGFR-TKIs.
- Pre-clinical text updated.
- Update of safety overview (OMO-1 exposure; SAEs, DLTs) of current OMO1.01.02 patient study. Safety overview as per 30 April 2018.
- Update of study rationale, core objectives, investigational plan and trial design to include Module 2.
- Exclusion criteria updated following feedback from investigators and to allow for better clarification of patient population.

- Criteria mandating discontinuation of study treatment updated. Study treatment must be discontinued if the patient is no longer receiving clinical benefit; study treatment may be discontinued if there is confirm disease progression (RECIST 1.1) and/or clinical evidence of disease progression.
- Update of SRC responsibilities.
- Text on prohibited concomitant medication therapy updated.
- Text updated to confirm that where appropriate, 90% CIs will be presented.
- The results from each study module will be reported separately.
- Text updated in line with new General Data Protection Regulation regulations.
- Secondary objective of PK deleted.
- Secondary objective of anti-tumour activity deleted.
- Text updated to state that entry to the study will be based on the local assessment of MET status; samples for central assessment of MET status will also be collected for those patients entered into the study, but entry is not dependent on the central results.
- Time window of ±30 minutes added for additional blood pressure measurements.
- Virology clarification as being only performed at screening in the study flow chart.
- Per protocol (PP) analysis set removed.
- Text updated for sample size, study power, and for efficacy analyses.
- Clinical research organisation's Medical Contact updated.

Protocol Addendum #1 (United Kingdom; dated 04 October 2018) was updated as follows:

- For all protocol versions as of Protocol Final Version 4.0 dated 24 May 2018, UK Investigational Sites were only permitted to recruit patients into Module 1.

Protocol Version 6.0 (dated 17 January 2019) was updated as follows:

- Text updated to exclude the following dose confirmation option: "OMO-1 given in combination with a small molecule EGFR-TKI (gefitinib/erlotinib, afatinib or osimertinib). OMO-1 administered at the monotherapy RP2D (defined from Module 1 Part A)." The revised Module 2 Part A design includes only dose escalation; Dose escalation: OMO-1 given in combination with a small molecule EGFR TKI (gefitinib/erlotinib, afatinib or osimertinib). OMO-1 administered from a dose (as defined by the SRC) which will be at or above the MBAD (defined from Module 1 Part A). Text referring to dose confirmation in Part A of Module 2 has been deleted throughout the protocol.

- Text updated to specify patients to be included must have recovered from prior therapies Common Terminology Criteria for Adverse Events (CTCAE) Grade ≤ 1 (instead of CTCAE Grade ≤ 2).
- Core exclusion criteria updated to exclude individuals with history of any seizure or seizure disorder: "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".
- Module 2 exclusion criteria text updated to exclude patients with diarrhoea CTCAE Grade >1 of any aetiology at the enrolment (instead of CTCAE Grade > 2).
- Study medication OMO-1 dosing interruption or delay text updated to include a 2-week time interval associated with persistent toxicities that require a treatment interruption or delay.
- Text updated to specify that the study therapy must be discontinued permanently in case of Grade 4 toxicity (with the exceptions for vomiting, diarrhoea and laboratory abnormalities).
- Text updated to change the platelet count threshold for restart of treatment following dose interruption or delay.
- Protocol text has been updated to redefine DLTs to include any AE/SAE or toxicity defined in the protocol text that is at least possibly related to OMO-1. The following toxicities were added to DLTs:
    - Any neutropenic fever
    - Aspartate transaminase (AST) or alanine transaminase (ALT) >3x upper limit of normal (ULN) (>2x baseline AND >3x ULN in patients with baseline elevation) AND total bilirubin >2x ULN (>2x baseline AND >2x ULN in patients with baseline elevation) or clinical jaundice, without initial findings of cholestasis AND no other immediately apparent identifiable possible causes of elevated liver enzymes and hyperbilirubinemia.
- DLT exceptions were modified for relevant text to include the following:
    - CTCAE Grade 3 nausea or CTCAE Grade 3-4 vomiting and diarrhoea that persist for less than 72 hours in patients who have not received optimal anti-emetic or anti-diarrhoea prophylaxis.
    - Grade 3 fatigue less than 5 days
    - Grade 3 laboratory abnormalities that are not clinically significant and return to normal (with or without intervention) within 72 hours
    - ≥ Grade 3 amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis

- Grade 3 AST, ALT elevations lasting < 7 days

- Lipase and amylase added as clinical chemistry parameters.

Protocol Version 7.0 (dated 22 July 2019) was updated as follows:

- Text aligned across the document to reflect that the starting dose of OMO-1 in combination modules will be one dose level below the RP2D in Module 1 (monotherapy).
- Core inclusion Criterion No.3 updated to delete "not considered by the Investigator (during site multidisciplinary meetings) to be appropriate for further conventional treatment".
- Core exclusion Criterion No.2 was updated to add; "for the primary tumour".
- Core exclusion Criterion No.3 was deleted.
- Pre-screening for Module 1 was updated:
  - Pre-screening for MET gene status: Mandatory for patients in the sequential biopsy cohorts in Part A; optional for patients recruited into dose escalation cohorts of Part A; optional for all patients recruited in Part B.
- Pre-screening for Module 2 was updated:
  - Pre-screening for MET gene status: Optional for all patients
- Text updated to reflect the current study status (i.e., Module 1 Part A had completed, and Part B was ongoing).
- Introduction section updated to reflected updates in the Investigator's Brochure (IB) and current available study results.
- Investigational Medicinal Product (IMP) information updated to match updates in the IB.
- OMO-1 dose, route and schedule restrictions updated to clarify and to align with label text and to consistently include missed dose/surgery/vomiting information.
- Text was deleted from Section 23.4.6 as fully captured under the pre-screening section.
- Updated to reflect: Current Sponsor address; change of Coordinating Investigator; change of clinical research organisation medical contact.

9.5.2 Changes to the Statistical Analysis Plan

No formal interim analysis was completed.

The analysis of data from Module 1 Part A, Module 1 Part B and Module 2 Part A were combined and analysed together.

Following OCTIMET Oncology NV quarterly board on 08 November 2018, it was decided that all MET selected patients enrolled in Module 1 Part A would actually be reported in Module 1 Part B, including the MET selected patients with additional sequential biopsies.

Study outputs were generated based on data until the cut-off date of 28 February 2020. At that time, there were 2 ongoing patients, and the data for these patients were analysed until cut-off date (i.e. 28 February 2020). Additional data collected into electronic data capture until last patient last visit (25 May 2020) are summarized in a separate narrative for each of these 2 patients (see Section 14.3.3).

As there was only one patient in Module 2 Part A, this patient was reported into narrative format (for more details refer to Section 14.3.3).

Additional data from the enrolment forms and tumour biopsies were provided by OCTIMET Oncology NV as follows (refer to Appendix 16.1.3):

- MET aberration data used for enrolment (from enrolment form)
- Paired tumour biopsy information
- Paired tumour biopsy analysis results for Patient 4001-002 (taken from the poster presented to the American Society of Clinical Oncology, 2019 [ASCO, 2019])

Additional PK figures (geometric mean plasma concentration-time profiles of OMO-1) were generated by OCTIMET Oncology NV (refer to Appendix 16.1.3).

10 STUDY PATIENTS

The database was locked on 05 August 2020. Study outputs were based on a data cut-off of 28 February 2020. At that time, 2 patients were still ongoing. For details of those 2 patients, please refer to Section 9.5.2. No further study outputs were generated at the date of database lock.

10.1 Disposition of Patients

This was a 11-centre study (United Kingdom [4 centres], Belgium [1 centre], France [3 centres], Netherlands [2 centres], United States [1 centre]) with 40 patients enrolled. Two additional centres in US as well as 3 centres in Taiwan were never initiated to enrol patients.

Module 1, Part A

Patient disposition for Module 1, Part A (dose escalation) is summarised in Table 10-1 and Figure 10-1. In total, 28 patients were screened, 4 patients failed screening, and 24 patients were enrolled in Module 1, Part A. All patients in Module 1, Part A were enrolled in the United Kingdom. Of these, the majority of patients (18/24 patients [75.0%]) completed the end-of-treatment visit after treatment discontinuation and the follow-up visit (17/24 patients [70.8%]).

The primary reason for treatment discontinuation was confirmed/clinical evidence of disease progression (13/24 patients [54.2%]). A total of 7 patients (29.2%) discontinued due to the following intolerable or persistent AEs of any severity (7/24 patients):

- Patients 1001-007 and 1003-004: nausea and vomiting
- Patient 1003-001: nausea and fatigue
- Patient 1001-009: allergic reaction. On Cycle 2 Day 1, the patient was re-started on 200 mg of OMO-1 capsules twice daily. On this date, the patient experienced shaking and retching after 1 hour of the study drug intake. These events were assessed as non-serious, Grade 2 and definitely related to OMO-1 by the investigator. As a result of the event, the treatment with OMO-1 was withdrawn (see Section 14.3.3).
- Patient 1003-006: mainly anorexia, combined with fatigue and intermittent vomiting
- Patient 1003-007: vomiting and fatigue
- Patient 1003-008: vomiting

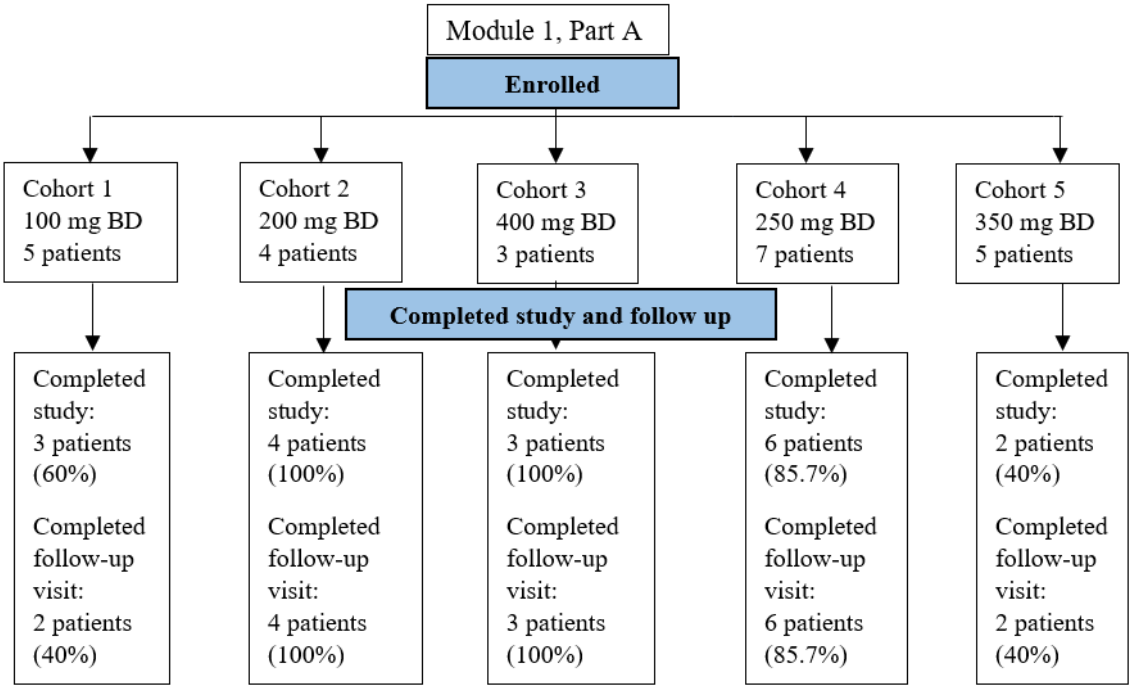
One (1) patient (4.2%) was discontinued due to life-threatening or other unacceptable toxicities. The patient (1002-002) was discontinued from the study due to events of diarrhoea, upper respiratory tract infection, increased blood creatinine, increased blood bilirubin, increased neutrophil count and nausea (see Section 14.3.3).

Table 10-1 Patient Disposition: Module 1, Part A (Safety Set)

	Cohort 1 100 mg BD (N=5) (%)	Cohort 2 200 mg BD (N=4) (%)	Cohort 3 400 mg BD (N=3) (%)	Cohort 4 250 mg BD (N=7) (%)	Cohort 5 350 mg BD (N=5) (%)	Total (N=24) (%)
Enrolled	5	4	3	7	5	24
Completed Study	3 (60.0)	4 (100)	3 (100)	6 (85.7)	2 (40.0)	18 (75.0)
Completed Follow-Up Visit	2 (40.0)	4 (100)	3 (100)	6 (85.7)	2 (40.0)	17 (70.8)
Main reason for treatment discontinuation						
Confirmed disease progression	2 (40.0)	2 (50.0)	1 (33.3)	3 (42.9)	1 (20.0)	9 (37.5)
Clinical evidence of disease progression	2 (40.0)	0	0	1 (14.3)	1 (20.0)	4 (16.7)
Intolerable or persistent AEs of any severity	0	2 (50.0)	1 (33.3)	2 (28.6)	2 (40.0)	7 (29.2)
Life-threatening or other unacceptable toxicities	0	0	1 (33.3)	0	0	1 (4.2)
Withdrawal of patient consent	1 (20.0)	0	0	0	0	1 (4.2)
Patients incorrectly initiated on OMO-1	0	0	0	0	1 (20.0)	1 (4.2)
Other	0	0	0	1 (14.3)	0	1 (4.2)

Abbreviations: AE=adverse event, BD=twice daily, N=number of patients.
The denominator for each percentage is the number of enrolled patients in the column. Enrolled is anybody with any data in the trial with any post-screening data. Completed Study is any patient completing the end-of-treatment visit
Source: Table 14.1.1

Figure 10-1: Patient Disposition (Module 1, Part A)



Abbreviations: AE=adverse event, BD=twice daily, N=number of patients.
The denominator for each percentage is the number of enrolled patients in the column. Enrolled is anybody with any data in the trial with any post-screening data. Completed Study is any patient completing the end-of-treatment visit
Source: Table 14.1.1

Module 1, Part B

Module 1, Part B was terminated early. Patient disposition for Module 1, Part B (MET-selected patients) is summarised in Table 10-2 and Figure 10-2. A total of 22 patients were screened, 7 patients failed screening and 15 patients were enrolled in Module 1, Part B. Of those enrolled, 6 patients were enrolled in the Netherlands, 4 patients were enrolled in the United Kingdom, 4 patients were enrolled in France and 1 patient was enrolled in Belgium. Only 2/15 patients (13.3%) completed the end-of-treatment visit after treatment discontinuation and 1/15 patient (6.7%) completed the follow-up visit.

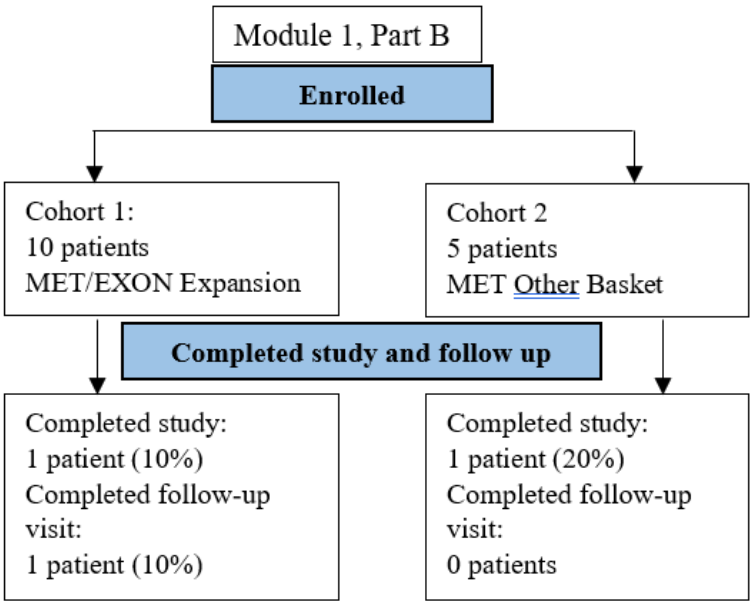
More than half of the patients (8/15 patients [53.4%]) discontinued treatment due to confirmed/clinical evidence of disease progress. Only 1 patient (1/15 patients [6.7%]) discontinued due to intolerable or persistent AEs. Two (2) patients (2/15 patients [13.3%]) withdrew consent and 3 patients (3/15 patients [20.0%]) had other reasons to discontinue treatment.

Table 10-2 Patient Disposition: Module 1, Part B (Safety Set)

	Cohort 1 MET/EXON expansion (N=10) (%)	Cohort 2 MET other basket (N=5) (%)	Total (N=15) (%)
Enrolled	10	5	15
Completed Study	1 (10.0)	1 (20.0)	2 (13.3)
Completed Follow-Up Visit	1 (10.0)	0	1 (6.7)
Main reason for treatment discontinuation			
Confirmed disease progression	5 (50.0)	2 (40.0)	7 (46.7)
Clinical evidence of disease progression	1 (10.0)	0	1 (6.7)
Intolerable or persistent AEs of any severity	1 (10.0)	0	1 (6.7)
Withdrawal of patient consent	1 (10.0)	1 (20.0)	2 (13.3)
Other	1 (10.0)	2 (40.0)	3 (20.0)

Abbreviations: AE=adverse event, BD=twice daily, N=number of patients.
The denominator for each percentage is the number of enrolled patients in the column. Enrolled is anybody with any data in the trial with any post-screening data.
Completed Study is any patient completing the end-of-treatment visit.
MET/EXON is any patient with MET EXON 14 mutated NSCLC. MET other basket is any patient with any MET aberration other than MET EXON 14 mutated NSCLC.
At time of Database cut-off, Patient 1002-009 (Cohort 1) had not completed treatment.
At time of Database cut-off, patient 3001-005 (Cohort 1) was known to have completed treatment, and is summarised as such in this table.
Main reason for treatment discontinuation omitted from CRF for Patients 1005-002 and 1005-003 (Cohort 2), but End of Study page completed (i.e., “Did the subject complete the study [Yes/No]”). Categorised as Other for summary purposes.
Source: Table 14.1.1

Figure 10-2: Patient Disposition (Module 1, Part B)



Abbreviations: AE=adverse event, BD=twice daily, N=number of patients.
The denominator for each percentage is the number of enrolled patients in the column. Enrolled is anybody with any data in the trial with any post-screening data.
Completed Study is any patient completing the end-of-treatment visit.
MET/EXON is any patient with MET EXON 14 mutated NSCLC. MET other basket is any patient with any MET aberration other than MET EXON 14 mutated NSCLC.
At time of Database cut-off, Patient 1002-009 (Cohort 1) had not completed treatment.
Main reason for treatment discontinuation omitted from CRF for Patients 1005-002 and 1005-003 (Cohort 2), but End of Study page completed. Categorised as Other for summary purposes.
Source: Table 14.1.1

Module 2, Part A

Module 2, Part A was terminated early. One patient was enrolled into Module 2, Part A and completed the study on 29 Jan 2020 (Listing 16.2.1.3). The patient did not complete the follow-up visit. The primary reason for treatment discontinuation was confirmed disease progression by RECIST 1.1 (see Listing 16.2.1.3.1).

10.2 Demographics

Module 1, Part A

Table 10-3 summarises patient demographic characteristics by cohort in Module 1, Part A. All 24 patients were Caucasian/White and the majority were male (16/24 patients [66.7%]). The cohorts were well balanced in age, height, weight and body mass index (BMI).

Table 10-3 Demographic Characteristics: Module 1, Part A (Safety Set)

		Cohort 1 100 mg BD (N=5)	Cohort 2 200 mg BD (N=4)	Cohort 3 400 mg BD (N=3)	Cohort 4 250 mg BD (N=7)	Cohort 5 350 mg BD (N=5)	Total (N=24)
Age (years)	N	5	4	3	7	5	24
	Mean (SD)	64.4 (4.8)	66.0 (10.3)	65.0 (1.0)	66.6 (15.3)	60.0 (9.5)	64.5 (10.0)
	Median (Range)	64.0 (59-72)	69.5 (51-74)	65.0 (64-66)	75.0 (42-84)	58.0 (48-74)	64.5 (42-84)
Gender	N	5	4	3	7	5	24
	Male	4 (80.0)	3 (75.0)	3 (100)	3 (42.9)	3 (60.0)	16 (66.7)
	Female	1 (20.0)	1 (25.0)	0	4 (57.1)	2 (40.0)	8 (33.3)
Race	N	5	4	3	7	5	24
	Caucasian/White	5 (100)	4 (100)	3 (100)	7 (100)	5 (100)	24 (100)
Height (cm)	N	5	4	3	7	5	24
	Mean (SD)	179.2 (4.3)	169.3 (11.6)	164.7 (8.7)	170.3 (7.7)	167.6 (11.5)	170.7 (9.4)
	Median (Range)	180 (173-185)	174.5 (152-176)	167.0 (155-172)	171.0 (159-181)	172.0 (153-180)	172.5 (152-185)
Weight (kg)	N	5	4	3	7	5	24
	Mean (SD)	76.50 (5.47)	79.65 (8.47)	80.37 (27.17)	79.26 (23.51)	74.52 (14.98)	77.90 (16.33)
	Median (Range)	79.10 (69.8-81.9)	78.15 (71.2-91.1)	78.10 (54.4-108.6)	73.40 (55.6-129.5)	78.60 (48.3-86.0)	78.20 (48.3-129.5)
BMI (kg/m^2)	N	5	4	3	7	5	24
	Mean (SD)	23.81 (1.21)	28.03 (4.20)	29.12 (7.10)	27.22 (7.44)	26.54 (5.27)	26.74 (5.40)
	Median (Range)	23.89 (22.0-25.3)	28.10 (23.0-32.9)	28.00 (22.6-36.7)	25.24 (22.0-43.8)	26.58 (19.3-33.4)	25.26 (19.3-43.8)

Abbreviations: BD=twice daily, BMI=body mass index, N=number of patients, SD=standard deviation.
The denominator for each percentage is the number of non-missing observations within the column
Age was calculated using DOB and date of informed consent and presented as age at last birthday
BMI is the patient's body weight in kilograms divided by the square of the patient's height in metres
Source: Table 14.1.3

Module 1, Part B

Table 10-4 summarises patient demographic characteristics by cohort in Module 1, Part B. Seven (7/15) patients (46.7%) were Caucasian/White and 8/15 patients (53.3%) had race recorded as "not applicable" due to local laws. The majority of patients were male (9/15 patients [60.0%]). The mean age of patients was higher in Cohort 1 (67.8 years [SD: 6.8 years]) than in Cohort 2 (55.2 years [SD: 10.0 years]).

Table 10-4 Demographic Characteristics: Module 1, Part B (Safety Set)

		Cohort 1 MET/EXON expansion (N=10) (%)	Cohort 2 MET other basket (N=5) (%)	Total (N=15)
Age (years)	N	10	5	15
	Mean (SD)	67.8 (6.8)	55.2 (10.0)	63.6 (9.8)
	Median (Range)	68.5 (56-80)	57.0 (44-67)	64.0 (44-80)
Gender	N	10	5	15
	Male	5 (50.0)	4 (80.0)	9 (60.0)
	Female	5 (50.0)	1 (20.0)	6 (40.0)
Race	N	10	5	15
	Caucasian/White	3 (30.0)	4 (80.0)	7 (46.7)
	Other	7 (70.0)	1 (20.0)	8 (53.3)
Height (cm)	N	10	5	15
	Mean (SD)	170.2 (8.9)	175.6 (6.5)	172.0 (8.4)
	Median (Range)	169.5 (157-185)	177.0 (165-182)	175.0 (157-185)
Weight (kg)	N	10	5	15
	Mean (SD)	73.29 (14.56)	78.42 (12.39)	75.0 (13.65)
	Median (Range)	77.30 (41.2-88.2)	75.10 (67.0-98.5)	75.60 (41.2-98.5)
BMI (kg/m^2)	N	10	5	15
	Mean (SD)	25.23 (4.58)	25.71 (6.02)	25.39 (4.89)
	Median (Range)	25.54 (15.7-31.6)	24.45 (21.4-36.2)	24.52 (15.7-36.2)

Abbreviations: BD=twice daily, BMI=body mass index, N=number of patients, SD=standard deviation.
The denominator for each percentage is the number of non-missing observations within the column
MET/EXON is any patient with MET EXON 14 mutated NSCLC. MET other basket is any patient with any MET aberration other than MET EXON 14 mutated NSCLC.
Age was calculated using DOB and date of informed consent and presented as age at last birthday

BMI is the patient's body weight in kilograms divided by the square of the patient's height in metres
Source: Table 14.1.3

Module 2, Part A

The one patient in Module 2, Part A was a 55 year old, Caucasian/White, female, with a weight of 68.3 kg, height of 162 cm and BMI of 26.0 kg/m^2 (Listing 16.2.4.1).

10.3 Cancer History

Cancer history is summarised for the Safety Set in Table 14.1.4.

Module 1, Part A

Of the 24 patients in Module 1, Part A, 10 patients (41.7%) had colorectal cancer, 6 patients (25.0%) had gastrointestinal cancer, 6 patients (25.0%) had another cancer and 2 patients

(8.3%) had lung cancer. Overall, the range of time since diagnosis was 40 to 678 weeks and approximately half of the patients (11/24 patients [45.8%]) had stage IV cancer at diagnosis.

Module 1, Part B

There were two expansion cohorts in Module 1, Part B: In Cohort 1 (MET/EXON), 10 patients with MET EXON 14 mutated NSCLC (lung cancer) were enrolled and in Cohort 2, 5 patients with any type of MET aberrations, except for MET EXON 14 mutated NSCLC were enrolled. Of the 5 patients enrolled in expansion Cohort 2 (MET Other basket), 2 patients (40.0%) had lung cancer, 2 patients had colorectal cancer (40.0%) and 1 patient had gastrointestinal cancer (20%). Overall, the range of time since diagnosis was 4 to 491 weeks and the majority of patients (10/15 patients [66.7%]) had stage IV cancer at diagnosis.

The MET aberration data are provided by patient in Table 10-5 for expansion Cohort 1 and in Table 10-6 for expansion Cohort 2.

Table 10-5 MET aberration data used for enrolment: Module 1, Part B (Cohort 1)

Subject Identification	Sample/Method	Sample Date	Months versus Study Entry	MET genotyping	Co-genomic Aberration
4001-002	Lung RBK right, biopsy FFPE NGS	09 Feb 18	4.18	MET EXON 14 mutation (c.3062A>G; p.Y1021C)	TP53 (43%)
4001-004	Cervical left nodule, biopsy	25 Jul 17	13.21	MET EXON 14 skipping mutation	KRAS (EXON2)
3001-001	Peritoneal metastasis, biopsy frozen NGS	22 May 18	3.07	MET EXON 14 mutation (12%) (c.3082G>A)	ERBB3 (51%) TP53 (7%) TSC1 (51%)
4001-005	Lung, biopsy FFPE NGS	31 Jul 18	1.21	MET EXON 14 mutation (70%) (C.3082+1G>C, p?, variant allele frequency: 70%)	TP53 (63%) PIK3CA (49%)
4001-006	Pleural fluid FFPE NGS	04 Aug 17	15.25	MET EXON 14 mutation (45%) (MET C.2942-37_2942-18del)	not detected
3001-003	Lung, Biopsy FFPE NGS	28 Oct 16	29.46	MET EXON 14 mutation (C.3082+1G>A)	not detected
2001-001	Lung, right, biopsy FFPE NGS	14 Jun 19	1.14	MET EXON 14 skipping mutation (41%) (C.3082+2T>C)	not detected
1002-008	Blood (cftDNA) FoundationOne	14 Aug 19	1.00	MET EXON 14 splice site (0.76%) (D1010H)	not detected
1002-009	Blood (cftDNA) FoundationOne	09 Jul 19	3.79	MET EXON 14 splice site (6,6%) (3028+2T>G)	not detected
3001-005	Metastasis delta right, biopsy NGS	02 Feb 18	22.89	MET EXON 14 mutation (32%) (C.3082+2T>G)	not detected

Abbreviations: cftDNA=cell-free circulating tumor DNA; FFPE=formalin-fixed paraffin-embedded; NGS=next generation sequencing; TP=tumour protein.
MET/EXON is any patient with MET EXON 14 mutated NSCLC.
Source: Table 13.1.3.1

Table 10-6 MET aberration data used for enrolment: Module 1, Part B (Cohort 2)

Subject Identification	Sample/Method	MET Genotyping
1005-002	No information	MET amplification
4002-001	Sequencing	MET amplification (8 copies)
1005-003	Liver, biopsy FFPE NGS	MET EXON 14 skipping mutation
4002-003	Fluorescence in situ hybridization	MET amplification (>7 copies)
3001-002	Liver, biopsy	MET amplification

Abbreviations: FFPE=formalin-fixed paraffin-embedded, NGS=next generation sequencing.
MET other basket is any patient with any MET aberration other than MET EXON 14 mutated NSCLC.
Source: Table 13.1.3.2

Module 2, Part A

The MET aberration data are provided for the one patient in Module 2 in Table 10-7.

Table 10-7 MET aberration data used for enrolment: Module 2, Part A

Subject Identification	Sample/Method	Sample Date	Months versus Study Entry	MET genotyping	Co-genomic Aberration
2001-002	Left nodule, punction NGS and silver in situ hybridization	08-Jul-19	1.07	9,36 fold MET amplification	TP53 (EXON 8) (5%) EGFR (EXON 21) (72%) TP53 (EXON 7) (18%)

Abbreviations: EGFR=epidermal growth factor receptor; NGS=next generation sequencing; TP=tumour protein.
Source: Table 13.1.3.3

11 EFFICACY EVALUATION

All Tables can be found in-text or in Section 14 and all Listings can be found in Appendix 16.2.

11.1 Efficacy Results and Tabulations of Individual Patient Data

11.1.1 Analysis of Efficacy

Preliminary efficacy of OMO-1 by RECIST 1.1. was assessed locally. Scans were also collected for central review. The data from this central review is reported in Appendix 16.1.4.

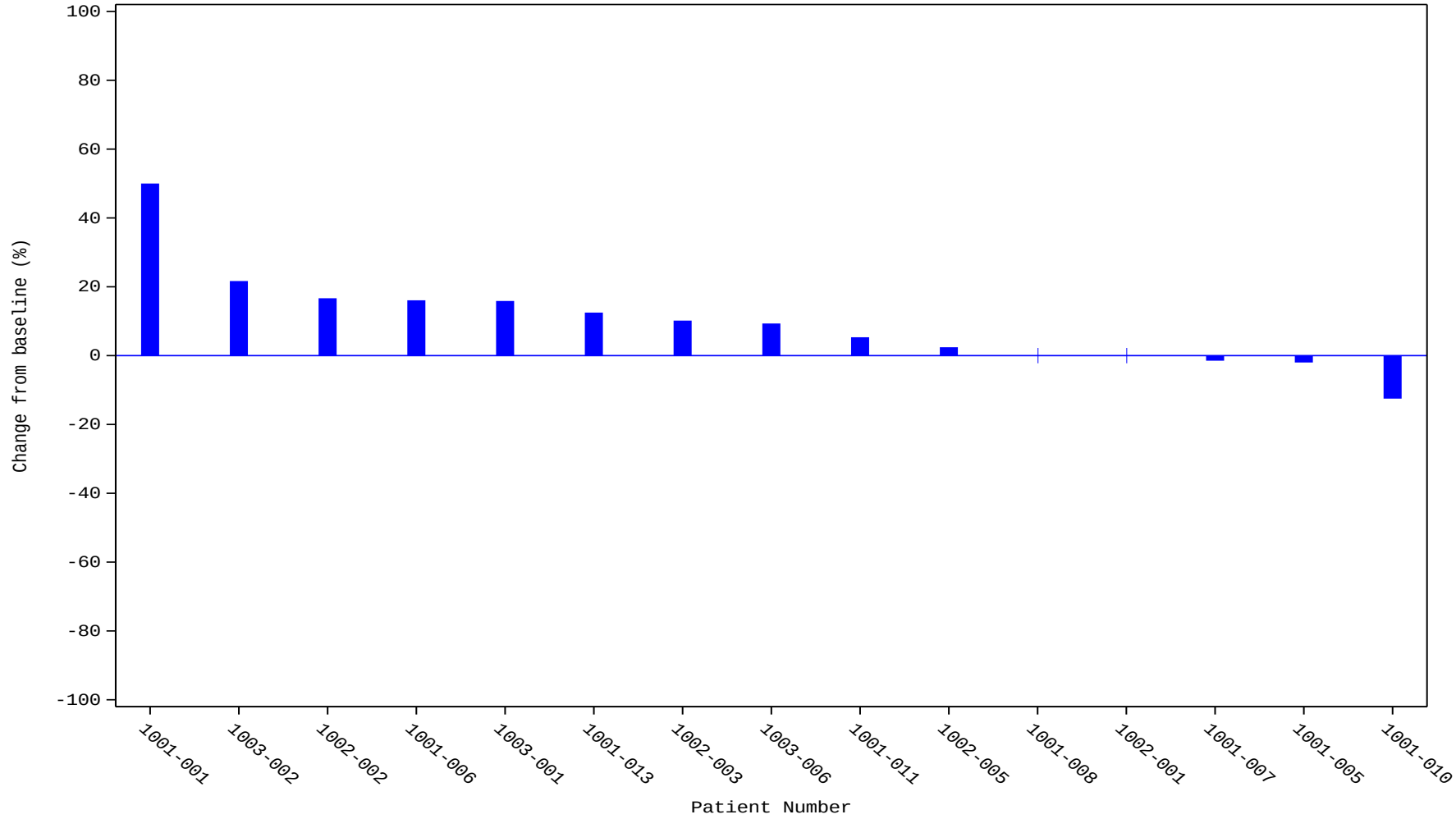
11.1.1.1 Best Percentage Change in Tumour Size

The best overall percentage change in tumour size is defined as the percentage change from baseline value that represents the largest decrease or smallest increase (data as provided by local assessment). The best percentage change in tumour size is summarised for the EE Set in Table 14.2.1.1.

Module 1, Part A

A waterfall plot of the best overall percentage change in tumour size is presented in Figure 11-1. Overall, the mean best overall percentage change in tumour size was 9.60% (SD: 14.44%). There were no apparent dose-related trends in best overall percentage change in tumour size, with mean best overall percentage change in tumour size ranging between 3.08% (SD: 10.60%) in Cohort 4 and 21.36% (SD: 26.40%) in Cohort 1.

Figure 11-1: Waterfall Plot of Best Overall Percentage Change in Tumour Size: Module 1; Part A (EE Set)

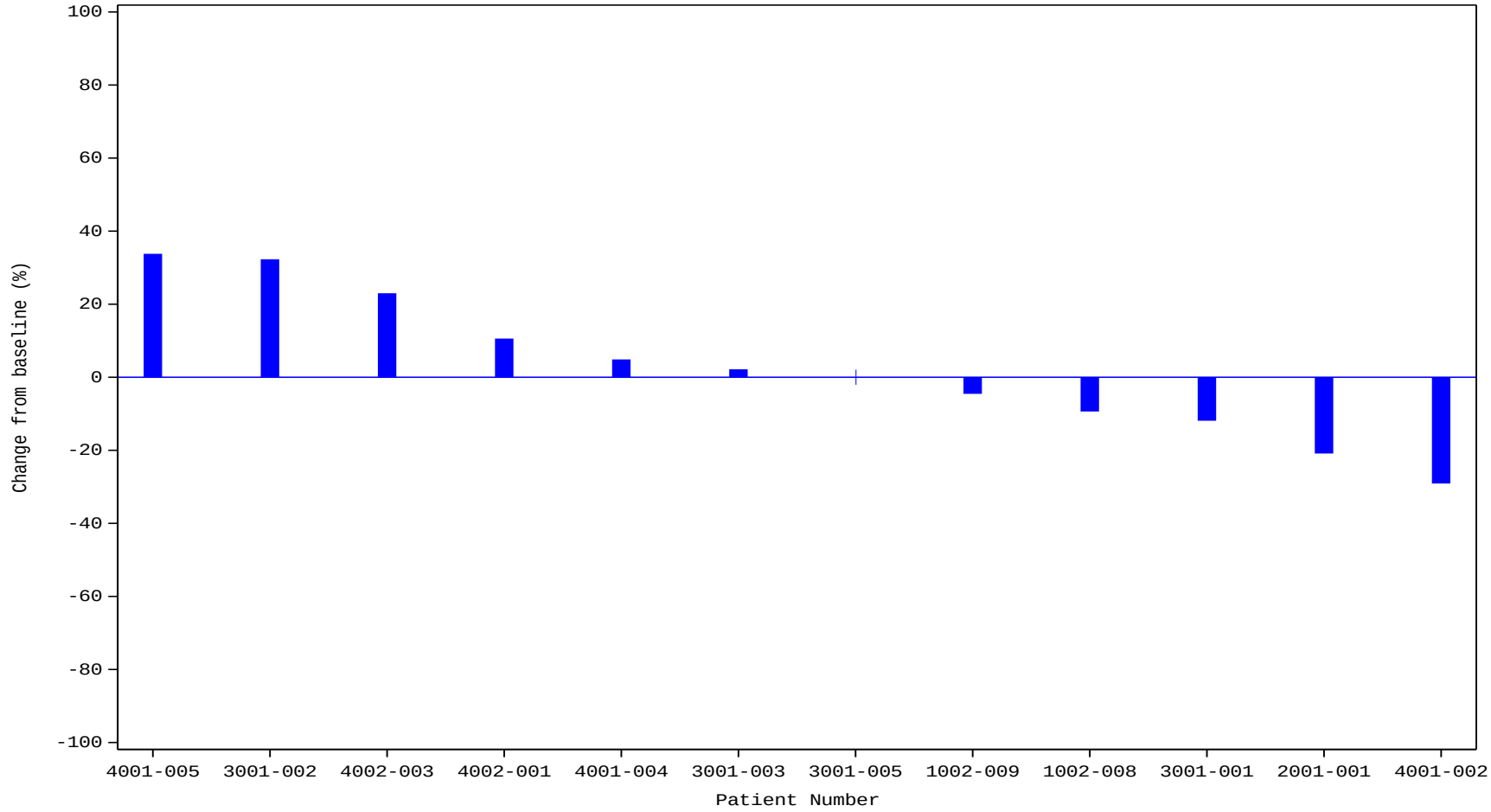


Source: Figure 16.2.6.1.1

Module 1, Part B

A waterfall plot of the best overall percentage change in tumour size is presented in Figure 11-2. Overall, the mean best overall percentage change in tumour size was 3.49% (SD: 18.40%). The MET/EXON patients in Cohort 1 recorded a decrease in tumour size, with a mean best overall percentage change in tumour size of -2.67% (SD: 16.29%), compared to an increase in tumour size in MET other basket patients in Cohort 2 (mean best overall percentage change in tumour size of 21.96% [10.89%]).

Figure 11-2: Waterfall Plot of Best Overall Percentage Change in Tumour Size: Module 1; Part B (EE Set)



Source: Figure 16.2.6.1.1

11.1.1.2 Clinical Benefit Rate

The clinical benefit rate is derived as the proportion of patients with a duration of SD of at least 8, 12, 16 or 20 weeks. The clinical benefit rate is summarised for the Safety Set in Table 14.2.1.2.

Module 1, Part A

In total, a clinical benefit duration of at least 8 weeks was recorded for 7/24 patients (29.2%). A clinical benefit rate duration of at least 12, 16 and 20 weeks was recorded for 6 (25.0%), 4 (16.7%) and 2 patients (8.3%), respectively.

The clinical benefit rate was highest in Cohort 2, with a clinical benefit duration of at least 16 weeks recorded for 3 patients (75.0%). The clinical benefit rate was lowest in the highest dose cohorts, with no clinical benefit of any length recorded for any patients in Cohorts 3 (400 mg BD) and 4 (350 mg BD).

Module 1, Part B

For MET/EXON patients (Cohort 1), a clinical benefit duration of at least 12 weeks was recorded for half of the patients (5/10 patients [50.0%]). A clinical benefit rate duration of at least 16 and 20 weeks was recorded for 3 (30.0%) and 1 patient (10.0%), respectively.

For MET other basket patients (Cohort 2), no clinical benefit of any length was recorded for any patients (5/5 patients).

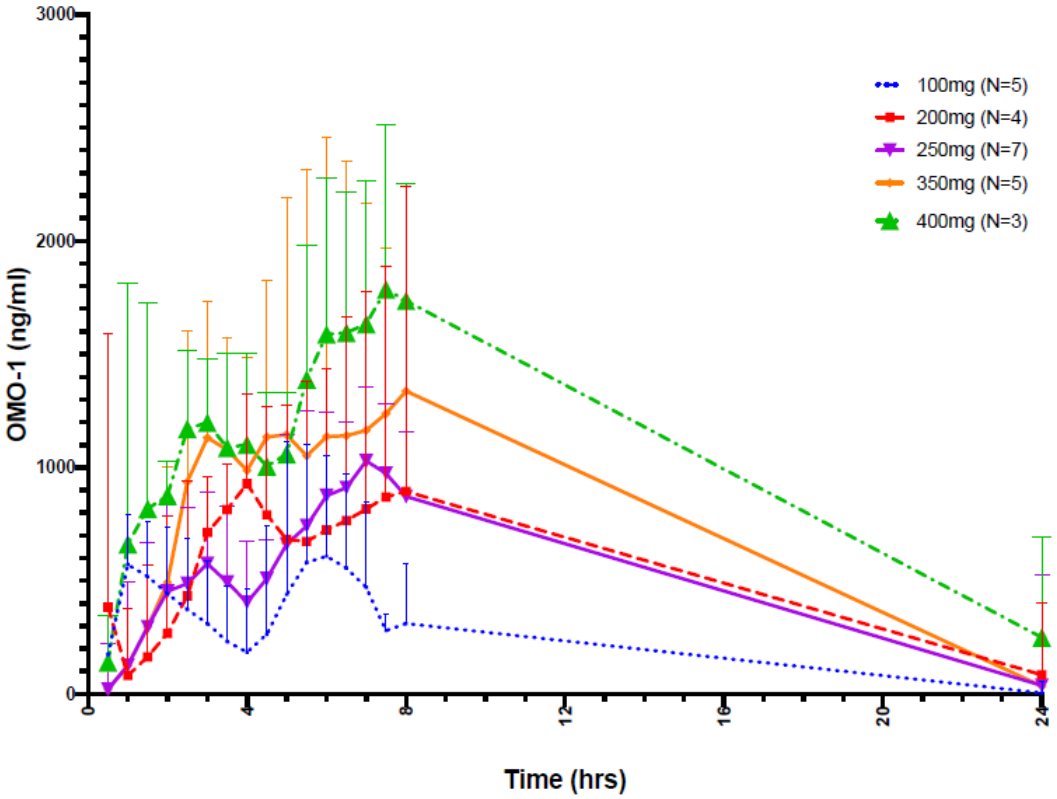
11.1.2 Pharmacokinetics

11.1.2.1 Plasma Concentration Data

Plasma concentrations of OMO-1 are summarised for the PK Set in Table 14.2.2.1. OMO-1 plasma PK concentration data are listed per patient in Listing 16.2.5.1. The calibration range of the validated bioanalytical method for determination of OMO-1 in plasma was 2.00 to 1000.00 ng/mL (see Appendix 16.1.4).

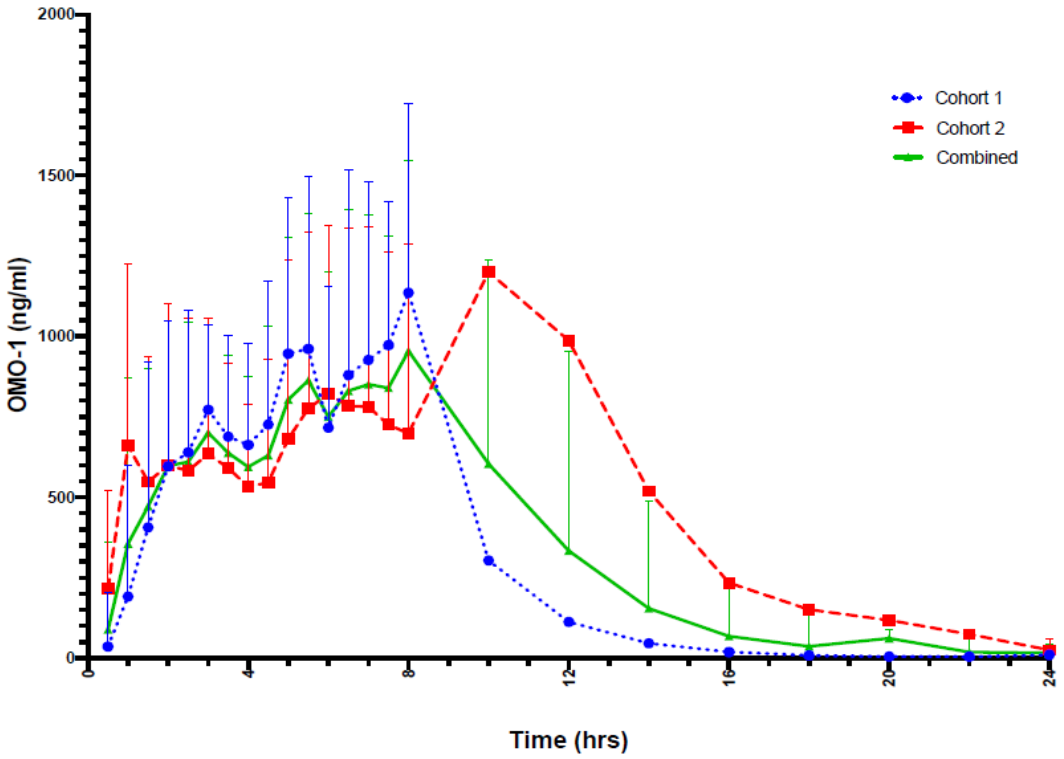
Additional PK figures were generated by OCTIMET Oncology NV (see Section 9.5.2). Geometric mean plasma concentration-time profiles of OMO-1 are presented by cohort for Module 1, Part A in Figure 11-3 and Module 1, Part B in Figure 11-4.

Figure 11-3: Geometric Mean Plasma Concentration-time Profiles of OMO-1 on Cycle 1 day 1 in Module 1, Part A (PK Set)



Source: Figure 13.1.3.2

Figure 11-4: Geometric Mean Plasma Concentration-time Profiles of OMO-1 on Cycle 1 day 1 in Module 1, Part B (PK Set)



Source: Figure 13.1.3.3

11.1.2.2 Pharmacokinetic Parameters

Module 1, Part A

PK parameters for Module 1, Part A are summarised in Table 11-1.

On Cycle 1, Day 1, the Geo Mean C_{max} was generally increasing with increases in OMO-1 dose, from 762.204 ng/nL (SD: 555.986 ng/nL) in Cohort 1 (100 mg BD) to 1910.125 ng/nL (SD: 698.880 ng/nL) in Cohort 3 (400 mg BD).

On Cycle 1, Day 1, the median T_{max} was generally similar across different OMO-1 doses and OMO-1 was generally rapidly absorbed. The lowest median T_{max} was recorded in Cohort 1 (5.000 hours [range: 1.00 to 5.57 hours]; 100 mg BD) and the highest median T_{max} was recorded in Cohort 2 (7.750 hours [range: 2.50 to 8.07 hours]; 200 mg BD).

On Cycle 1, Day 1, Geo Mean area under the curve (AUC; $AUC_{0\text{-}8\ hours}$, $AUC_{0\text{-}12\ hours}$, $AUC_{0\text{-}last}$, AUC_{∞}) generally increased with dose. The Geo Mean $AUC_{0\text{-}last}$ ranged from 4625.200 h×ng/mL (SD: 4762.919 h×ng/mL) in Cohort 1 (100 mg BD) to 22372.257 h×ng/mL (SD: 10995.252 h×ng/mL) in Cohort 3 (400 mg BD). The Geo Mean

AUC_{∞} ranged from 4687.622 h×ng/mL (SD: 5131.338 h×ng/mL) in Cohort 1 (100 mg BD) to 52821.298 h×ng/mL (SD: not recorded) in Cohort 3 (400 mg BD).

On Cycle 1, Day 1, the median $t_{1/2}$ was generally similar across different OMO-1 doses; however, due to the limited number of samples following the second dose the elimination phase was not very well characterized, with few profiles allowing reliable estimation of $t_{1/2}$ ($t_{1/2}$ only calculated for 12/24 patients [50.0%]). The lowest median $t_{1/2}$ was recorded in Cohort 1 (2.464 hours [range: 20.4 to 5.02 hours]; 100 mg BD).

Overall, Cycle 2, Day 1, PK parameters were comparable to Cycle 1, Day 1. As Cycle 2, Day 1 values were similar to those at Cycle 1, Day 1, there was no evidence for accumulation.

PK parameters are listed per patient in Listing 16.2.5.2.

Table 11-1 Summary of PK Parameters: Module 1, Part A (PK Set)

		Cohort 1 100 mg BD (N=5)	Cohort 2 200 mg BD (N=4)	Cohort 3 400 mg BD (N=3)	Cohort 4 250 mg BD (N=7)	Cohort 5 350 mg BD (N=5)
C_{max} (ng/mL)						
Cycle 1 Day 1	N	5	4	3	7	5
	Geo Mean (SD)	762.204 (555.986)	1398.953 (1124.907)	1910.125 (698.880)	1330.432 (345.111)	1731.969 (1123.935)
	Min	487.00	919.00	1200.00	814.00	1020.00
	Max	1840.00	3290.00	2430.00	1720.00	3800.00
Cycle 2 Day 1	N	3	3	1	3	1
	Geo Mean (SD)	1013.795 (992.926)	1526.054 (457.092)	708.000 (-)	1689.022 (235.160)	4440.000 (-)
	Min	562.00	1050.00	708.00	1460.00	4440.00
	Max	2380.00	1870.00	708.00	1930.00	4440.00
T_{max} (h)						
Cycle 1 Day 1	N	5	4	3	7	5
	Median (SD)	5.000 (2.355)	7.750 (2.690)	7.470 (3.907)	6.050 (2.746)	6.020 (3.042)
	Min - Max	1.00 - 5.57	2.50 - 8.07	1.00 - 8.03	1.00 - 7.53	1.50 - 8.02
Cycle 2 Day 1	N	3	3	1	3	1
	Median (SD)	1.000 (2.887)	1.000 (4.041)	1.000 (-)	6.030 (0.569)	7.980 (-)
	Min - Max	1.00 - 6.00	1.00 - 8.00	1.00 - 1.00	6.00 - 7.00	7.98 - 7.98
AUC_{0-8} (h*ng/mL)						
Cycle 1 Day 1	N	5	4	3	7	5
	Geo.Mean (SD)	3333.987 (2572.746)	5451.656 (2580.927)	9690.110 (3227.673)	5541.555 (1243.451)	7508.068 (4296.726)
	Min	1854.87	4302.54	6754.68	3273.34	5041.07
	Max	8342.41	9661.07	13204.98	6883.33	15354.09
Cycle 2 Day 1	N	3	3	0	3	1
	Geo.Mean (SD)	4070.695 (6044.249)	5990.071 (2861.809)	0	7836.978 (1102.735)	17295.214 (-)
	Min	1640.44	3285.53	0	6848.04	17295.21
	Max	12805.92	8761.10	0	9044.27	17295.21

		Cohort 1 100 mg BD (N=5)	Cohort 2 200 mg BD (N=4)	Cohort 3 400 mg BD (N=3)	Cohort 4 250 mg BD (N=7)	Cohort 5 350 mg BD (N=5)
AUC $_{0-12}$ (h*ng/mL)						
Cycle 1 Day 1	N	5	4	3	7	5
	Geo.Mean (SD)	4137.056 (3469.313)	8488.468 (5883.851)	15219.847 (5164.641)	8085.280 (1899.064)	11078.598 (5341.961)
	Min	2372.24	5468.65	10303.44	5022.24	7301.55
	Max	10942.32	18279.40	20531.68	10716.04	20643.57
Cycle 2 Day 1	N	3	3	0	3	1
	Geo.Mean (SD)	5343.679 (10611.411)	8167.139 (5165.965)	0	10367.799 (1242.695)	30286.381 (-)
	Min	1756.55	3510.48	0	9525.72	30286.38
	Max	21194.80	12525.31	0	11835.23	30286.38
AUC $_{0-t}$ (h*ng/mL)						
Cycle 1 Day 1	N	5	4	3	7	5
	Geo.Mean (SD)	4625.200 (4762.919)	12070.767 (7555.696)	22372.257 (10995.252)	10742.607 (6178.766)	13333.539 (6209.996)
	Min	2546.24	6218.26	13629.47	6834.53	9101.21
	Max	14111.12	23372.03	35553.22	24691.23	24438.48
Cycle 2 Day 1	N	3	3	1	3	1
	Geo.Mean (SD)	6965.373 (21267.049)	10526.555 (8124.712)	1752.461 (-)	11780.296 (1663.620)	42372.697 (-)
	Min	1825.38	3856.89	1752.46	10788.34	42372.70
	Max	39983.24	19487.32	1752.46	13771.42	42372.70
AUC $_{0-inf}$ (h*ng/mL)						
Cycle 1 Day 1	N	5	1	1	4	1
	Geo.Mean (SD)	4687.622 (5131.338)	6328.622 (-)	52821.298 (-)	9555.401 (3887.726)	24777.566 (-)
	Min	2549.18	6328.62	52821.30	7223.33	24777.57
	Max	14950.46	6328.62	52821.30	15782.40	24777.57

		Cohort 1 100 mg BD (N=5)	Cohort 2 200 mg BD (N=4)	Cohort 3 400 mg BD (N=3)	Cohort 4 250 mg BD (N=7)	Cohort 5 350 mg BD (N=5)
Cycle 2 Day 1	N	2	2	0	2	0
	Geo.Mean (SD)	2920.415 (2003.824)	10071.132 (14959.722)	0	12416.126 (2044.019)	0
	Min	1829.08	4027.51	0	11054.63	0
	Max	4662.91	25183.75	0	13945.31	0
$T_{½}$ (h)						
Cycle 1 Day 1	N	5	1	1	4	1
	Median (SD)	2.464 (1.213)	4.069 (-)	13.182 (-)	3.945 (1.372)	3.273 (-)
	Min - Max	2.04 - 5.02	4.07 - 4.07	13.18 - 13.18	2.30 - 5.18	3.27 - 3.27
Cycle 2 Day 1	N	2	2	0	2	0
	Min - Max	2.57 - 2.93	7.30 - 10.23	0	2.62 - 3.28	0

Abbreviations: BD=twice daily; Geo Mean=geometric mean; max=maximum; min=minimum; N=number of patients; SD=standard deviation
Source: Table 14.2.2.2

Module 1, Part B

PK parameters for Module 1, Part B are summarised in Table 11-2.

On Cycle 1, Day 1, overall Geo Mean C_{max} was 1232.206 ng/mL (SD: 543.531 ng/mL), with Geo Mean C_{max} similar across both cohorts.

On Cycle 1, Day 1, overall median T_{max} was 6.500 hours (range: 0.52 to 8.40 hours), with median T_{max} higher in Cohort 1 (7.950 hours [range: 5.00 to 8.40 hours]) than in Cohort 2 (2.580 hours [range: 0.52 to 7.97 hours]). Overall, median T_{max} in both cohorts was comparable to overall median T_{max} in Module 1, Part A.

On Cycle 1, Day 1, Geo Mean $AUC_{0\text{-}8\ hours}$ and $AUC_{0\text{-}12\ hours}$ were similar across both cohorts. Overall, Geo Mean $AUC_{0\text{-}last}$ was 5950.798 h×ng/mL (SD: 4972.901 h×ng/mL), with Geo Mean $AUC_{0\text{-}last}$ higher in Cohort 2 (8206.786 h×ng/mL [SD: 5738.218 h×ng/mL]) than in Cohort 1 (5067.297 h×ng/mL [SD: 4395.460 h×ng/mL]). Overall, Geo Mean AUC_{∞} was 10048.076 h×ng/mL (SD: 5058.522 h×ng/mL), higher in Cohort 1 (11146.595 h×ng/mL [SD: 4705.265 h×ng/mL]) than in Cohort 2 (9376.556 h×ng/mL [SD: 6316.806 h×ng/mL]).

On Cycle 1, Day 1, overall median $t_{1/2}$ was 2.627 hours (range: 1.95 to 3.41 hours), with median $t_{1/2}$ similar across both cohorts; however, $t_{1/2}$ was only calculated for 5/15 patients (33.3%).

On Cycle 2, Day 1, overall Geo Mean C_{max} was 1351.275 ng/mL (SD: 771.936 ng/mL), with Geo Mean C_{max} similar to Cycle 1, Day 1.

On Cycle 2, Day 1, overall median T_{max} was 6.000 hours (range: 1.98 to 8.00 hours), with median T_{max} similar to Cycle 1, Day 1.

On Cycle 2, Day 1, Geo Mean $AUC_{0\text{-}8\ hours}$ and $AUC_{0\text{-}12\ hours}$ increased from Cycle 1, Day 1 in Cohort 1, and decreased from Cycle 1, Day 1 in Cohort 2. Overall, Geo Mean $AUC_{0\text{-}last}$ (7716.994 h×ng/mL [SD: 7290.711 h×ng/mL]) increased at Cycle 2, Day 1. Overall, Geo Mean AUC_{∞} at Cycle 2, Day 1 (9953.661 h×ng/mL [SD: 4031.570 h×ng/mL]) was similar to Cycle 1, Day 1. As Cycle 2, Day 1 values were similar to those at Cycle 1, Day 1, there was no evidence for accumulation.

On Cycle 2, Day 1, overall median $t_{1/2}$ was 2.810 hours (range: 2.27 to 2.96 hours), with median $t_{1/2}$ similar to Cycle 1, Day 1; however, due to the limited number of samples following the second dose the elimination phase was not very well characterized, with few profiles allowing reliable estimation of $t_{1/2}$ ($t_{1/2}$ only calculated for 4/15 patients [26.7%]).

Overall, Geo Mean C_{max}, median T_{max}, Geo Mean AUCs and median $t_{1/2}$ in Module 1, Part B were all generally comparable to values in the 200 mg BD and 250 mg BD cohorts in Module 1, Part A.

PK parameters are listed per patient in Listing 16.2.5.2.

Table 11-2 Summary of PK Parameters: Module 1, Part B (PK Set)

		Cohort 1 MET/EXON expansion (N=10) (%)	Cohort 2 MET other basket (N=5) (%)	Total (N=15)
C_{max} (ng/mL)				
Cycle 1 Day 1	N	10	5	15
	Geo Mean (SD)	1250.490 (594.025)	1196.436 (482.153)	1232.206 (543.531)
	Min	655.00	751.00	655.00
	Max	2240.00	1780.00	2240.00
Cycle 2 Day 1	N	8	4	12
	Geo Mean (SD)	1542.165 (818.237)	1037.454 (629.130)	1351.275 (771.936)
	Min	970.00	480.00	480.00
	Max	3330.00	1820.00	3330.00
T_{max} (h)				
Cycle 1 Day 1	N	10	5	15
	Median (SD)	7.950 (1.160)	2.580 (3.161)	6.500 (2.650)
	Min-Max	5.00 - 8.40	0.52 - 7.97	0.52 - 8.40
Cycle 2 Day 1	N	8	4	12
	Median (SD)	6.000 (0.970)	4.500 (3.207)	6.000 (1.970)
	Min-Max	5.00 - 8.00	1.98 - 8.00	1.98 - 8.00
AUC_{0-8} (h*ng/mL)				
Cycle 1 Day 1	N	6	4	10
	Geo.Mean (SD)	6166.106 (2100.862)	5800.329 (3043.556)	6017.105 (2353.832)
	Min	3133.74	2688.88	2688.88
	Max	9611.79	9873.86	9873.86
Cycle 2 Day 1	N	8	4	12
	Geo.Mean (SD)	6719.052 (4084.002)	4529.024 (4141.618)	5891.242 (4017.978)
	Min	2840.00	1732.12	1732.12
	Max	14973.32	10357.53	14973.32
AUC_{0-12} (h*ng/mL)				
Cycle 1 Day 1	N	4	4	8
	Geo.Mean (SD)	8476.962 (3476.626)	8405.543 (4268.792)	8441.177 (3611.601)
	Min	4848.10	3349.97	3349.97
	Max	13096.90	12421.79	13096.90
Cycle 2 Day 1	N	5	2	7
	Geo.Mean (SD)	10622.169 (6567.275)	5495.712 (7417.914)	8799.233 (6506.600)
	Min	6023.04	2351.82	2351.82
	Max	22342.20	12842.33	22342.20

		Cohort 1 MET/EXON expansion (N=10) (%)	Cohort 2 MET other basket (N=5) (%)	Total (N=15)
AUC $_{0-t}$ (h*ng/mL)				
Cycle 1 Day 1	N	10	5	15
	Geo.Mean (SD)	5067.297 (4395.460)	8206.786 (5738.218)	5950.798 (4972.901)
	Min	1581.69	3552.45	1581.69
	Max	14879.34	15513.85	15513.85
Cycle 2 Day 1	N	8	4	12
	Geo.Mean (SD)	8738.700 (7750.813)	6017.981 (6994.603)	7716.994 (7290.711)
	Min	2840.00	2547.24	2547.24
	Max	27191.71	17235.34	27191.71
AUC $_{0-inf}$ (h*ng/mL)				
Cycle 1 Day 1	N	2	3	5
	Geo.Mean (SD)	11146.595 (4705.265)	9376.556 (6316.806)	10048.076 (5058.522)
	Min	8305.43	3872.46	3872.46
	Max	14959.68	15771.83	15771.83
Cycle 2 Day 1	N	4	0	4
	Geo.Mean (SD)	9953.661 (4031.570)	0	9953.661 (4031.570)
	Min	6643.31	0	6643.31
	Max	15698.98	0	15698.98
$T_{½}$ (h)				
Cycle 1 Day 1	N	2	3	5
	Median (SD)	2.290 (0.476)	2.980 (0.593)	2.627 (0.579)
	Min-Max	1.95 - 2.63	2.24 - 3.41	1.95 - 3.41
Cycle 2 Day 1	N	4	0	4
	Median (SD)	2.810 (0.305)	0	2.810 (0.305)
	Min-Max	2.27 - 2.96	0	2.27 - 2.96

Abbreviations: BD= twice daily; Geo Mean=geometric mean; max=maximum; min=minimum; N=number of patients; SD=standard deviation
MET/EXON is any patient with MET EXON 14 mutated NSCLC. MET other basket is any patient with any MET aberration other than MET EXON 14 mutated NSCLC.
Source: Table 14.2.2.2

11.1.3 Pharmacodynamics

11.1.3.1 Tumour Biopsy Data

Paired tumour biopsy information was provided by OCTIMET Oncology NV (see Section 9.5.2) and is presented by patient in Table 11-3.

One patient (Patient 4001-002; MET EXON 14 mutated NSCLC patient dosed at 200 mg BD) had paired tumour biopsy analysis with no issues (Table 11-3). The analysis results of

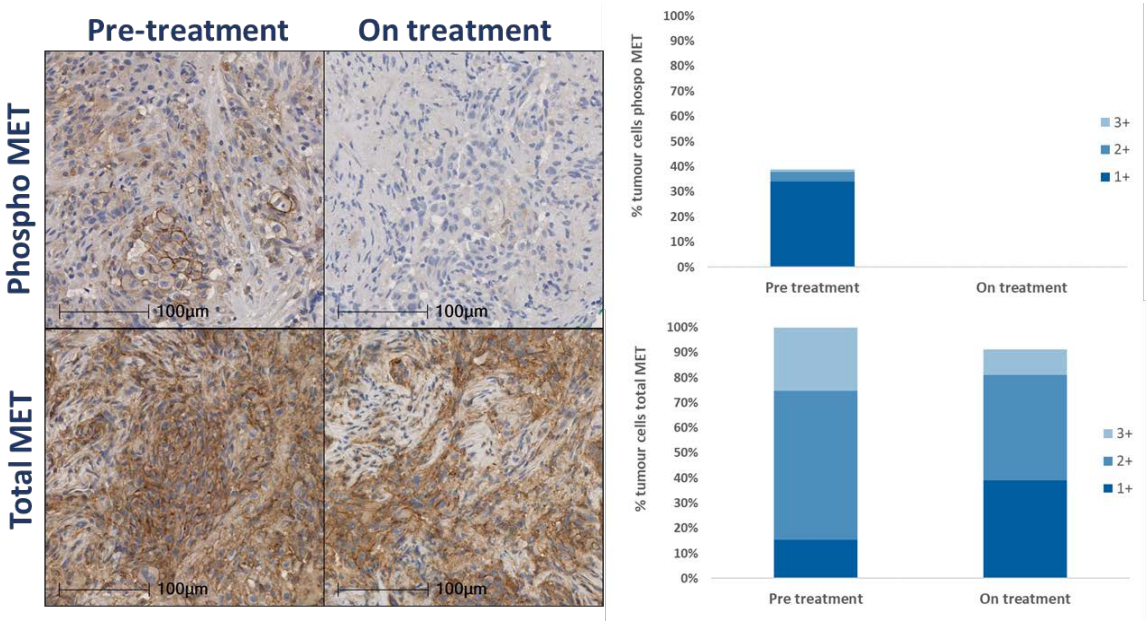
the paired tumour biopsy are presented in Figure 11-5 (ASCO, 2019). The on-treatment biopsy showed near-complete inhibition of phosphorylated MET, without affecting total MET.

Table 11-3 Within Module 1 Part B: Overview of patients with paired biopsy

			Issue for paired biopsy analysis		
Subject Identification	**Expansion Cohort**	**Dose Level**	**No biopsy/tumor tissue for one of the paired biopsy samples**	**No OMO-1 intake before on treatment biopsy sampling**	**None**
4002-001	C2	200mg BD	x		
4002-003	C2	250mg BD	x		
1005-002	C2	200mg BD		x	
1005-003	C2	250mg BD		x	
4001-002	C1	200mg BD			X*
4001-004	C1	250mg BD	x		

Abbreviations: BD=twice daily.
* Data available in Figure 11-5 (source: ASCO, 2019)
Source: Table 13.1.3.4

Figure 11-5: Analysis Results Paired Tumour Biopsy (Patient 4001-002)



IHC analysis results on paired tumour biopsies from a MET EXON 14 mutated NSCLC patient dosed at 200 mg BD OMO 1 (Patient 4001-002)
Near-complete inhibition of phosphorylated MET upon OMO-1 dosing, without affecting total MET levels
Source: Figure 13.1.3.1

11.1.3.2 Serum Creatinine

It is recognised that an increase in serum creatinine for some drugs may be due to inhibition of renal transporters without potential renal injury. The transporter OCT2 is involved in the active secretion of creatinine; OMO-1 is known to be a potent inhibitor of OCT2. It has been recommended that for cases in which a new molecular entity is known to inhibit OCT2 at clinically relevant concentrations, assessment of renal function markers other than creatinine should help evaluate renal function in clinical trials (Arya & Yang et al, 2014).

Creatinine data are presented in Section 12.4.2.1.

12 SAFETY EVALUATION

12.1 Extent of Exposure

Module 1, Part A

Study drug exposure is summarised in Table 12-1 for Module 1, Part A. Overall, the majority of patients had either 1 cycle (10/24 patients [41.75%]) or 2 cycles (5/24 patients [20.8%]). The mean number of cycles per patient was 3.1 cycles (SD: 2.8 cycles). The mean treatment duration was 8.43 weeks (SD: 9.64 weeks).

The highest mean number of cycles (5.8 cycles [SD: 3.0 cycles]) and mean treatment duration in weeks (17.85 weeks [SD: 9.45 weeks]) and days (125.00 days [SD: 66.15 days]) were recorded in Cohort 2.

In total, 5/24 patients (20.8%) recorded at least 1 dose reduction. The proportion of patients with at least 1 dose reduction was highest in Cohort 3 (2/3 patients [66.7%]).

The total number of patients with ≥75% of dosing was 19/24 patients (79.2%). The proportion of patients with ≥75% of dosing was highest in Cohorts 1 and 5 (both 5/5 patients [100%]).

The extent of exposure was highest in Cohorts 1 and 2, with an apparent reduction in the extent of exposure in the higher dose cohorts.

Table 12-1 Study Drug Exposure: Module 1, Part A (Safety Set)

		Cohort 1 100 mg BD (N=5)	Cohort 2 200 mg BD (N=4)	Cohort 3 400 mg BD (N=3)	Cohort 4 250 mg BD (N=7)	Cohort 5 350 mg BD (N=5)	Total (N=24)
Number of cycles per patient, by category (N [%])	N	5	4	3	7	5	24
	1 cycle	2 (40.0)	0	1 (33.3)	3 (42.9)	4 (80.0)	10 (41.7)
	2 cycles	0	1 (25.0)	2 (66.7)	2 (28.6)	0	5 (20.8)
	3 cycles	0	0	0	0	1 (20.0)	1 (4.2)
	4 cycles	1 (20.0)	0	0	1 (14.3)	0	2 (8.3)
	5 cycles	0	1 (25.0)	0	0	0	1 (4.2)
	6 cycles	1 (20.0)	0	0	1 (14.3)	0	2 (8.3)
	7 cycles	0	1 (25.0)	0	0	0	1 (4.2)
	9 cycles	0	1 (25.0)	0	0	0	1 (4.2)
	11 cycles	1 (20.0)	0	0	0	0	1 (4.2)
Number of cycles per patient (N [%])	N	5	4	3	7	5	24
	Mean (SD)	4.6 (4.2)	5.8 (3.0)	1.7 (0.6)	2.4 (1.9)	1.4 (0.9)	3.1 (2.8)
	Median (Range)	4.0 (1-11)	6.0 (2-9)	2.0 (1-2)	2.0 (1-6)	1.0 (1-3)	2.0 (1-11)
Treatment duration (days)	N	5	4	3	7	5	24
	Mean (SD)	95.20 (97.94)	125.00 (66.15)	17.33 (13.87)	45.43 (43.32)	14.20 (17.48)	59.04 (67.52)
	Median (Range)	83.00 (1.0-246.0)	120.50 (49.0-210)	21.00 (2.0-29.0)	42.00 (3.0-119.0)	4.00 (1.0-42.0)	35.50 (1.0-246.0)
Treatment duration (weeks)	N	5	4	3	7	5	24
	Mean (SD)	13.60 (13.98)	17.85 (9.45)	2.47 (1.96)	6.47 (6.19)	2.02 (2.51)	8.43 (9.64)
	Median (Range)	11.90 (0.1-35.1)	17.20 (7.0-30.0)	3.00 (0.3-4.1)	6.00 (0.4-17.0)	0.60 (0.1-6.0)	5.05 (0.1-35.1)
Number of patients with at least one dose reduction (%)	N	0	1 (25.0)	2 (66.7)	2 (28.6)	0	5 (20.8)
Number of patients ≥75% of dosing (%)	N	5 (100)	3 (75.0)	1 (33.3)	5 (71.4)	5 (100)	19 (79.2)

Abbreviations: BD=twice daily, N=number of patients, SD=standard deviation.
The table presents number of events (n) and number and percentage of patients (N[%])
The denominator for each percentage is the number of patients within the column
Source: Table 14.3.8

Module 1, Part B

Study drug exposure is summarised in Table 12-2 for Module 1, Part B. Patient in Module 1, Part B were grouped into cohorts by MET selection criteria. Patients within each cohort in Module 1, Part B may have received doses of either 200 mg BD or 250 mg BD. In Cohort 1, 1 patient received doses of 200 mg BD and 9 patients received doses of 250 mg BD. In

Cohort 2, 2 patients received doses of 200 mg BD and 3 patients received doses of 250 mg BD.

Overall, the vast majority of patients had 2 cycles or more (14/15 patients [93.3%]). The mean number of cycles per patient was 3.6 cycles (SD: 2.1 cycles). The mean treatment duration was 11.10 weeks (SD: 7.38 weeks).

The highest mean number of cycles (4.5 cycles [SD: 2.0 cycles]) and mean treatment duration (14.50 weeks [SD: 6.68 weeks]) were recorded for MET/EXON patients in Cohort 1, which was much higher than for MET other basket patients in Cohort 2 (1.8 cycles [SD: 0.4 cycles]; 4.30 weeks [SD: 1.85 weeks]).

In total, 5/15 patients (33.3%) recorded at least 1 dose reduction. The proportion of patients with at least 1 dose reduction was similar in both Cohort 1 (3/10 patients [30.0%]) and Cohort 2 (2/5 patients [40.0%]).

The total number of patients with ≥75% of dosing was 11/15 patients (73.3%). The proportion of patients with ≥75% of dosing was similar in both Cohort 1 (7/10 patients [70.0%]) and Cohort 2 (4/5 patients [80.0%]).

Extent of exposure was much higher for MET/EXON patients (Cohort 1) than for MET other basket patients (Cohort 2).

Table 12-2 Study Drug Exposure: Module 1, Part B (Safety Set)

		Cohort 1 MET/EXON expansion (N=10) (%)	Cohort 2 MET other basket (N=5) (%)	Total (N=15)
Number of cycles per patient, by category (N [%])	N	10	5	15
	1 cycle	0	1 (20.0)	1 (6.7)
	2 cycles	3 (30.0)	4 (80.0)	7 (46.7)
	4 cycles	1 (10.0)	0	1 (6.7)
	5 cycles	3 (30.0)	0	3 (20.0)
	6 cycles	2 (20.0)	0	2 (13.3)
	8 cycles	1 (10.0)	0	1 (6.7)
Number of cycles per patient (N [%])	N	10	5	15
	Mean (SD)	4.5 (2.0)	1.8 (0.4)	3.6 (2.1)
	Median (Range)	5.0 (2-8)	2.0 (1-2)	2.0 (1-8)
Treatment duration (days)	N	10	5	15
	Mean (SD)	101.50 (46.78)	30.00 (12.98)	77.67 (51.70)
	Median (Range)	100.50 (34.0-169.0)	28.00 (11.0-46.0)	65.00 (11.0-169.0)
Treatment duration (weeks)	N	10	5	15
	Mean (SD)	14.50 (6.68)	4.30 (1.85)	11.10 (7.38)
	Median (Range)	14.35 (4.9-24.1)	4.00 (1.6-6.6)	9.30 (1.6-24.1)
Number of patients with at Least one dose reduction (%)	N	3 (30.0)	2 (40.0)	5 (33.3)
Number of patients ≥75% of dosing (%)	N	7 (70.0)	4 (80.0)	11 (73.3)

Abbreviations: BD=twice daily, N=number of patients, SD=standard deviation.
The table presents number of events (n) and number and percentage of patients (N[%])
The denominator for each percentage is the number of patients within the column
MET/EXON is any patient with MET EXON 14 mutated NSCLC. MET other basket is any patient with any MET aberration other than MET EXON 14 mutated NSCLC.
Source: Table 14.3.9

Module 2, Part A

The 1 patient in Module 2, Part A completed dosing from 19 August 2019 until 28 January 2020; Section 14.3.3), for a total treatment duration of 142 days (with a dose delay of 53 days [from 24 October 2019 to 16 December 2019). As of 17 December 2019, the dose was reduced from 200 mg to 100 mg BD due to fluctuating renal markers (Listing 16.2.1.4).

12.2 Adverse Events

12.2.1 Brief Summary of Adverse Events

Module 1, Part A

Treatment-emergent adverse events (TEAEs) are summarised in Table 12-3 for Module 1, Part A. A total of 258 TEAEs were recorded for all 24 patients in Module 1, Part A (31 events in Cohort 1; 79 events in Cohort 2; 31 events in Cohort 3; 58 events in Cohort 4; 59 events in Cohort 5). Of the 258 TEAEs, the vast majority were Grade 1 (mild) or Grade 2 (moderate) in severity (235/258 events [91.1%]; 23/24 [95.8%] and 20/24 patients [83.3%], respectively). A total of 23 events were Grade 3 (severe) (13 patients [54.2%]). No events of Grade 4 or Grade 5 severity were recorded.

Of the 258 TEAEs, 129 events were considered drug related (50.0%). The 129 drug-related TEAEs were recorded for 23/24 patients (95.8%), with at least 1 drug-related TEAE recorded for all patients in Cohorts 1 to 4 (100%), and 4/5 patients (80%) in Cohort 5. Refer to Section 12.2.2.4 for more detail.

A total of 23 severe TEAEs (23/258 TEAEs [8.9%]) were recorded for 13 patients (54.2%), including: 5 events for 2 patients (40.0%) in Cohort 1; 6 events for 3 patients (75.0%) in Cohort 2; 3 events for 2 patients (66.7%) in Cohort 3; 4 events for 3 patients (42.9%) in Cohort 4; 5 events for 3 patients (60.0%) in Cohort 5. Refer to Section 12.2.2.2 for more detail.

In total, 24 treatment-emergent SAEs (24/258 TEAEs [9.3%]) were recorded for 11 patients (45.8%), including: 8 events for 3 patients (60.0%) in Cohort 1; 1 event for 1 patient (25.0%) in Cohort 2; 10 events for 3 patients (100%) in Cohort 3; 2 events for 1 patient (14.3%) in Cohort 4; 3 events for 3 patients (60.0%) in Cohort 5. Refer to Section 12.2.2.3 for more detail.

Of the 24 SAEs, 11 SAEs recorded for 7 patients (29.2%) were considered drug related. Refer to Section 12.2.2.5 for more detail.

A total of 18 TEAEs that led to study drug discontinuation (18/258 TEAEs [7.0%]) were recorded for 9 patients (37.5%), including: 1 event for 1 patient (20.0%) in Cohort 1; 1 event for 1 patient (25.0%) in Cohort 2; 5 events for 2 patients (66.7%) in Cohort 3; 7 events for 2 patients (28.6%) in Cohort 4; 4 events for 3 patients (60.0%) in Cohort 5. Refer to Section 12.2.2.6 for more detail.

Table 12-3 Summary of Treatment-emergent Adverse Events: Module 1, Part A (Safety Set)

	Cohort 1 100 mg BD (N=5)		Cohort 2 200 mg BD (N=4)		Cohort 3 400 mg BD (N=3)		Cohort 4 250 mg BD (N=7)		Cohort 5 350 mg BD (N=5)		Total (N=24)	
	n	N (%)	n	N (%)	n	N (%)	n	N (%)	n	N (%)	n	N (%)
Treatment-emergent Adverse Events	31	5 (100.0)	79	4 (100.0)	31	3 (100.0)	58	7 (100.0)	59	5 (100.0)	258	24 (100.0)
Severe Treatment-emergent Adverse Events	5	2 (40.0)	6	3 (75.0)	3	2 (66.7)	4	3 (42.9)	5	3 (60.0)	23	13 (54.2)
Serious Treatment-emergent Adverse Events	8	3 (60.0)	1	1 (25.0)	10	3 (100.0)	2	1 (14.3)	3	3 (60.0)	24	11 (45.8)
Drug-Related Treatment-emergent Adverse Events	17	5 (100.0)	43	4 (100.0)	16	3 (100.0)	30	7 (100.0)	23	4 (80.0)	129	23 (95.8)
Serious Drug-related Treatment-emergent Adverse Events	2	2 (40.0)	1	1 (25.0)	6	2 (66.7)	1	1 (14.3)	1	1 (20.0)	11	7 (29.2)
Treatment-emergent Adverse Events leading to Study Drug Discontinuation	1	1 (20.0)	1	1 (25.0)	5	2 (66.7)	7	2 (28.6)	4	3 (60.0)	18	9 (37.5)
Severity												
Grade 1	19	5 (100.0)	55	4 (100.0)	15	3 (100.0)	36	7 (100.0)	35	4 (80.0)	160	23 (95.8)
Grade 2	7	4 (80.0)	18	3 (75.0)	13	3 (100.0)	18	6 (85.7)	19	4 (80.0)	75	20 (83.3)
Grade 3	5	2 (40.0)	6	3 (75.0)	3	2 (66.7)	4	3 (42.9)	5	3 (60.0)	23	13 (54.2)
Grade 4		0		0		0		0		0		0
Grade 5		0		0		0		0		0		0

Abbreviations: BD=twice daily, N=number of patients.
The table presents number of events (n) and number and percentage of patients (N[%])
The denominator for each percentage is the number of patients within the column
Source: Table 14.3.1.1.1

Module 1, Part B

Treatment-emergent adverse events (TEAEs) are summarised in Table 12-4 for Module 1, Part B. A total of 178 TEAEs were recorded for all 15 patients (100%) in Module 1, Part B (132 events in Cohort 1; 46 events in Cohort 2). Of the 178 TEAEs, the majority were Grade 1 or Grade 2 in severity (155 events [87.1%]; 14 [93.3%] and 13 patients [86.7%], respectively). A total of 20 events were Grade 3 in severity (10 patients [66.7%]) and 1 event was Grade 4 in severity (1 patient [6.7%]). No events of Grade 5 severity were recorded.

Of the 178 TEAEs, 65 events were considered drug related (36.5%). At least 1 drug-related TEAE was recorded for all 15 patients (100%). Refer to Section 12.2.2.4 for more detail.

A total of 23 severe TEAEs (23/178 TEAEs [12.9%]) were recorded for 11 patients (73.3%), including 13 events for 6 patients (60.0%) in Cohort 1 and 10 events for 5 patients (100%) in Cohort 2. Refer to Section 12.2.2.2 for more detail.

In total, 14 treatment-emergent SAEs (14/178 TEAEs [7.9%]) were recorded for 9 patients (60.0%), including 9 events for 6 patients (60.0%) in Cohort 1 and 5 events for 3 patients (60.0%) in Cohort 2. Refer to Section 12.2.2.3 for more detail.

Of the 14 SAEs, 2 SAEs recorded for 2 patients (13.3%; 1 patient in each cohort) were considered drug related. Refer to Section 12.2.2.5 for more detail.

A total of 3 TEAEs that led to study drug discontinuation (3/178 TEAEs [1.7%]) were recorded for 3 patients (20.0%), including 2 events for 2 patients (20.0%) in Cohort 1 and 1 event for 1 patient (20.0%) in Cohort 2. Refer to Section 12.2.2.6 for more detail.

Table 12-4 Summary of Treatment-emergent Adverse Events: Module 1, Part B (Safety Set)

	Cohort 1 MET/EXON expansion (N=10) n N (%)	Cohort 2 MET other basket (N=5) n N (%)	Total (N=15) n N (%)
Treatment-emergent Adverse Events	132 10 (100.0)	46 5 (100.0)	178 15 (100.0)
Severe Treatment-emergent Adverse Events	13 6 (60.0)	10 5 (100.0)	23 11 (73.3)
Serious Treatment-emergent Adverse Events	9 6 (60.0)	5 3 (60.0)	14 9 (60.0)
Drug-related Treatment-emergent Adverse Events	52 10 (100.0)	13 5 (100.0)	65 15 (100.0)
Serious Drug-related Treatment-emergent Adverse Events	1 1 (10.0)	1 1 (20.0)	2 2 (13.3)
Treatment-emergent Adverse Events leading to Study Drug Discontinuation	2 2 (20.0)	1 1 (20.0)	3 3 (20.0)
Severity			
Grade 1	75 10 (100.0)	26 4 (80.0)	101 14 (93.3)
Grade 2	44 10 (100.0)	10 3 (60.0)	54 13 (86.7)
Grade 3	10 5 (50.0)	10 5 (100.0)	20 10 (66.7)
Grade 4	1 1 (10.0)	0	1 1 (6.7)
Grade 5	0	0	0

Abbreviations: BD=twice daily, N=number of patients.
The table presents number of events (n) and number and percentage of patients (N[%])
The denominator for each percentage is the number of patients within the column
MET/EXON is any patient with MET EXON 14 mutated NSCLC. MET other basket is any patient with any MET aberration other than MET EXON 14 mutated NSCLC.
Source: Table 14.3.1.1.1

Module 2, Part A

The one patient in Module 2, Part A had 5 TEAEs recorded. Three (3; nausea, diarrhoea and vomiting) of the 5 TEAEs were non-serious, Grade 1 in severity, considered possibly related to the IMP, and were resolved at the end of the study. The patient also had 1 TEAE (increased cystatin C) recorded that was non-serious, had no severity reported, was considered definitely related to the IMP, and was ongoing at the end of the study (Listing 16.2.7.1).

The patient had 1 SAE of seizure recorded that was considered not related to the IMP (see Section 12.3.1.2).

As there was only one patient in Module 2, Part A, this patient was reported into narrative format (for more details refer to Section 14.3.3).

12.2.2 Display of Adverse Events

12.2.2.1 Treatment-emergent Adverse Events

Module 1, Part A

TEAEs in >1 patient are summarised by system organ class (SOC) and preferred term (PT) in Table 12-5 for Module 1, Part A. The most common TEAEs (≥10 patients) by SOC were:

- gastrointestinal disorders (67 events; 21 patients [87.5%]);
- investigations (42 events; 14 patients [58.3%]);
- general disorders and administration site conditions (29 events; 13 patients [54.2%]);
- nervous system disorders (22 events; 13 patients [54.2%]).

In Module 1, Part A, the most common TEAEs (≥5 patients) by PT were:

- increased blood creatinine (15 events; 11 patients [45.8%]);
- nausea (14 events; 11 patients [45.8%]);
- vomiting (21 events; 10 patients [41.7%]);
- fatigue (18 events; 10 patients [41.7%]);
- headache (11 events; 7 patients [29.2%]);
- diarrhoea (10 events; 6 patients [25.0%]);
- anaemia (8 events; 5 patients [20.8%]);
- abdominal pain and decreased appetite (both 6 events; 5 patients [20.8%]);
- dizziness (5 events; 5 patients [20.8%]).

In the 200 mg, 400 mg and 250 mg cohorts, 4 patients (100%), 3 patients (100%) and 4 patients (57.1%), respectively, had increased blood creatinine values reported as TEAEs whereas no events were recorded for the 100 mg and 350 mg cohorts. Fatigue was recorded for 2 patients (66.7%), 3 patients (42.9%) and 3 patients (60.0%) in the 400 mg, 250 mg and 350 mg cohorts, respectively, and only in 1 patient in both the 100 mg and 200 mg cohorts (20.0% and 25.5%, respectively).

Most TEAEs were generally recorded in similar proportions of patients across treatment cohorts and there were no apparent dose-dependent trends in TEAEs in Module 1, Part A.

Table 12-5 Summary of Treatment-emergent Adverse Events in >1 patient by System Organ Class and Preferred Term: Module 1, Part A (Safety Set)

	Cohort 1 100 mg BD (N=5) n N (%)	Cohort 2 200 mg BD (N=4) n N (%)	Cohort 3 400 mg BD (N=3) n N (%)	Cohort 4 250 mg BD (N=7) n N (%)	Cohort 5 350 mg BD (N=5) n N (%)	Total (N=24) n N (%)
Any Treatment-emergent Adverse Events	31 5 (100)	79 4 (100)	31 3 (100)	58 7 (100)	59 5 (100)	258 24 (100)
Blood and lymphatic system disorders	**1 1 (20.0)**	**4 2 (50.0)**	**2 1 (33.3)**	**3 2 (28.6)**	**1 1 (20.0%)**	**11 7 (29.2%)**
Anaemia	0	4 2 (50.0)	2 1 (33.3)	1 1 (14.3)	1 1 (20.0)	8 5 (20.8)
Cardiac disorders	**0**	**0**	**1 1 (33.3)**	**1 1 (14.3)**	**1 1 (20.0)**	**3 3 (12.5)**
Tachycardia	0	0	1 1 (33.3)	0	1 1 (20.0)	2 2 (8.3)
Gastrointestinal disorders	**13 5 (100)**	**21 4 (100)**	**4 2 (66.7)**	**15 5 (71.4)**	**14 5 (100)**	**67 21 (87.5)**
Abdominal discomfort	0	0	0	1 1 (14.3)	1 1 (20.0)	2 2 (8.3)
Abdominal pain	1 1 (20.0)	1 1 (25.0)	0	2 2 (28.6)	2 1 (20.0)	6 5 (20.8)
Constipation	1 1 (20.0)	0	0	1 1 (14.3)	0	2 2 (8.3)
Diarrhoea	1 1 (20.0)	6 3 (75.0)	2 1 (33.3)	1 1 (14.3)	0	10 6 (25.0)
Dyspepsia	0	2 1 (25.0)	0	0	1 1 (20.0)	3 2 (8.3)
Nausea	2 2 (40.0)	5 3 (75.0)	1 1 (33.3)	4 4 (57.1)	2 1 (20.0)	14 11 (45.8)
Vomiting	4 1 (20.0)	5 2 (50.0)	0	6 3 (42.9)	6 4 (80.0)	21 10 (41.7)
General disorders and administration site conditions	**3 2 (40.0)**	**6 2 (50.0)**	**5 3 (100)**	**8 3 (42.9)**	**7 3 (60.0)**	**29 13 (54.2)**
Chills	0	1 1 (25.0)	0	0	2 1 (20.0)	3 2 (8.3)
Fatigue	1 1 (20.0)	2 1 (25.0)	3 2 (66.7)	8 3 (42.9)	4 3 (60.0)	18 10 (41.7)
Infections and infestations	**3 1 (20.0)**	**6 2 (50.0)**	**3 2 (66.7)**	**4 3 (42.9)**	**1 1 (20.0)**	**17 9 (37.5)**
Lower respiratory tract infection	0	3 2 (50.0)	1 1 (33.3)	0	0	4 3 (12.5)
Oral candidiasis	1 1 (20.0)	0	0	1 1 (14.3)	0	2 2 (8.3)
Urinary tract infection	1 1 (20.0)	0	0	1 1 (14.3)	0	2 2 (8.3)

	Cohort 1 100 mg BD (N=5) n N (%)	Cohort 2 200 mg BD (N=4) n N (%)	Cohort 3 400 mg BD (N=3) n N (%)	Cohort 4 250 mg BD (N=7) n N (%)	Cohort 5 350 mg BD (N=5) n N (%)	Total (N=24) n N (%)
Investigations	**0**	**14 4 (100.0)**	**6 3 (100.0)**	**11 5 (71.4)**	**11 2 (40.0)**	**42 14 (58.3)**
Alanine aminotransferase increased	0	0	0	1 1 (14.3)	2 1 (20.0)	3 2 (8.3)
Blood alkaline phosphatase increased	0	0	0	0	4 2 (40.0)	4 2 (8.3)
Blood bilirubin increased	0	0	1 1 (33.3)	0	2 1 (20.0)	3 2 (8.3)
Blood creatinine increased	0	6 4 (100.0)	3 3 (100.0)	6 4 (57.1)	0	15 11 (45.8)
Blood uric acid increased	0	2 2 (50.0)	0	0	0	2 2 (8.3)
Lymphocyte count decreased	0	1 1 (25.0)	0	1 1 (14.3)	0	2 2 (8.3)
Troponin increased	0	1 1 (25.0)	1 1 (33.3)	0	0	2 2 (8.3)
Weight decreased	0	0	0	2 2 (28.6)	0	2 2 (8.3)
Metabolism and nutrition disorders	**2 2 (40.0)**	**3 2 (50.0)**	**0**	**2 1 (14.3)**	**6 2 (40.0)**	**13 7 (29.2)**
Decreased appetite	2 2 (40.0)	1 1 (25.0)	0	2 1 (14.3)	1 1 (20.0)	6 5 (20.8)
Hypoalbuminaemia	0	1 1 (25.0)	0	0	1 1 (20.0)	2 2 (8.3)
Hyponatraemia	0	1 1 (25.0)	0	0	1 1 (20.0)	2 2 (8.3)
Musculoskeletal and connective tissue disorders	**2 1 (20.0)**	**4 3 (75.0)**	**2 1 (33.3)**	**0**	**4 3 (60.0)**	**12 8 (33.3)**
Arthralgia	1 1 (20.0)	0	0	0	1 1 (20.0)	2 2 (8.3)
Back pain	0	2 2 (50.0)	0	0	0	2 2 (8.3)
Pain in extremity	0	0	1 1 (33.3)	0	2 1 (20.0)	3 2 (8.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0**	**0**	**1 1 (14.3)**	**2 2 (40.0)**	**3 3 (12.5)**
Metastases to central nervous system	0	0	0	0	2 2 (40.0)	2 2 (8.3)
Nervous system disorders	**2 2 (40.0)**	**8 3 (75.0)**	**3 3 (100.0)**	**3 3 (42.9)**	**6 2 (40.0)**	**22 13 (54.2)**
Dizziness	1 1 (20.0)	1 1 (25.0)	0	2 2 (28.6)	1 1 (20.0)	5 5 (20.8)
Headache	1 1 (20.0)	5 3 (75.0)	1 1 (33.3)	1 1 (14.3)	3 1 (20.0)	11 7 (29.2)
Renal and urinary disorders	**1 1 (20.0)**	**0**	**0**	**2 2 (28.6)**	**1 1 (20.0)**	**4 4 (16.7)**

	Cohort 1 100 mg BD (N=5) n N (%)	Cohort 2 200 mg BD (N=4) n N (%)	Cohort 3 400 mg BD (N=3) n N (%)	Cohort 4 250 mg BD (N=7) n N (%)	Cohort 5 350 mg BD (N=5) n N (%)	Total (N=24) n N (%)
Pollakiuria	1 1 (20.0)	0	0	1 1 (14.3)	0	2 2 (8.3)
Respiratory, thoracic and mediastinal disorders	**1 1 (20.0)**	**4 2 (50.0)**	**1 1 (33.3)**	**3 2 (28.6)**	**3 2 (40.0)**	**12 8 (33.3)**
Cough	0	0	0	1 1 (14.3)	1 1 (20.0)	2 2 (8.3)
Dyspnoea	0	1 1 (25.0)	1 1 (33.3)	2 1 (14.3)	1 1 (20.0)	5 4 (16.7)
Productive cough	1 1 (20.0)	1 1 (25.0)	0	0	0	2 2 (8.3)
Skin and subcutaneous tissue disorders	**3 3 (60.0)**	**4 2 (50.0)**	**0**	**3 2 (28.6)**	**1 1 (20.0)**	**11 8 (33.3)**
Dry skin	1 1 (20.0)	1 1 (25.0)	0	0	0	2 2 (8.3)
Pruritus	1 1 (20.0)	1 1 (25.0)	0	0	1 1 (20.0)	3 3 (12.5)
Vascular disorders	**0**	**3 2 (50.0)**	**2 1 (33.3)**	**1 1 (14.3)**	**0**	**6 4 (16.7)**
Superior vena cava occlusion	0	0	1 1 (33.3)	1 1 (14.3)	0	2 2 (8.3)

Abbreviations: BD=twice daily, N=number of patients.
The table presents number of events (n) and number and percentage of patients (N [%])
The denominator for each percentage is the number of patients within the column
Source: Table 14.3.1.2

Module 1, Part B

Treatment-emergent AEs in >1 patient are summarised by SOC and PT in Table 12-6 for Module 1, Part B. The most common TEAEs (≥8 patients) by SOC were:

- gastrointestinal disorders (43 events; 13 patients [86.7%]);
- general disorders and administration site conditions (20 events; 12 patients [80.0%]);
- respiratory, thoracic and mediastinal disorders (18 events; 10 patients [66.7%]);
- investigations (27 events; 8 patients [53.3%]).

The most common TEAEs (≥5 patients) by PT were:

- nausea (18 events; 10 patients [66.7%]);
- vomiting (12 events; 7 patients [46.7%]);
- increased blood creatinine (10 events; 5 patients [33.3%]);
- fatigue (8 events; 5 patients [33.3%]);
- cough (5 events; 5 patients [33.3%]).

The most common TEAEs recorded in Module 1, Part B were similar to those in Module 1, Part A.

Table 12-6 Summary of Treatment-emergent Adverse Events in >1 patient by System Organ Class and Preferred Term: Module 1, Part B (Safety Set)

	Cohort 1 MET/EXON expansion (N=10)		Cohort 2 MET other basket (N=5)		Total (N=15)	
	n	N (%)	n	N (%)	n	N (%)
Any Treatment-emergent Adverse Events	132	10 (100.0)	46	5 (100.0)	178	15 (100.0)
Blood and lymphatic system disorders	**2**	**2 (20.0)**	**4**	**2 (40.0)**	**6**	**4 (26.7)**
Anaemia	2	2 (20.0)	2	2 (40.0)	4	4 (26.7)
Cardiac disorders	**8**	**4 (40.0)**	**1**	**1 (20.0)**	**9**	**5 (33.3)**
Atrial fibrillation	5	3 (30.0)		0	5	3 (20.0)
Tachycardia	2	2 (20.0)	1	1 (20.0)	3	3 (20.0)
Eye disorders	**2**	**2 (20.0)**		**0**	**2**	**2 (13.3)**
Gastrointestinal disorders	**31**	**9 (90.0)**	**12**	**4 (80.0)**	**43**	**13 (86.7)**
Constipation	2	2 (20.0)	2	2 (40.0)	4	4 (26.7)
Diarrhoea	3	3 (30.0)		0	3	3 (20.0)
Nausea	14	8 (80.0)	4	2 (40.0)	18	10 (66.7)
Vomiting	10	6 (60.0)	2	1 (20.0)	12	7 (46.7)
General disorders and administration site conditions	**16**	**9 (90.0)**	**4**	**3 (60.0)**	**20**	**12 (80.0)**
Asthenia	1	1 (10.0)	1	1 (20.0)	2	2 (13.3)
Chest pain	2	2 (20.0)		0	2	2 (13.3)
Chronic fatigue syndrome	2	2 (20.0)		0	2	2 (13.3)
Fatigue	7	4 (40.0)	1	1 (20.0)	8	5 (33.3)
Oedema peripheral	2	2 (20.0)		0	2	2 (13.3)
Pain	1	1 (10.0)	1	1 (20.0)	2	2 (13.3)
Infections and infestations	**10**	**4 (40.0)**		**0**	**10**	**4 (26.7)**
Bronchitis	2	2 (20.0)		0	2	2 (13.3)
Investigations	**15**	**7 (70.0)**	**12**	**1 (20.0)**	**27**	**8 (53.3)**
Blood creatinine increased	10	5 (50.0)		0	10	5 (33.3)
Metabolism and nutrition disorders	**9**	**5 (50.0)**	**7**	**2 (40.0)**	**16**	**7 (46.7)**
Decreased appetite	5	3 (30.0)	1	1 (20.0)	6	4 (26.7)
Hypokalaemia	2	1 (10.0)	1	1 (20.0)	3	2 (13.3)
Hyponatraemia		0	3	2 (40.0)	3	2 (13.3)
Musculoskeletal and connective tissue disorders	**4**	**2 (20.0)**	**1**	**1 (20.0)**	**5**	**3 (20.0)**
Nervous system disorders	**9**	**4 (40.0)**	**1**	**1 (20.0)**	**10**	**5 (33.3)**
Respiratory, thoracic and mediastinal disorders	**15**	**8 (80.0)**	**3**	**2 (40.0)**	**18**	**10 (66.7)**

	Cohort 1 MET/EXON expansion (N=10) n N (%)	Cohort 2 MET other basket (N=5) n N (%)	Total (N=15) n N (%)
Cough	3 3 (30.0)	2 2 (40.0%)	5 5 (33.3)
Dyspnoea	4 3 (30.0)	0	4 3 (20.0)
Pleural effusion	2 2 (20.0)	0	2 2 (13.3)
Skin and subcutaneous tissue disorders	**7 5 (50.0%)**	**0**	**7 5 (33.3)**
Rash	2 2 (20.0)	0	2 2 (13.3)

Abbreviations: BD=twice daily, N=number of patients.
The table presents number of events (n) and number and percentage of patients (N [%])
The denominator for each percentage is the number of patients within the column
MET/EXON is any patient with MET EXON 14 mutated NSCLC. MET other basket is any patient with any MET aberration other than MET EXON 14 mutated NSCLC.
Source: Table 14.3.1.2

12.2.2.2 Severe Treatment-emergent Adverse Events

Module 1, Part A

Severe TEAEs are summarised by SOC and PT in Table 12-7 for Module 1, Part A. In total, 23 severe TEAEs were recorded for 13 patients (54.2%; Cohort 1: 5 events for 2 patients [40.0%]; Cohort 2: 6 events for 3 patients [75.0%]; Cohort 3: 3 events for 2 patients [66.7%]; Cohort 4: 4 events for 3 patients [42.9%]; Cohort 5: 5 events for 3 patients [60.0%]).

Of the 23 severe TEAEs, only vomiting (3 events for 3 patients [12.5%] and metastases to central nervous system (2 events for 2 patients [8.3%]) were recorded for more than 1 patient.

There were no apparent dose-dependent trends in severe TEAEs recorded.

Table 12-7 Summary of Severe Treatment-emergent Adverse Events by System Organ Class and Preferred Term: Module 1, Part A (Safety Set)

	Cohort 1 100 mg BD (N=5) n N (%)	Cohort 2 200 mg BD (N=4) n N (%)	Cohort 3 400 mg BD (N=3) n N (%)	Cohort 4 250 mg BD (N=7) n N (%)	Cohort 5 350 mg BD (N=5) n N (%)	Total (N=24) n N (%)
Any Severe Treatment-emergent Adverse Events	5 2 (40.0)	6 3 (75.0)	3 2 (66.7)	4 3 (42.9)	5 3 (60.0)	23 13 (54.2)
Blood and lymphatic system disorders	**0**	**1 1 (25.0)**	**0**	**0**	**0**	**1 1 (4.2)**
Anaemia	0	1 1 (25.0)	0	0	0	1 1 (4.2)
Gastrointestinal disorders	**4 2 (40.0)**	**3 2 (50.0)**	**0**	**0**	**0**	**7 4 (16.7)**
Abdominal pain upper	1 1 (20.0)	0	0	0	0	1 1 (4.2)
Diarrhoea	0	1 1 (25.0)	0	0	0	1 1 (4.2)
Nausea	1 1 (20.0)	0	0	0	0	1 1 (4.2)
Rectal haemorrhage	1 1 (20.0)	0	0	0	0	1 1 (4.2)
Vomiting	1 1 (20.0)	2 2 (50.0)	0	0	0	3 3 (12.5)
General disorders and administration site conditions	**0**	**0**	**1 1 (33.3)**	**2 1 (14.3)**	**0**	**3 2 (8.3)**
Fatigue	0	0	0	2 1 (14.3)	0	2 1 (4.2)
Influenza like illness	0	0	1 1 (33.3)	0	0	1 1 (4.2)
Infections and infestations	**1 1 (20.0)**	**0**	**0**	**0**	**0**	**1 1 (4.2)**
Urinary tract infection	1 1 (20.0)	0	0	0	0	1 1 (4.2)
Investigations	**0**	**0**	**1 1 (33.3)**	**1 1 (14.3)**	**2 2 (40.0)**	**4 4 (16.7)**
Blood alkaline phosphatase increased	0	0	0	0	1 1 (20.0)	1 1 (4.2)
Blood creatinine increased	0	0	0	1 1 (14.3)	0	1 1 (4.2)
Gamma-glutamyltransferase increased	0	0	0	0	1 1 (20.0)	1 1 (4.2)
Troponin increased	0	0	1 1 (33.3)	0	0	1 1 (4.2)
Metabolism and nutrition disorders	**0**	**0**	**0**	**0**	**1 1 (20.0)**	**1 1 (4.2)**

	Cohort 1 100 mg BD (N=5) n N (%)	Cohort 2 200 mg BD (N=4) n N (%)	Cohort 3 400 mg BD (N=3) n N (%)	Cohort 4 250 mg BD (N=7) n N (%)	Cohort 5 350 mg BD (N=5) n N (%)	Total (N=24) n N (%)
Hyponatraemia	0	0	0	0	1 1 (20.0)	1 1 (4.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0**	**0**	**0**	**2 2 (40.0)**	**2 2 (8.3)**
Metastases to central nervous system	0	0	0	0	2 2 (40.0)	2 2 (8.3)
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**0**	**1 1 (14.3)**	**0**	**1 1 (4.2)**
Dyspnoea	0	0	0	1 1 (14.3)	0	1 1 (4.2)
Vascular disorders	**0**	**2 1 (25.0)**	**1 1 (33.3)**	**0**	**0**	**3 2 (8.3)**
Hypertension	0	2 1 (25.0)	0	0	0	2 1 (4.2)
Superior vena cava occlusion	0	0	1 1 (33.3)	0	0	1 1 (4.2)

Abbreviations: BD=twice daily, N=number of patients.
The table presents number of events (n) and number and percentage of patients (N [%])
The denominator for each percentage is the number of patients within the column
Source: Table 14.3.1.3

Module 1, Part B

Severe TEAEs are summarised by SOC and PT in Table 12-8 for Module 1, Part B. In total, 23 severe TEAEs were recorded for 11 patients (73.3%), including 13 events for 6 patients (60.0%) in Cohort 1 and 10 events for 5 patients (100%) in Cohort 2.

Of the 23 severe TEAEs, only dyspnoea (2 events for 2 patients [13.3%]) was recorded for more than 1 patient.

There were no apparent trends in severe TEAEs recorded.

Table 12-8 Summary of Severe Treatment-emergent Adverse Events by System Organ Class and Preferred Term: Module 1, Part B (Safety Set)

	Cohort 1 MET/EXON expansion (N=10) n N (%)	Cohort 2 MET other basket (N=5) n N (%)	Total (N=15) n N (%)
Any Severe Treatment-emergent Adverse Events	13 6 (60.0)	10 5 (100.0)	23 11 (73.3)
Blood and lymphatic system disorders	**0**	**1 1 (20.0)**	**1 1 (6.7)**
Anaemia	0	1 1 (20.0)	1 1 (6.7)
Gastrointestinal disorders	**0**	**2 2 (40.0)**	**2 2 (13.3)**
Ascites	0	1 1 (20.0)	1 1 (6.7)
Vomiting	0	1 1 (20.0)	1 1 (6.7)
General disorders and administration site conditions	**0**	**2 2 (40.0)**	**2 2 (13.3)**
Fatigue	0	1 1 (20.0)	1 1 (6.7)
Pyrexia	0	1 1 (20.0)	1 1 (6.7)
Infections and infestations	**3 2 (20.0)**	**0**	**3 2 (13.3)**
Abscess	1 1 (10.0%)	0	1 1 (6.7)
Pulmonary sepsis	1 1 (10.0%)	0	1 1 (6.7)
Pyelonephritis	1 1 (10.0%)	0	1 1 (6.7)
Investigations	**3 2 (20.0)**	**2 1 (20.0)**	**5 3 (20.0)**
Blood alkaline phosphatase increased	0	1 1 (20.0)	1 1 (6.7)
Blood bilirubin increased	0	1 1 (20.0)	1 1 (6.7)
Blood creatinine increased	1 1 (10.0)	0	1 1 (6.7)
Cystatin C increased	1 1 (10.0)	0	1 1 (6.7)
Renal function test abnormal	1 1 (10.0)	0	1 1 (6.7)
Metabolism and nutrition disorders	**1 1 (10.0)**	**1 1 (20.0)**	**2 2 (13.3)**
Hypokalaemia	1 1 (10.0)	0	1 1 (6.7)
Hyponatraemia	0	1 1 (20.0)	1 1 (6.7)
Musculoskeletal and connective tissue disorders	**1 1 (10.0)**	**0**	**1 1 (6.7)**
Musculoskeletal pain	1 1 (10.0)	0	1 1 (6.7)
Nervous system disorders	**0**	**1 1 (20.0)**	**1 1 (6.7)**
Spinal cord compression	0	1 1 (20.0)	1 1 (6.7)
Product issues	**0**	**1 1 (20.0)**	**1 1 (6.7)**
Device occlusion	0	1 1 (20.0)	1 1 (6.7)
Respiratory, thoracic and mediastinal disorders	**5 4 (40.0)**	**0**	**5 4 (26.7)**
Dyspnoea	2 2 (20.0)	0	2 2 (13.3)

	Cohort 1 MET/EXON expansion (N=10) n N (%)	Cohort 2 MET other basket (N=5) n N (%)	Total (N=15) n N (%)
Lung disorder	1 1 (10.0)	0	1 1 (6.7)
Pleural effusion	1 1 (10.0)	0	1 1 (6.7)
Pneumothorax	1 1 (10.0)	0	1 1 (6.7)

Abbreviations: BD=twice daily, N=number of patients.
The table presents number of events (n) and number and percentage of patients (N [%])
The denominator for each percentage is the number of patients within the column
MET/EXON is any patient with MET EXON 14 mutated NSCLC. MET other basket is any patient with any MET aberration other than MET EXON 14 mutated NSCLC.
Source: Table 14.3.1.3

12.2.2.3 Serious Treatment-emergent Adverse Events

For individual patient narratives refer to Section 14.3.3.

Module 1, Part A

Serious TEAEs are summarised by SOC and PT in Table 12-9 for Module 1, Part A. In total, 24 serious TEAEs were recorded for 11 patients (45.8%), including 8 events for 3 patients (60.0%) in Cohort 1, 1 event for 1 patient (25.0%) in Cohort 2, and 10 events for 3 patients (100%) in Cohort 3, 2 events for 1 patient (14.3%) in Cohort 4 and 3 events for 3 patients (60.0%) in Cohort 5.

Of the 24 SAEs, the following SAEs were recorded for more than 1 patient:

- nausea (3 events; 3 patients [12.5%]);
- vomiting (3 events; 2 patients [8.3]);
- metastases to central nervous system and superior vena cava occlusion (both 2 events; 2 patients [8.3%]).

There were no apparent dose-dependent trends in SAEs recorded.

Table 12-9 Summary of Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term: Module 1, Part A (Safety Set)

	Cohort 1 100 mg BD (N=5)			Cohort 2 200 mg BD (N=4)			Cohort 3 400 mg BD (N=3)			Cohort 4 250 mg BD (N=7)			Cohort 5 350 mg BD (N=5)			Total (N=24)		
	n	N	(%)	n	N	(%)	n	N	(%)	n	N	(%)	n	N	(%)	n	N	(%)
Any Serious Treatment-emergent Adverse Events	8	3	(60.0)	1	1	(25.0)	10	3	(100.0)	2	1	(14.3)	3	3	(60.0)	24	11	(45.8)
Gastrointestinal disorders	**6**	**3**	**(60.0)**	**0**			**2**	**1**	**(33.3)**	**1**	**1**	**(14.3)**	**1**	**1**	**(20.0)**	**10**	**6**	**(25.0)**
Abdominal pain	1	1	(20.0)	0			0			0			0			1	1	(4.2)
Abdominal pain upper	1	1	(20.0)	0			0			0			0			1	1	(4.2)
Diarrhoea	0			0			1	1	(33.3)	0			0			1	1	(4.2)
Large intestinal obstruction	1	1	(20.0)	0			0			0			0			1	1	(4.2)
Nausea	1	1	(20.0)	0			1	1	(33.3)	1	1	(14.3)	0			3	3	(12.5)
Vomiting	2	1	(20.0)	0			0			0			1	1	(20.0)	3	2	(8.3)
General disorders and administration site conditions	**0**			**1**	**1**	**(25.0)**	**1**	**1**	**(33.3)**	**0**			**0**			**2**	**2**	**(8.3)**
Chills	0			1	1	(25.0)	0			0			0			1	1	(4.2)
Influenza like illness	0			0			1	1	(33.3)	0			0			1	1	(4.2)
Infections and infestations	**2**	**1**	**(20.0)**	**0**			**1**	**1**	**(33.3)**	**0**			**0**			**3**	**2**	**(8.3)**
Pneumonia	1	1	(20.0)	0			0			0			0			1	1	(4.2)
Upper respiratory tract infection	0			0			1	1	(33.3)	0			0			1	1	(4.2)
Urinary tract infection	1	1	(20.0)	0			0			0			0			1	1	(4.2)
Investigations	**0**			**0**			**4**	**2**	**(66.7)**	**0**			**0**			**4**	**2**	**(8.3)**
Blood bilirubin increased	0			0			1	1	(33.3)	0			0			1	1	(4.2)
Blood creatinine increased	0			0			1	1	(33.3)	0			0			1	1	(4.2)
Neutrophil count increased	0			0			1	1	(33.3)	0			0			1	1	(4.2)
Troponin increased	0			0			1	1	(33.3)	0			0			1	1	(4.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**			**0**			**0**			**0**			**2**	**2**	**(40.0)**	**2**	**2**	**(8.3)**
Metastases to central nervous system	0			0			0			0			2	2	(40.0)	2	2	(8.3)
Respiratory, thoracic and mediastinal disorders	**0**			**0**			**1**	**1**	**(33.3)**	**0**			**0**			**1**	**1**	**(4.2)**
Dyspnoea	0			0			1	1	(33.3)	0			0			1	1	(4.2)
Vascular disorders	**0**			**0**			**1**	**1**	**(33.3)**	**1**	**1**	**(14.3)**	**0**			**2**	**2**	**(8.3)**
Superior vena cava occlusion	0			0			1	1	(33.3)	1	1	(14.3)	0			2	2	(8.3)

Abbreviations: BD=twice daily, N=number of patients.
The table presents number of events (n) and number and percentage of patients (N [%])

The denominator for each percentage is the number of patients within the column
Source: Table 14.3.1.4.

Module 1, Part B

Serious TEAEs are summarised by SOC and PT in Table 12-10 for Module 1, Part B. In total, 14 serious TEAEs were recorded for 9 patients (60.0%), with similar proportions of patients across both cohorts (9 events for 6 patients [60.0%] in Cohort 1; 5 events for 3 patients [60.0%] in Cohort 2).

Of the 14 SAEs, no SAEs were recorded for more than 1 patient. There were no apparent trends in SAEs recorded.

Table 12-10 Summary of Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term: Module 1, Part B (Safety Set)

	Cohort 1 MET/EXON expansion (N=10) n N (%)	Cohort 2 MET other basket (N=5) n N (%)	Total (N=15) n N (%)
Any Serious Treatment-emergent Adverse Events	9 6 (60.0)	5 3 (60.0)	14 9 (60.0)
Cardiac disorders	**1 1 (10.0)**	**1 1 (20.0)**	**2 2 (13.3)**
Atrial fibrillation	1 1 (10.0)	0	1 1 (6.7)
Tachycardia	0	1 1 (20.0)	1 1 (6.7)
Gastrointestinal disorders	**0**	**1 1 (20.0)**	**1 1 (6.7)**
Vomiting	0	1 1 (20.0)	1 1 (6.7)
General disorders and administration site conditions	**1 1 (10.0)**	**1 1 (20.0)**	**2 2 (13.3)**
Chills	1 1 (10.0)	0	1 1 (6.7)
Pyrexia	0	1 1 (20.0)	1 1 (6.7)
Infections and infestations	**3 3 (30.0)**	**0**	**3 3 (20.0)**
Lung infection	1 1 (10.0)	0	1 1 (6.7)
Pulmonary sepsis	1 1 (10.0)	0	1 1 (6.7)
Pyelonephritis	1 1 (10.0)	0	1 1 (6.7)
Investigations	**1 1 (10.0)**	**0**	**1 1 (6.7)**
Blood creatinine increased	1 1 (10.0)	0	1 1 (6.7)
Nervous system disorders	**0**	**1 1 (20.0)**	**1 1 (6.7)**
Spinal cord compression	0	1 1 (20.0)	1 1 (6.7)
Product issues	**0**	**1 1 (20.0)**	**1 1 (6.7)**
Device occlusion	0	1 1 (20.0)	1 1 (6.7)
Renal and urinary disorders	**1 1 (10.0)**	**0**	**1 1 (6.7)**
Calculus urinary	1 1 (10.0)	0	1 1 (6.7)
Respiratory, thoracic and mediastinal disorders	**2 2 (20.0)**	**0**	**2 2 (13.3)**
Dyspnoea	1 1 (10.0)	0	1 1 (6.7)
Lung disorder	1 1 (10.0)	0	1 1 (6.7))

Abbreviations: BD=twice daily, N=number of patients.
The table presents number of events (n) and number and percentage of patients (N [%])
The denominator for each percentage is the number of patients within the column
MET/EXON is any patient with MET EXON 14 mutated NSCLC. MET other basket is any patient with any MET aberration other than MET EXON 14 mutated NSCLC.
Source: Table 14.3.1.4

12.2.2.4 Drug-related Treatment-emergent Adverse Events

Module 1, Part A

Drug-related TEAEs are summarised by SOC and PT in Table 12-11 for Module 1, Part A. In total, 129 drug-related TEAEs were recorded for 23 patients (95.8%), with similar proportions of patients across all cohorts (17 events for 5 patients [100%] in Cohort 1, 43 events for 4 patients [100%] in Cohort 2, and 16 events for 3 patients [100%] in Cohort 3, 30 events for 7 patients [100%] in Cohort 4 and 23 events for 4 patients [80.0%] in Cohort 5).

In Module 1, Part A, the most common drug-related TEAEs (≥10 patients) by SOC were:

- gastrointestinal disorders (44 events; 16 patients [66.7%]);
- general disorders and administration site conditions (18 events; 12 patients [50.0%]);
- investigations (22 events; 10 patients [41.7%]).

In Module 1, Part A, the most common drug-related TEAEs (≥5 patients) by PT were:

- nausea (13 events; 11 patients [45.8%]);
- fatigue (14 events; 10 patients [41.7%]);
- vomiting (17 events; 9 patients [37.5%]);
- increased blood creatinine (12 events; 9 patients [37.5]);
- headache (8 events; 5 patients [20.8%]).

A higher proportion of patients in the 200 mg, 400 mg and 250 mg cohorts (3 patients [75.0%], 3 patients [100%] and 3 patients [42.9%], respectively) had increased blood creatinine values than in the 100 mg and 350 mg cohorts (no events for either cohort). Fatigue was recorded for a higher proportion of patients in the 400 mg, 250 mg and 350 mg cohorts (2 patients [66.7%], 3 patients [42.9%] and 3 patients [60.0%], respectively) than in the 100 mg and 200 mg cohorts (1 patient in both cohorts [20.0% and 25.5%, respectively]).

With the exceptions of increased blood creatinine and fatigue, most drug-related TEAEs were generally recorded in similar proportions of patients across treatment cohorts. There were no apparent dose-dependent trends in drug-related TEAEs recorded.

Table 12-11 Summary of Drug-related Treatment-emergent Adverse Events in >1 patient by System Organ Class and Preferred Term: Module 1, Part A (Safety Set)

	Cohort 1 100 mg BD (N=5)		Cohort 2 200 mg BD (N=4)		Cohort 3 400 mg BD (N=3)		Cohort 4 250 mg BD (N=7)		Cohort 5 350 mg BD (N=5)		Total (N=24)	
	n	N (%)	n	N (%)	n	N (%)	n	N (%)	n	N (%)	n	N (%)
Any Drug-related Treatment-emergent Adverse Events	17	5 (100.0)	43	4 (100.0)	16	3 (100.0)	30	7 (100.0)	23	4 (80.0)	129	23 (95.8)
Blood and lymphatic system disorders	**0**		**3**	**2 (50.0)**	**1**	**1 (33.3)**	**1**	**1 (14.3)**	**0**		**5**	**4 (16.7)**
Anaemia	0		3	2 (50.0)	1	1 (33.3)	1	1 (14.3)	0		5	4 (16.7)
Cardiac disorders	**0**		**0**		**1**	**1 (33.3)**	**1**	**1 (14.3)**	**1**	**1 (20.0)**	**3**	**3 (12.5)**
Tachycardia	0		0		1	1 (33.3)	0		1	1 (20.0)	2	2 (8.3)
Gastrointestinal disorders	**7**	**3 (60.0)**	**5**	**4 (100.0)**	**4**	**2 (66.7)**	**11**	**4 (57.1)**	**7**	**3 (60.0)**	**44**	**16 (66.7)**
Diarrhoea	0		5	2 (50.0)	2	1 (33.3)	1	1 (14.3)	0		8	4 (16.7)
Nausea	2	2 (40.0)	4	3 (75.0)	1	1 (33.3)	4	4 (57.1)	2	1 (20.0)	13	11 (45.8)
Vomiting	3	1 (20.0)	4	2 (50.0)	0		6	3 (42.9)	4	3 (60.0)	17	9 (37.5)
General disorders and administration site conditions	**1**	**1 (20.0)**	**2**	**2 (50.0)**	**3**	**3 (100.0)**	**7**	**3 (42.9)**	**5**	**3 (60.0)**	**18**	**12 (50.0)**
Chills	0		1	1 (25.0)	0		0		2	1 (20.0)	3	2 (8.3)
Fatigue	1	1 (20.0)	1	1 (25.0)	2	2 (66.7)	7	3 (42.9)	3	3 60.0)	14	10 (41.7)
Investigations	**0**		**10**	**3 (75.0)**	**5**	**3 (100.0)**	**7**	**4 (57.1)**	**0**		**22**	**10 (41.7)**
Blood creatinine increased	0		5	3 (75.0)	3	3 (100.0)	4	3 (42.9)	0		12	9 (37.5)
Lymphocyte count decreased	0		1	1 (25.0)	0		1	1 (14.3)	0		2	2 (8.3)
Metabolism and nutrition disorders	**1**	**1 (20.0)**	**2**	**2 (50.0)**	**0**		**2**	**1 (14.3)**	**3**	**2 (40.0)**	**8**	**6 (25.0)**
Decreased appetite	1	1 (20.0)	1	1 (25.0)	0		2	1 (14.3)	1	1 (20.0)	5	4 (16.7)
Hyponatraemia	0		1	1 (25.0)	0		0		1	1 (20.0)	2	2 (8.3)

	Cohort 1 100 mg BD (N=5) n N (%)	Cohort 2 200 mg BD (N=4) n N (%)	Cohort 3 400 mg BD (N=3) n N (%)	Cohort 4 250 mg BD (N=7) n N (%)	Cohort 5 350 mg BD (N=5) n N (%)	Total (N=24) n N (%)
Musculoskeletal and connective tissue disorders	**2 1 (20.0)**	**0**	**0**	**0**	**1 1 (20.0)**	**3 2 (8.3)**
Arthralgia	1 1 (20.0)	0	0	0	1 1 (20.0)	2 2 (8.3)
Nervous system disorders	**2 2 (40.0)**	**7 3 (75.0)**	**1 1 (33.3)**	**1 1 (14.3)**	**3 2 (40.0)**	**14 9 (37.5)**
Dizziness	1 1 (20.0)	1 1 (25.0)	0	1 1 (14.3)	1 1 (20.0)	4 4 (16.7)
Headache	1 1 (20.0)	5 3 (75.0)	0	0	2 1 (20.0)	8 5 (20.8)
Renal and urinary disorders	**1 1 (20.0)**	**0**	**0**	**0**	**1 1 (20.0)**	**2 2 (8.3)**
Skin and subcutaneous tissue disorders	**2 2 (40.0)**	**2 2 (50.0)**	**0**	**0**	**1 1 (20.0)**	**5 5 (20.8)**
Pruritus	1 1 (20.0)	0	0	0	1 1 (20.0)	2 2 (8.3)
Vascular disorders	**0**	**2 2 (50.0)**	**0**	**0**	**0**	**2 2 (8.3)**

Abbreviations: BD=twice daily, N=number of patients.
The table presents number of events (n) and number and percentage of patients (N [%])
The denominator for each percentage is the number of patients within the column
Source: Table 14.3.1.5

Module 1, Part B

Drug-related TEAEs are summarised by SOC and PT in Table 12-12 for Module 1, Part B. In total, 65 drug-related TEAEs were recorded for 15 patients (100%).

In Module 1, Part B, the most common drug-related TEAEs (≥8 patients) by SOC were:

- gastrointestinal disorders (23 events; 9 patients [60.0%]).

In Module 1, Part B, the most common TEAEs (≥5 patients) by PT were:

- nausea (13 events; 7 patients [46.7%]);
- increased blood creatinine (10 events; 5 patients [33.3%]).

All events of increased blood creatinine were recorded for patients in Cohort 1.

With the exceptions of increased blood creatinine, most drug-related TEAEs were generally recorded for similar proportions of patients across both cohorts. There were no apparent trends in drug-related TEAEs recorded. Drug-related TEAEs recorded in Module 1, Part B were similar to those recorded in Module 1, Part A.

Table 12-12 Summary of Drug-related Treatment-emergent Adverse Events in >1 patient by System Organ Class and Preferred Term: Module 1, Part B (Safety Set)

	Cohort 1 MET/EXON expansion (N=10)			Cohort 2 MET other basket (N=5)			Total (N=15)		
	n	**N**	**(%)**	**n**	**N**	**(%)**	**n**	**N**	**(%)**
Any Drug-related Treatment-emergent Adverse Events	52	10	(100.0)	13	5	(100.0)	65	15	(100.0)
Cardiac disorders	**3**	**2**	**(20.0)**	**0**			**3**	**2**	**(13.3)**
Atrial fibrillation	2	2	20.0)	0			2	2	(13.3)
Gastrointestinal disorders	**15**	**6**	**(60.0)**	**8**	**3**	**(60.0)**	**23**	**9**	**(60.0)**
Nausea	9	5	(50.0)	4	2	(40.0)	13	7	(46.7)
Vomiting	5	3	(30.0)	2	1	(20.0)	7	4	(26.7)
General disorders and administration site conditions	**6**	**3**	**(30.0)**	**1**	**1**	**(20.0)**	**7**	**4**	**(26.7)**
Fatigue	6	3	(30.0)	1	1	(20.0)	7	4	(26.7)
Investigations	**13**	**6**	**(60.0)**	**2**	**1**	**(20.0)**	**15**	**7**	**(46.7)**
Blood creatinine increased	10	5	(50.0)	0			10	5	(33.3)
Metabolism and nutrition disorders	**6**	**5**	**(50.0)**	**1**	**1**	**(20.0)**	**7**	**6**	**(40.0)**
Decreased appetite	4	3	(30.0)	1	1	(20.0)	5	4	(26.7)
Nervous system disorders	**4**	**3**	**(30.0)**	**0**			**4**	**3**	**(20.0)**

	Cohort 1 MET/EXON expansion (N=10) n N (%)	Cohort 2 MET other basket (N=5) n N (%)	Total (N=15) n N (%)
Skin and subcutaneous tissue disorders	**3 3 (30.0)**	**0**	**3 3 (20.0)**

Abbreviations: BD=twice daily, N=number of patients.
The table presents number of events (n) and number and percentage of patients (N [%])
The denominator for each percentage is the number of patients within the column
MET/EXON is any patient with MET EXON 14 mutated NSCLC. MET other basket is any patient with any MET aberration other than MET EXON 14 mutated NSCLC.
Source: Table 14.3.1.5.1

12.2.2.5 Serious Drug-related Treatment-emergent Adverse Events

Serious drug-related TEAEs are summarised by SOC and PT in Table 14.3.1.6.

Module 1, Part A

In total, 11 drug-related SAEs were recorded for 7 patients (29.2%), including 2 events for 2 patients (40.0%) in Cohort 1, 1 event for 1 patient (25.0%) in Cohort 2, 6 events for 2 patients (66.7%) in Cohort 3, 1 event for 1 patient (14.3%) in Cohort 4 and 1 event for 1 patient (20.0) in Cohort 5.

Of the 11 drug-related SAEs, the following SAEs were recorded for more than 1 patient:

- nausea (3 events; 3 patients [12.5%]);
- vomiting (2 events; 2 patients [8.3]).

More than half of the drug-related SAEs (6/11 drug related SAEs [54.5%]) were recorded for 2 patients (66.7%) in the highest dose cohort (Cohort 3).

Module 1, Part B

In total, 2 drug-related SAEs were recorded for 2 patients (13.3%), including 1 patient (10.0%) in Cohort 1 (increased blood creatinine) and 1 patient (20.0%) in Cohort 2 (vomiting).

No drug-related SAE was recorded for more than 1 patient.

12.2.2.6 Treatment-emergent Adverse Events Leading to Study Drug Discontinuation

Treatment-emergent AEs leading to study drug discontinuation are summarised by SOC and PT in Table 14.3.1.7.

Module 1, Part A

In total, 18 TEAEs leading to IMP discontinuation were recorded for 9 patients (37.5%), including: 1 event for 1 patient (20.0%) in Cohort 1; 1 event for 1 patient (25.0%) in

Cohort 2; 5 events for 2 patients (66.7%) in Cohort 3; 7 events for 2 patients (28.6%) in Cohort 4; 4 events for 3 patients (60.0%) in Cohort 5.

Of the 18 TEAEs leading to IMP discontinuation, the following TEAEs were recorded for more than 1 patient:

- fatigue (6 events; 4 patients [16.7%]);
- vomiting (3 events; 3 patients [12.5%]);
- nausea (2 events; 2 patients [8.3%]).

The vast majority of TEAEs leading to IMP discontinuation (16/18 TEAEs [88.9%]) were recorded for patients in the 3 highest dose cohorts (Cohorts 3, 4 and 5).

Module 1, Part B

In total, 3 TEAEs leading to IMP discontinuation were recorded for 3 patients (20.0%), including 2 events (increased blood creatinine and increased cystatin C) for 2 patients (20.0%) in Cohort 1 and 1 event (spinal cord compression) for 1 patient (20.0%) in Cohort 2.

No TEAE leading to IMP discontinuation was recorded for more than 1 patient. The range of TEAEs leading to IMP discontinuation reported in Module 1, Part B was similar for the Cohort 1 and 2 dose groups in Module 1, Part A.

12.2.3 Analysis of Adverse Events

Module 1, Part A

The frequency of TEAEs was consistent across all cohorts, with 100% of patients having at least 1 TEAE. The majority of TEAEs were considered Grade 1 or Grade 2 in severity (235 of 258 events [91.1%]; see Section 12.2.1).

Half of the TEAEs in Module 1, Part A were considered drug related (129 of 258 events [50.0%]; see Table 12-3), with at least 1 drug-related TEAE for 100% of patients in Cohorts 1 to 4, and 80.0% of patients in Cohort 5. Of the 129 drug-related TEAEs, over half were in the gastrointestinal disorders (44 events), investigations (22 events) and general disorders and administration site conditions (18 events) SOCs (see Section 12.2.2.4). The most common drug-related TEAEs by PT were vomiting (17 events), fatigue (14 events), nausea (13 events), increased blood creatinine (12 events) and headache (8 events; see Table 12-11). Most drug-related TEAEs were generally recorded in similar proportions of patients across treatment cohorts. In total, 11 drug-related SAEs were recorded for 7 patients (29.2%; see Section 12.2.2.5). The most common drug-related SAEs by PT were nausea (3 events) and vomiting (2 events).

With the exception of the majority of TEAEs leading to IMP discontinuation being recorded at the higher dose levels, there were no apparent dose-dependent trends in TEAEs recorded across all 5 cohorts.

Module 1, Part B

The frequency of reported TEAEs was consistent across both cohorts, with 100% of patients reporting at least 1 TEAE. The majority of TEAEs were considered Grade 1 or Grade 2 in severity (155 of 178 events [87.1%]; see Section 12.2.1).

Approximately one third of the TEAEs reported in Module 1, Part B were considered drug related (65 of 178 events [36.5%]; see Table 12-4), with at least 1 drug-related TEAE recorded for 100% of patients in both cohorts. Of the 65 drug-related TEAEs, 23 events were in the gastrointestinal disorders SOC (see Section 12.2.2.4). The most common drug-related TEAEs by PT were nausea (13 events) and increased blood creatinine (10 events; see Table 12-12). All 10 events of increased blood creatinine were reported in Cohort 1. With the exception of increased blood creatinine, most drug-related TEAEs were generally recorded in similar proportions of patients across both cohorts. In total, 2 drug-related SAEs were recorded for 2 patients (13.3%), including 1 event of increased blood creatinine and 1 event of vomiting (see Section 12.2.2.5).

There were no apparent trends in TEAEs recorded across both cohorts.

12.2.4 Listing of Adverse Events by Patient

Refer to Listing 16.2.7.1 (Adverse Event Listing), Listing 16.2.7.1.1 (Related Adverse Event Listing), Listing 16.2.7.2 (DLT Listing) and Listing 16.2.7.3 (Adverse Events Module 1, Part A, Cycle 1 Listing).

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1.1 Deaths

Module 1, Part A

No patients died in Module 1, Part A (Listing 16.2.1.3).

Module 1, Part B

In Module 1, Part B, 3 patients died after discontinuation of treatment as follows (Listing 16.2.1.3):

- Patient 3001-002 (Cohort 2): Patient completed the last study visit on 21 Nov 2018 and was recorded as having completed the study on 04 Dec 2018 but did not completed the follow-up visit as the patient was hospitalized for falling health conditions. The patient died on 04 Dec 2018 died due to a major disease progression (peritoneal carcinosis, liver progression and probable paraneoplastic leukemogenic response). An autopsy was not performed (refer to Section 14.3.3).

- Patient 4002-001 (Cohort 2): Patient was permanently withdrawn from the study on 26 Jun 2018 due to progressive disease and died on 06 Jul 2018.
- Patient 4002-003 (Cohort 2): Patient was permanently withdrawn from the study on 19 Dec 2018 as the wish of the patient was to have no more follow up. The patient did not complete the follow-up visit. The patient died on 09 Jan 2019 due to disease progression.

None of the deaths were considered related to IMP.

One additional patient (Patient 1003-005), who signed the informed consent form but did not receive IMP, died due to respiratory failure on 05 Jun 2018 during the screening period (refer to Section 14.3.3).

No Grade 5 (fatal) TEAEs were recorded for any patients in either Module 1, Part A or Part B or in Module 2 (Listing 16.2.7.1).

12.3.1.2 Other Serious Adverse Events

Module 1, Part A

The following 25 SAEs were recorded for 11 patients in Module 1, Part A:

- Patient 1001-001 (Cohort 1, 100 mg BD) recorded the following SAEs:
  - On 19 Aug 2017 (prior to first dose of IMP), the patient recorded an event of constipation which was Grade 2 in severity and considered not related to IMP. Following treatment with concomitant medication and procedures, the event resolved with sequelae on 20 Aug 2017. No action was taken with IMP.
  - On 29 Aug 2017 (Cycle 1), the patient recorded an event of abdominal pain which was Grade 2 in severity and considered not related to IMP. Following treatment with concomitant medication, the event resolved with sequelae on 02 Sep 2017. Due to the event, IMP was stopped temporarily.
  - On 11 Sep 2017 (Cycle 1), the patient recorded an event of vomiting which was Grade 3 in severity and considered possibly related to IMP. Following treatment with concomitant medication, the event resolved with sequelae on 12 Sep 2017. Due to the event, IMP was stopped temporarily.
  - On 27 Sep 2017 (Cycle 1), the patient recorded another event of vomiting which was Grade 2 in severity and considered not related to IMP. Following treatment with concomitant medication, the event resolved on 29 Sep 2017. No action was taken with IMP.
- Patient 1001-004 (Cohort 1, 100 mg BD) recorded the following SAEs:
  - On 09 Oct 2017 (Cycle 1), the patient recorded events of nausea, pneumonia and urinary tract infection which were Grade 3, 1 and 3 in severity, respectively. The event of nausea was considered definitely related to IMP

and the events of pneumonia and urinary tract infection were considered not related to IMP. Following treatment with concomitant medication, the event of nausea resolved on 12 Oct 2017 and no action was taken with IMP. Following treatment with concomitant medication, the event of pneumonia resolved on 13 Oct 2017. Following treatment with concomitant medication and procedures, the event of urinary tract infection resolved on 13 Oct 2017. Due to the events of pneumonia and urinary tract infection, treatment with IMP was stopped temporarily.

  - On 10 Oct 2017 (Cycle 1), the patient recorded an event of abdominal pain upper which was Grade 3 in severity and considered not related to IMP. Following treatment with concomitant medication, the event resolved with sequelae on 12 Oct 2017. Due to the event, IMP was stopped temporarily.

- Patient 1001-006 (Cohort 1, 100 mg BD): On 21 Jan 2018 (Cycle 4), the patient recorded an event of large intestinal obstruction which was Grade 2 in severity and considered not related to IMP. Following treatment with concomitant medication and procedures, the event resolved with sequelae on 02 Feb 2018. Due to the event, IMP was permanently discontinued.
- Patient 1002-001 (Cohort 2, 200 mg BD): On 28 Dec 2017 (Cycle 2), the patient recorded an event of chills which was Grade 2 in severity and considered definitely related to IMP. Following treatment with concomitant medication, the event resolved on the same day (28 Dec 2017). Due to the event, IMP was stopped temporarily.
- Patient 1001-009 (Cohort 3, 400 mg BD): On 06 Mar 2018 (Cycle 1), the patient recorded an event of influenza like illness which was Grade 3 considered possibly related to IMP. Following treatment with concomitant medication and procedures, the event resolved on 09 Mar 2018. Due to the event, IMP was stopped temporarily.
- Patient 1002-002 (Cohort 3, 400 mg BD) recorded the following SAEs:
  - On 22 Feb 2018 (Cycle 1), the patient recorded events of diarrhoea, nausea and upper respiratory tract infection which were Grade 2, 1 and 2 in severity, respectively. The events of diarrhoea and nausea were considered definitely related to IMP and the event of upper respiratory tract infection was considered not related to IMP. All events resolved on 26 Feb 2018, with no action taken. Due to the events, IMP was stopped temporarily.
  - On 22 Feb 2018 (Cycle 1), the patient recorded an event of neutrophil count increased which was Grade 1 in severity and considered possibly related to IMP. The event resolved on 24 Feb 2018, with no action taken. Due to the event, IMP was stopped temporarily.
  - On 23 Feb 2018 (Cycle 1), the patient recorded an event of blood creatinine increased which was Grade 1 in severity and considered possibly related to

IMP. The event resolved on 21 Mar 2018, with no action taken. Due to the event, IMP was stopped temporarily.

  - On 23 Feb 2018 (Cycle 1), the patient recorded an event of blood bilirubin increased which was Grade 1 in severity and considered possibly related to IMP. The event resolved on 24 Feb 2018, with no action taken. Due to the event, IMP was permanently discontinued.

- Patient 1003-002 (Cohort 3, 400 mg BD) recorded the following SAEs:
  - On 12 Mar 2018 (Cycle 2), the patient recorded an event of superior vena cava occlusion which was Grade 3 in severity and considered not related to IMP. Following treatment with concomitant medication and procedures, the event resolved on 13 Mar 2018. No action was taken with IMP.
  - On 14 Mar 2018 (Cycle 2), the patient recorded events of dyspnoea and troponin increased which were Grade 2 and 3 in severity, respectively. Both events were considered not related to IMP. The event of troponin increased was treated with concomitant medication. Both events did not recover/resolve and no action was taken with the IMP.
- Patient 1002-004 (Cohort 4, 250 mg BD) recorded the following SAEs:
  - On 22 Jun 2018 (Cycle 1), the patient recorded an event of nausea which was Grade 2 in severity and considered definitely related to IMP. The event was treated with concomitant medication and did not recover/resolve. No action was taken with IMP.
  - On 28 Jun 2018 (Cycle 1), the patient recorded an event of superior vena cava occlusion which was Grade 2 in severity and considered not related to IMP. The event was treated with concomitant medication and did not recover/resolve. No action was recorded with IMP.
- Patient 1001-012 (Cohort 5, 350 mg BD): On 21 Aug 2018 (Cycle 1), the patient recorded an event of metastases to central nervous system which was Grade 3 in severity and considered not related to IMP. Following treatment with procedures, the event resolved on 08 Sep 2018. No action was taken with IMP.
- Patient 1002-005 (Cohort 5, 350 mg BD): On 07 Nov 2018 (more than 28 days after Day 1 of last cycle), the patient recorded an event of metastases to central nervous system which was Grade 3 in severity and considered not related to IMP. The event was treated with concomitant medication and was considered ongoing. Due to the event, IMP was permanently discontinued.
- Patient 1003-008 (Cohort 5, 350 mg BD): On 27 Oct 2018 (Cycle 1), the patient recorded an event of vomiting which was Grade 2 in severity and considered definitely related to IMP. The event resolved on 28 Oct 2018, with no action taken. Due to the event, IMP was permanently discontinued.

Module 1, Part B

The following 15 SAEs were recorded by 10 patients in Module 1, Part B:

- Patient 1002-008 (Cohort 1): On 05 Oct 2019 (Cycle 1), the patient recorded an event of atrial fibrillation which was Grade 2 in severity and considered not related to IMP. Following treatment with concomitant medication, the event resolved with sequelae on 07 Oct 2019. No action was taken with IMP.
- Patient 2001-001 (Cohort 1): On 08 Sep 2019 (Cycle 2), the patient recorded an event of dyspnoea which was Grade 3 in severity and considered not related to IMP. Following treatment with procedures, the event resolved on 18 Sep 2019. No action was recorded with IMP.
- Patient 3001-001 (Cohort 1) recorded the following SAEs:
    - On 06 Nov 2018 (Cycle 3), the patient recorded an event of chills which was Grade 2 in severity and considered not related to IMP. The event resolved on 09 Nov 2018, with no action taken. No action was taken with IMP.
    - On 07 Dec 2018 (Cycle 5), the patient recorded an event of lung infection which was Grade 2 in severity and considered not related to IMP. Following treatment with concomitant medication, the event resolved on 13 Dec 2018. No action was taken with IMP.
- Patient 3001-003 (Cohort 1) recorded the following SAEs:
    - On 10 Jun 2019 (Cycle 6), the patient recorded events of pyelonephritis and lung disorder which were both Grade 3 in severity and considered not related to IMP. Following treatment with concomitant medication and procedures, the event of pyelonephritis resolved on 21 Jun 2019. Following treatment with concomitant medication, the event of lung disorder resolved on 21 Jun 2019. Due to the event of pyelonephritis, IMP was temporarily stopped. Due to the event of lung disorder, IMP was permanently discontinued.
    - On 16 Jul 2019 (more than 28 days after Day 1 of last cycle), the patient recorded an event of calculus urinary which was Grade 2 in severity and considered not related to IMP. The event resolved on 18 Jul 2019, with no action taken. No action was taken with IMP.
- Patient 4001-002 (Cohort 1): On 27 Jun 2018 (Cycle 1), the patient recorded an event of pulmonary sepsis which was Grade 3 in severity and considered not related to IMP. Following treatment with concomitant medication, the event resolved on 03 Jul 2018. Due to the event, IMP was stopped temporarily.
- Patient 4001-006 (Cohort 1): On 29 Oct 2018 (Cycle 1), the patient recorded an event of blood creatinine increased which was Grade 4 in severity and considered possibly related to IMP. Following treatment with procedures, the event resolved on 04 Nov 2018. Due to the event, IMP was stopped temporarily.

- Patient 1005-002 (Cohort 2): On 04 Jun 2018 (Cycle 2), the patient recorded an event of spinal cord compression which was Grade 3 in severity and considered not related to IMP. Following treatment with procedures, the event resolved with sequelae on 19 Jun 2018. Due to the event, IMP was permanently discontinued.
- Patient 1005-003 (Cohort 2) recorded the following SAEs:
  - On 05 Aug 2018 (Cycle 2), the patient recorded events of pyrexia and tachycardia which were Grade 3 and 1 in severity, respectively, and considered not related to IMP. Following treatment with concomitant medication, the event of pyrexia resolved on 06 Aug 2018. The event of tachycardia resolved on 06 Aug 2018, with no action taken. Due to the event of pyrexia and tachycardia, IMP was stopped temporarily.
  - On 16 Aug 2018 (Cycle 1), the patient recorded an event of device occlusion which was Grade 3 in severity and considered not related to IMP. Following treatment with concomitant medication and procedures, the event resolved with sequelae on 23 Aug 2018. No action was taken with IMP.
- Patient 3001-002 (Cohort 2): On 13 Nov 2018 (Cycle 2), the patient recorded an event of vomiting which was Grade 3 in severity and considered definitely related to IMP. Following treatment with concomitant medication, the event resolved on 21 Nov 2018. Due to the event, IMP was stopped temporarily.
- Patient 4002-003 (Cohort 2): On 26 Oct 2018 (prior to first dose of IMP), the patient recorded an event of respiratory tract infection viral which was Grade 1 in severity and considered not related to IMP. Following treatment with concomitant medication and procedures, the event resolved on 28 Oct 2018. No action was taken with IMP.

Module 2, Part A

One SAE was recorded by 1 patient in Module 2, Part A:

- Patient 2001-002 (Cohort 2): On 10 Nov 2019 (Cycle 4), the patient recorded an event of seizure which was Grade 2 in severity and considered not related to IMP. Following treatment with concomitant medication and procedures, the event resolved on 11 Nov 2019. No action was taken with IMP.

For more information regarding the SAEs, refer to the individual patient narratives in Section 14.3.3.

12.3.1.3 Other Significant Adverse Events

Module 1, Part A

The following 18 AEs that led to permanent withdrawal of IMP were recorded by 9 patients in Module 1, Part A:

- Patient 1001-006 (Cohort 1, 100 mg BD): Patient recorded a serious event of large intestinal obstruction (Refer to Section 12.3.1.2).
- Patient 1003-001 (Cohort 2, 200 mg BD): On 29 Dec 2017 (Cycle 1), the patient recorded an event of fatigue which was not serious, Grade 1 in severity and considered not related to IMP. The event was treated with concomitant medication and was considered ongoing. Due to the event, IMP was permanently discontinued.
- Patient 1001-009 (Cohort 3, 400 mg BD): On 21 Mar 2018 (Cycle 2), the patient recorded an event of hypersensitivity which was not serious, Grade 2 in severity and considered definitely related to IMP. Following treatment with concomitant medication, the event resolved on 21 Mar 2018. Due to the event, IMP was permanently discontinued.
- Patient 1002-002 (Cohort 3, 400 mg BD) recorded the following AEs that led to permanent withdrawal of the IMP:
    - Patient recorded a serious event of blood bilirubin increased (Refer to Section 12.3.1.2).
    - On 26 Feb 2018 (Cycle 1), the patient recorded an event of diarrhoea which was not serious, Grade 1 in severity and considered possibly related to IMP. The event resolved on 28 Feb 2018, with no action taken. Due to the event, IMP was permanently discontinued.
    - On 27 Feb 2018 (Cycle 1), the patient recorded an event of headache which was not serious, Grade 1 in severity and considered not related to IMP. Following treatment with concomitant medication, the event resolved on 27 Feb 2018. Due to the event, IMP was permanently discontinued.
    - On 01 Mar 2018 (Cycle 1), the patient recorded an event of fatigue which was not serious, Grade 1 in severity and considered possibly related to IMP. No treatment was given for the event and it was considered ongoing. Due to the event, IMP was permanently discontinued.
- Patient 1003-004 (Cohort 4, 250 mg BD): On 30 Apr 2018 (Cycle 1), the patient recorded events of nausea and vomiting which were both not serious, Grade 1 in severity and considered possibly related to IMP. The events were treated with concomitant medication and were considered ongoing. Due to the events, IMP was permanently discontinued.
- Patient 1003-006 (Cohort 4, 250 mg BD) recorded the following AEs that led to permanent withdrawal of the IMP:
    - On 27 Jun 2018 (Cycle 1), the patient recorded events of fatigue and nausea which were both not serious, Grade 1 in severity and considered possibly related to IMP. The event of fatigue resolved on 31 Jul 2018, with no action taken. Following treatment with concomitant medication, the event of nausea

resolved on 15 Aug 2018. Due to the events, IMP was permanently discontinued.

- On 01 Aug 2018 (Cycle 2), the patient recorded events of decreased appetite and fatigue which were both not serious, Grade 2 in severity and considered possibly related and definitely related to IMP, respectively. The events resolved on 25 Aug 2018 and 14 Aug 2018, respectively, with no action taken. Due to the events, IMP was permanently discontinued.
- On 14 Aug 2018 (Cycle 2), the patient recorded an event of fatigue which was not serious, Grade 1 in severity and considered not related to IMP. The event resolved on 05 Sep 2018, with no action taken. Due to the event, IMP was permanently discontinued.

- Patient 1002-005 (Cohort 5, 350 mg BD) recorded a serious event of metastases to central nervous system (Refer to Section 12.3.1.2).
- Patient 1003-007 (Cohort 5, 350 mg BD): On 18 Jul 2018 (Cycle 1), the patient recorded events of fatigue and vomiting which were not serious, Grade 1 in severity and considered possibly related and definitely related to IMP, respectively. The events were considered ongoing, following no action taken for the event of fatigue and treatment with concomitant medication for the event of vomiting. Due to the events, IMP was permanently discontinued.
- Patient 1003-008 (Cohort 5, 350 mg BD) recorded a serious event of vomiting (Refer to Section 12.3.1.2).

Module 1, Part B

The following 3 AEs that led to permanent withdrawal of IMP were recorded by 3 patients in Module 1, Part B:

- Patient 2001-001 (Cohort 1): On 26 Aug 2019 (Cycle 2), the patient recorded an event of cystatin C increased which was not serious, had no severity grade recorded and was considered possibly related to IMP. No treatment was given for the event and it was considered ongoing. Due to the event, IMP was permanently discontinued.
- Patient 4001-006 (Cohort 1): On 18 Dec 2018 (Cycle 2), the patient recorded an event of blood creatinine increased which was not serious, Grade 2 in severity and considered definitely related to IMP. No treatment was given for the event and it was considered ongoing. Due to the event, IMP was permanently discontinued.
- Patient 1005-002 (Cohort 2) recorded a serious event of spinal cord compression (Refer to Section 12.3.1.2).

12.3.1.4 Dose-limiting Toxicities

No DLTs were recorded for any patient in Module 1 or Module 2 (Listing 16.2.7.2). However, the qualitative nature of the AEs reported in the 400mg BD and 350mg BD, along

with the high rate of TEAEs leading to withdrawal resulted in the SRC deciding that these doses were not in keeping with long term dosing; therefore, 250mg BD was chosen as the monotherapy RP2D.

12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

Refer to Section 14.3.3.

12.3.3 Analysis and Discussion of deaths, Other Serious Adverse Events and Other Significant Adverse Events

No Grade 5 (fatal) TEAEs were recorded for any patients in either Module 1, Part A or Part B or Module 2, Part A (see Section 12.3.1.1). No patients died in Module 1, Part A or Module 2, Part A. In Module 1, Part B, 3 patients died following treatment discontinuation (Listing 16.2.1.3). No deaths were considered related to IMP.

A similar number of patients in Module 1, Part A had SAEs (24 SAEs; 11 patients [45.8%]) when compared to Module 1, Part B (15 SAEs; 10 patients [66.7%]; see Sections 12.2.2.3 and 12.3.1.2). In Module 1, Part A, SAEs of nausea (3 events; 3 patients [12.5%]), vomiting (3 events; 2 patients [8.3]) and metastases to central nervous system and superior vena cava occlusion (both 2 events; 2 patients [8.3%]) were recorded for more than 1 patient (see Section 12.2.2.3). In Module 1, Part B, no SAE was recorded for more than 1 patient; however, SAEs in both Module 1 Part A and Part B included: vomiting and increased blood creatinine. One (1) SAE of seizure was recorded in Module 2, Part A, which was not considered related to IMP.

Of the 41 SAEs recorded overall, 13 SAEs recorded for 9 patients (23.1%) were considered related to IMP, with a higher proportion of patients in Module 1, Part A (11 SAEs; 7 patients [29.2%]) than in Module 1, Part B (2 SAEs; 2 patients [13.3%]). SAEs of nausea, vomiting and increased blood creatinine were all considered related to IMP (see Sections 12.2.2.5 and 12.3.1.2).

There were no apparent dose-dependent trends in SAEs across the dose escalation cohorts in Module 1, Part A, with the exception of more than half of the drug-related SAEs (6/11 drug related SAEs [54.5%]) were recorded for 2 patients (66.7%) in the highest dose cohort (Cohort 3, 400 mg BD). Similarly, there were no apparent trends in SAEs recorded across the two dose expansion cohorts in Module 1, Part B.

In total, 21 TEAEs leading to permanent withdrawal of IMP were recorded for 12 patients (30.1%), including 18 TEAEs leading to IMP discontinuation for 9 patients (37.5%) in Module 1, Part A and 3 TEAEs leading to IMP discontinuation for 3 patients (20.0%) in Module 1, Part B (see Sections 12.2.2.6 and 12.3.1.3). Of the 21 TEAEs, 15 TEAEs were considered to be either possibly or definitely related to IMP.

The vast majority of TEAEs leading to IMP discontinuation (16/18 TEAEs [88.9%]) were recorded for patients in the 3 highest dose cohorts in Module 1, Part A. There were no

apparent dose-dependent trends in TEAEs leading to permanent withdrawal of IMP recorded in the two dose expansion cohorts in Module 1, Part B.

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value

Clinical chemistry, haematology, urinalysis measurements and other laboratory, coagulation, tumour markers and renal markers (including assessment of clinical significance) are listed per patient in Listings 16.2.8.1, 16.2.8.2, 16.2.8.3 and 16.2.8.4, respectively. Renal markers were evaluated both locally and centrally. All other safety markers were evaluated locally only. For all locally performed evaluations an assessment of clinical significance was included (i.e., no assessment of clinical significance was provided for centrally assessed renal markers).

12.4.2 Evaluation of each Laboratory Parameter

On the recommendation of a nephrologist, the following **centrally measured** renal assessments were also included in the safety parameters:

- Serum creatinine;
- Serum cystatin C, a further indirect measure of glomerular filtration rate (GFR);
- Urine kidney injury molecule-1 (KIM-1), a marker of renal damage.

Refer to Appendix 16.1.4 for a review of these data by an independent nephrologist.

12.4.2.1 Laboratory Values over Time

Creatinine

Module 1, Part A

Serum creatinine values over time are summarised for Module 1, Part A in Table 12-13.

At Baseline, in total, mean creatinine was 80.0 µmol/L (SD: 21.4 µmol/L), with comparable baseline mean creatinine across Cohorts 1, 4 and 5 (73.0 µmol/L [SD: 17.6 µmol/L], 72.7 µmol/L [SD: 23.9 µmol/L] and 69.6 µmol/L [SD: 15.5 µmol/L], respectively) and higher baseline mean creatinine in Cohorts 2 and 3 (101.0 µmol/L [SD: 11.5 µmol/L] and 98.3 µmol/L [SD: 16.9 µmol/L], respectively).

Mean creatinine was higher than baseline for all cohorts at all timepoints measured throughout the study (ranging from 6.6% increase from baseline to 121.5% increase from baseline); however, throughout the study, overall mean creatinine was within the normal ranges.

At end-of-treatment, in total, mean creatinine was 95.5 µmol/L (SD: 28.7 µmol/L). An increase in mean creatinine was recorded for all cohorts at end-of-treatment, with the

exception of Cohort 3 (400 mg BD) where a decrease in mean creatinine was recorded (89.5 µmol/L [SD: 6.4 µmol/L]).

Changes in mean creatinine over time were lowest in Cohort 1 (100 mg BD).

The most commonly recorded laboratory TEAE was increased blood creatinine (15 events; 11 patients [45.8%]; see Section 12.2.2.1). The TEAEs were based on locally assessed creatinine data (i.e., clinically significant increase reported as a TEAE).

Table 12-13 Summary of Laboratory Parameters: Serum Renal Markers – Creatinine; Module 1, Part A (Safety Set)

Creatinine (µmol/L)		Cohort 1 100 mg BD (N=5)	Cohort 2 200 mg BD (N=4)	Cohort 3 400 mg BD (N=3)	Cohort 4 250 mg BD (N=7)	Cohort 5 350 mg BD (N=5)	Total (N=24)
Baseline	N	5	4	3	7	5	24
	Mean (SD)	73.0 (17.6)	101.0 (11.5)	98.3 (16.9)	72.7 (23.9)	69.6 (15.5)	80.0 (21.4)
	Median (Min-Max)	74.0 (54-95)	101.0 (87-115)	106.0 (79-110)	78.0 (43-114)	78.0 (51-85)	79.0 (43-115)
Cycle 1 Day 8	N	3	4	1	5	2	15
	Mean (SD)	82.7 (20.8)	134.3 (19.7)	209.0 (-)	115.2 (21.6)	80.5 (43.1)	115.4 (39.3)
	Median (Min-Max)	91.0 (59-98)	133.0 (116-155)	209.0 (209-209)	118.0 (95-148)	80.5 (50-111)	116.0 (50-209)
Cycle 1 Day 15	N	4	3	0	5	2	14
	Mean (SD)	77.8 (23.7)	140.7 (20.4)	-	139.0 (27.6)	79.5 (47.4)	113.4 (39.9)
	Median (Min-Max)	79.0 (53-100)	132.0 (126-164)	-	142.0 (95-168)	79.5 (46-113)	119.5 (46-168)
Cycle 2 Day 1	N	3	4	2	5	1	15
	Mean (SD)	80.0 (16.5)	111.3 (15.3)	110.5 (30.4)	115.0 (32.9)	119.0 (-)	106.7 (25.7)
	Median (Min-Max)	88.0 (61-91)	114.5 (90-126)	110.5 (89-132)	102.0 (86-167)	119.0 (119-119)	102.0 (61-167)
Cycle 3 Day 1	N	3	4	0	3	1	11
	Mean (SD)	88.7 (17.9)	130.8 (7.3)	-	149.3 (37.6)	107.0 (-)	122.2 (31.2)
	Median (Min-Max)	99.0 (68-99)	133.5 (120-136)	-	168.0 (106-174)	107.0 (107-107)	120 (68-174)
Cycle 4 Day 1	N	3	3	0	2	0	8
	Mean (SD)	83.0 (19.9)	131.0 (6.6)	-	121.0 (5.7)	-	110.5 (25.8)
	Median (Min-Max)	94.0 (60-95)	130.0 (125-138)	-	121.0 (117-125)	-	121.0 (60-138)
Cycle 5 Day 1	N	2	3	0	1	0	6
	Mean (SD)	95.0 (5.7)	116.3 (25.0)	-	151.0 (-)	-	115.0 (26.0)
	Median (Min-Max)	95.0 (91-99)	122.0 (89-138)	-	151.0 (151-151)	-	110.5 (89-151)
Cycle 6 Day 1	N	2	2	0	1	0	5
	Mean (SD)	88.0 (2.8)	123.0 (4.2)	-	161.0 (-)	-	116.6 (30.5)
	Median (Min-Max)	88.0 (86-90)	123.0 (120-126)		161.0 (161-161)	-	120.0 (86-161)

Creatinine (µmol/L)		Cohort 1 100 mg BD (N=5)	Cohort 2 200 mg BD (N=4)	Cohort 3 400 mg BD (N=3)	Cohort 4 250 mg BD (N=7)	Cohort 5 350 mg BD (N=5)	Total (N=24)
End of Treatment	N	3	4	2	5	3	17
	Mean (SD)	76.7 (31.8)	107.0 (13.3)	89.5 (6.4)	109.0 (37.7)	80.3 (28.5)	95.5 (28.7)
	Median (Min-Max)	93.0 (40-97)	105.5 (93-124)	89.5 (85-94)	94.0 (75-164)	82.0 (51-108)	94.0 (40-164)
Follow-Up	N	2	4	2	5	2	15
	Mean (SD)	86.5 (6.4)	96.8 (13.7)	87.5 (4.9)	70.0 (10.0)	72.0 (2.8)	81.9 (14.5)
	Median (Min-Max)	86.5 (82-91)	96.0 (81-114)	87.5 (84-91)	69.0 (55-81)	72.0 (70-74)	81.0 (55-114)

Abbreviations: BD=twice daily; max=maximum; min=minimum; N=number of patients; SD=standard deviation
Source: Table 14.3.2.6

Module 1, Part B

Serum creatinine values over time are summarised for Module 1, Part B in Table 12-14.

At Baseline, in total, mean creatinine was 72.7 µmol/L (SD: 18.3 µmol/L), with baseline mean creatinine of 80.0 µmol/L (SD: 16.8 µmol/L) in Cohort 1 and 58.0 µmol/L (SD: 11.7 µmol/L) in Cohort 2.

Mean creatinine was higher than baseline for both cohorts at all timepoints measured throughout the study from Cycle 1, Day 8 (ranging from 7.4% increase from baseline to 106.3% increase from baseline), with an apparent larger increase in MET EXON patients.

At end-of-treatment, in total, mean creatinine was 87.4 µmol/L (SD: 21.3 µmol/L). An increase in mean creatinine was recorded for Cohort 1 at end-of-treatment (94.8 µmol/L [SD: 15.6 µmol/L]). At end-of-treatment, only 1 patient in Cohort 2 had available creatinine samples.

The most commonly reported laboratory TEAE was increased blood creatinine (10 events; 5 patients [33.3%]; see Section 12.2.2.1). The TEAEs were based on locally assessed creatinine data (i.e., clinically significant increase reported as a TEAE).

Table 12-14 Summary of Laboratory Parameters: Serum Renal Markers – Creatinine; Module 1, Part B (Safety Set)

Creatinine (µmol/L)		Cohort 1 MET/EXON Expansion (N=10)	Cohort 2 MET other Basket (N=5)	Total (N=15)
Baseline	N	10	5	15
	Mean (SD)	80.0 (16.8)	58.0 (11.7)	72.7 (18.3)
	Median (Min-Max)	85.0 (52-105)	60.0(41-72)	72.0 (41-105)
Cycle 1 Day 1	N	1	0	1
	Mean (SD)	78.0 (-)	-	78.0 (-)
	Median (Min-Max)	78.0 (78-78)	-	78.0 (78-78)
Cycle 1 Day 8	N	9	4	13
	Mean (SD)	127.4 (33.1)	71.3 (32.6)	110.26 (41.5)
	Median (Min-Max)	124.0 (81-187)	67.5 (40-110)	110.0 (40-187)
Cycle 1 Day 15	N	10	4	14
	Mean (SD)	165.0 (148.6)	62.3 (21.2)	135.6 (133.1)
	Median (Min-Max)	123.5 (61-580)	60.0 (39-90)	113.0 (39-580)
Cycle 2 Day 1	N	10	4	14
	Mean (SD)	106.1 (31.9)	63.0 (14.6)	93.8 (34.1)
	Median (Min-Max)	115.0 (58-147)	66.5 (44-75)	88.0 (44-147)
Cycle 3 Day 1	N	7	0	7
	Mean (SD)	130.1 (39.3)	-	130.1 (39.3)
	Median (Min-Max)	128.0 (72-184)	-	128.0 (72-184)
Cycle 4 Day 1	N	6	0	6
	Mean (SD)	126.0 (39.6)	-	126.0 (39.6)
	Median (Min-Max)	131.0 (61-171)	-	131.0 (61-171)
Cycle 5 Day 1	N	7	0	7
	Mean (SD)	129.7 (36.0)	-	129.7 (36.0)
	Median (Min-Max)	119.0 (86-190)	-	119.0 (86-190)
Cycle 6 Day 1	N	3	0	3
	Mean (SD)	107.3 (32.5)	-	107.3 (32.5)
	Median (Min-Max)	109.0 (74-139)	-	109.0 (74-139)
End of Treatment	N	4	1	5
	Mean (SD)	94.8 (15.6)	58.0 (-)	87.4 (21.3)
	Median (Min-Max)	88.0 (85-118)	58.0 (58-58)	86.0 (58-118)

Abbreviations: max=maximum; min=minimum; N=number of patients; SD=standard deviation
MET/EXON is any patient with MET EXON 14 mutated NSCLC. MET other basket is any patient with any MET aberration other than MET EXON 14 mutated NSCLC.
Source: Table 14.3.2.6

Cystatin C

Module 1, Part A

Serum cystatin C values over time are summarised for Module 1, Part A in Table 12-15.

At Baseline, in total, mean cystatin C was 1.116 mg/L (SD: 0.317 mg/L), with comparable baseline mean cystatin C across Cohorts 1 (1.086 mg/L [SD: 0.416 mg/L]) and 4 (1.083 mg/L [SD: 0.354 mg/L]), higher baseline mean cystatin C in Cohorts 2 (1.288 mg/L [SD: 0.183 mg/L]) and 3 (1.247 mg/L [SD: 0.465 mg/L]) and lower baseline mean cystatin C in Cohort 5 (0.978 mg/L [SD: 0.117 mg/L]).

Mean cystatin C was generally higher than baseline for all cohorts at all timepoints measured throughout the study (ranging from 0.2% increase from baseline to 59.6% increase from baseline), with the exception of Cohort 1, where cystatin C was lower than baseline at all timepoints measured (ranging from 9.8% decrease from baseline to 21.7% decrease from baseline).

At end-of-treatment, in total, mean cystatin C was 1.274 mg/L (SD: 0.375 mg/L). An increase in mean cystatin C was recorded for all cohorts at end-of-treatment, with the exception of Cohort 1 (100 mg BD) where a decrease in mean cystatin C was recorded (0.910 mg/L [SD: 0.140 mg/L]).

Table 12-15 Summary of Laboratory Parameters: Serum Renal Markers – Cystatin C; Module 1, Part A (Safety Set)

Cystatin C (mg/L)		Cohort 1 100 mg BD (N=5)	Cohort 2 200 mg BD (N=4)	Cohort 3 400 mg BD (N=3)	Cohort 4 250 mg BD (N=7)	Cohort 5 350 mg BD (N=5)	Total (N=24)
Baseline	N	5	4	3	7	5	24
	Mean (SD)	1.086 (0.416)	1.288 (0.183)	1.247 (0.465)	1.083 (0.354)	0.978 (0.117)	1.116 (0.317)
	Median (Min-Max)	0.890 (0.85-1.82)	1.260 (1.13-1.50)	1.030 (0.93-1.78)	0.940 (0.70-1.55)	1.010 (0.84-1.10)	1.025 (0.70-1.82)
Cycle 1 Day 8	N	3	4	1	5	2	15
	Mean (SD)	0.967 (0.093)	1.428 (0.291)	1.990 (-)	1.192 (0.313)	1.100 (0.042)	1.251 (0.342)
	Median (Min-Max)	0.940 (0.89-1.07)	1.360 (1.17-1.82)	1.990 ()	1.200 (0.72-1.57)	1.100 (1.07-1.13)	1.170 (0.72-1.99)
Cycle 1 Day 15	N	4	3	0	5	2	14
	Mean (SD)	0.945 (0.099)	1.687 (0.228)	-	1.382 (0.388)	1.030 (0.127)	1.272 (0.380)
	Median (Min-Max)	0.925 (0.85-1.08)	1.730 (1.44-1.89)	-	1.500 (0.76-1.70)	1.030 (0.94-1.12)	1.195 (0.76-1.89)
Cycle 2 Day 1	N	3	4	2	5	1	15
	Mean (SD)	0.903 (0.025)	1.450 (0.346)	1.545 (0.488)	1.266 (0.377)	1.260 (-)	1.279 (0.364)
	Median (Min-Max)	0.900 (0.88-0.93)	1.330 (1.19-1.95)	1.545 (1.20-1.89)	1.280 (0.77-1.77)	1.260 (-)	1.250 (0.77-1.95)
Cycle 3 Day 1	N	3	4	0	3	1	11
	Mean (SD)	0.863 (0.227)	1.355 (0.147)	-	1.373 (0.516)	1.140 (-)	1.206 (0.351)
	Median (Min-Max)	0.900 (0.62-1.07)	1.335 (1.21-1.54)	-	1.620 (0.78-1.72)	1.140 (-)	1.210 (0.62-1.72)
Cycle 4 Day 1	N	3	3	0	2	0	8
	Mean (SD)	0.953 (0.119)	1.290 (0.052)	-	1.250 (0.594)	-	1.154 (0.288)
	Median (Min-Max)	.900 (0.87-1.09)	1.320 (1.23-1.32)	-	1.250 (0.83-1.67)	-	1.160 (0.83-1.67)
Cycle 5 Day 1	N	2	3	0	1	0	6
	Mean (SD)	0.980 (0.057)	1.180 (0.030)	-	1.550 (-)	-	1.175 (0.211)
	Median (Min-Max)	0.980 (0.94-1.02)	1.180 (1.15-1.21)	-	1.550 (-)	-	1.165 (0.94-1.55)
Cycle 6 Day 1	N	2	2	0	1	0	5
	Mean (SD)	0.850 (0.184)	1.090 (0.057)	-	1.470 (-)	-	1.070 (0.271)
	Median (Min-Max)	0.850 (0.72-0.98)	1.090 (1.05-1.13)	-	1.470 (-)	-	1.180 (1.08-1.29)

Cystatin C (mg/L)		Cohort 1 100 mg BD (N=5)	Cohort 2 200 mg BD (N=4)	Cohort 3 400 mg BD (N=3)	Cohort 4 250 mg BD (N=7)	Cohort 5 350 mg BD (N=5)	Total (N=24)
End of Treatment	N	3	4	2	5	3	17
	Mean (SD)	0.910 (0.140)	1.360 (0.176)	1.745 (0.742)	1.342 (0.351)	1.097 (0.208)	1.274 (0.375)
	Median (Min-Max)	0.910 (0.77-1.05)	1.395 (1.12-1.53)	1.745 (1.22-2.27)	1.480 (0.76-1.63)	1.140 (0.87-1.28)	1.280 (0.76-2.27)
Follow-Up	N	2	4	2	5	2	15
	Mean (SD)	0.915 (0.134)	1.475 (0.234)	1.515 (0.474)	1.194 (0.402)	1.070 (0.184)	1.258 (0.352)
	Median (Min-Max)	0.915 (0.82-1.01)	1.540 (1.14-1.68)	1.515 (1.18-1.85)	1.130 (0.76-1.68)	1.070 (0.94-1.20)	1.180 (0.76-1.85)

Abbreviations: BD=twice daily; max=maximum; min=minimum; N=number of patients; SD=standard deviation
Source: Table 14.3.2.6

Module 1, Part B

Serum cystatin C values over time are summarised for Module 1, Part B in Table 12-16

At Baseline, in total, mean cystatin C was 1.081 mg/L (SD: 0.174 mg/L), with comparable baseline mean cystatin C across Cohorts 1 (1.060 mg/L [SD: 0.125 mg/L]) and 2 (1.124 mg/L [SD: 0.259 mg/L]).

Mean cystatin C was generally higher than baseline for both cohorts at most timepoints measured throughout the study (ranging from 7.0% increase from baseline to 41.7% increase from baseline), with the exception of Cycle 1, Day 1 for Cohort 1 (1.9% decrease from baseline), and Cycle 1, Day 15, for Cohort 2 (3.0% decrease from baseline) where cystatin C was lower than baseline.

At end-of-treatment, in total, mean cystatin C was 1.484 mg/L (SD: 0.387 mg/L). An increase in mean cystatin C was recorded for both cohorts at end-of-treatment.

Table 12-16 Summary of Laboratory Parameters: Serum Renal Markers – Cystatin C; Module 1, Part B (Safety Set)

Cystatin C (mg/L)		Cohort 1 MET/EXON Expansion (N=10)	Cohort 2 MET other Basket (N=5)	Total (N=15)
Baseline	N	10	5	15
	Mean (SD)	1.060 (0.125)	1.124 (0.259)	1.081 (0.174)
	Median (Min-Max)	1.065 (0.89-1.21)	1.130 (0.84-1.50)	1.100 (0.84-1.50)
Cycle 1 Day 1	N	1	0	1
	Mean (SD)	1.040 (-)	-	1.040 (-)
	Median (Min-Max)	1.040 (-)	-	1.040 (-)
Cycle 1 Day 8	N	9	4	13
	Mean (SD)	1.251 (0.206)	1.208 (0.285)	1.238 (0.221)
	Median (Min-Max)	1.310 (0.99-1.53)	1.210 (0.90-1.51)	1.310 (0.90-1.53)
Cycle 1 Day 15	N	10	4	14
	Mean (SD)	1.502 (0.642)	1.090 (0.207)	1.384 (0.577)
	Median (Min-Max)	1.400 (0.97-3.16)	1.060 (0.88-1.36)	1.230 (0.88-3.16)
Cycle 2 Day 1	N	10	4	14
	Mean (SD)	1.170 (0.125)	1.203 (0.400)	1.179 (0.219)
	Median (Min-Max)	1.140 (0.98-1.33)	1.065 (0.89-1.79)	1.095 (0.89-1.79)
Cycle 3 Day 1	N	7	0	7
	Mean (SD)	1.296 (0.252)	-	1.296 (0.252)
	Median (Min-Max)	1.270 (0.98-1.61)	-	1.270 (0.98-1.61)
Cycle 4 Day 1	N	6	0	6
	Mean (SD)	1.298 (0.264)	-	1.298 (0.264)
	Median (Min-Max)	1.300 (0.96-1.69)	-	1.300 (0.96-1.69)
Cycle 5 Day 1	N	7	0	7
	Mean (SD)	1.407 (0.324)	-	1.407 (0.324)
	Median (Min-Max)	1.370 (1.04-2.00)	-	1.370 (1.04-2.00)
Cycle 6 Day 1	N	3	0	3
	Mean (SD)	1.213 (0.206)	-	1.213 (0.206)
	Median (Min-Max)	1.120 (1.07-1.45)	-	1.120 (1.07-1.45)
End of Treatment	N	4	1	5
	Mean (SD)	1.358 (0.305)	1.990 (-)	1.484 (0.387)
	Median (Min-Max)	1.385 (0.96-1.70)	1.990 (-)	1.420 (0.96-1.99)

Abbreviations: max=maximum; min=minimum; N=number of patients; SD=standard deviation
MET/EXON is any patient with MET EXON 14 mutated NSCLC. MET other basket is any patient with any MET aberration other than MET EXON 14 mutated NSCLC.
Source: Table 14.3.2.6

Kidney Injury Molecule-1 (KIM-1)

Module 1, Part A

Urine KIM-1 values over time are summarised for Module 1, Part A in Table 12-17.

At Baseline, in total, mean KIM-1 was 1.6833 µg/g (SD: 1.2296 µg/g), with comparable baseline mean KIM-1 across Cohorts 1, 2, 3 and 4 (1.7320 µg/g [SD: 1.4646 µg/g], 1.4150 µg/g [SD: 1.2331 µg/g], 1.1500 µg/g [SD: 0.3579 µg/g] and 1.3129 µg/g [SD: 0.6092 µg/g], respectively) and higher baseline mean KIM-1 in Cohort 5 (2.6880 µg/g [SD: 1.73122 µg/g]).

Mean KIM-1 was higher than baseline at all timepoints measured throughout the study for patients in Cohort 3 (ranging from 50.0% increase from baseline to 55.7% increase from baseline). Mean KIM-1 was generally lower than baseline at all timepoints measured throughout the study for patients in Cohorts 1, 2, 4 and 5 (ranging from 8.9% decrease from baseline to 85.5% decrease from baseline).

At end-of-treatment, in total, mean KIM-1 was 2.3964 µg/g (SD: 3.0776 µg/g). An increase in mean KIM-1 was recorded for Cohorts 3, 4 and 5 at end-of-treatment. For the lowest dose cohorts (Cohorts 1 and 2), a decrease in mean KIM-1 was recorded at end-of-treatment.

Table 12-17 Summary of Laboratory Parameters: Urine Renal Markers – Kidney Injury Molecule-1; Module 1, Part A (Safety Set)

Kidney injury molecule-1 (µg/g)		Cohort 1 100 mg BD (N=5)	Cohort 2 200 mg BD (N=4)	Cohort 3 400 mg BD (N=3)	Cohort 4 250 mg BD (N=7)	Cohort 5 350 mg BD (N=5)	Total (N=24)
Baseline	N	5	4	3	7	5	24
	Mean (SD)	1.7320 (1.4646)	1.4150 (1.2331)	1.1500 (0.3579)	1.3129 (0.6092)	2.6880 (1.7312)	1.6833 (1.2296)
	Median (Min-Max)	1.7500 (0.480-4.060)	1.0800 (0.370-3.130)	1.2600 (0.750-1.440)	1.2200 (0.470-2.290)	3.0700 (0.740-4.630)	1.2750 (0.370-4.630)
Cycle 1 Day 8	N	2	4	1	5	2	14
	Mean (SD)	0.6900 (0.5798)	0.4750 (0.2710)	1.7900 (-)	1.1960 (1.6920)	1.0250 (0.5586)	0.9350 (1.0519)
	Median (Min-Max)	0.6900 (0.280-1.100)	0.4500 (0.240-0.750)	1.7900 (1.790-1.790)	0.4300 (0.370-4.220)	1.0250 (0.630-1.420)	0.5950 (0.240-4.220)
Cycle 1 Day 15	N	4	3	0	5	2	14
	Mean (SD)	0.8750 (0.6115)	0.9233 (0.2940)	-	1.7460 (1.7505)	0.6650 (6.152)	1.1664 (1.1310)
	Median (Min-Max)	0.7950 (0.260-1.650)	0.8400 (0.680-1.250)	-	0.9100 (0.270-4.290)	0.6650 (0.230-1.100)	0.8750 (0.230-4.290)
Cycle 2 Day 1	N	3	4	2	4	1	14
	Mean (SD)	0.7364 (0.7090)	1.1061 (1.1004)	1.7250 (0.5303)	1.7425 (1.2723)	1.2300 (-)	1.3060 (0.9619)
	Median (Min-Max)	0.4700 (0.199-1.540)	1.0300 (0.074-2.290)	1.7250 (1.350-2.100)	1.6700 (0.470-3.160)	1.2300 (1.230-1.230)	1.2900 (0.074-3.160)
Cycle 3 Day 1	N	2	4	0	3	1	10
	Mean (SD)	0.2769 (0.1600)	1.0275 (0.5706)	-	0.7033 (0.5338)	1.3300 (-)	0.8104 (0.5410)
	Median (Min-Max)	0.2769 (0.164-0.390)	1.0750 (0.350-1.610)	-	0.6300 (0.210-1.270)	1.3300 (1.330-1.330)	0.7050 (0.164-1.610)
Cycle 4 Day 1	N	3	3	0	2	0	8
	Mean (SD)	0.6967 (0.6150)	0.7667 (0.4159)	-	0.6550 (0.636)	-	0.7150 (0.4001)
	Median (Min-Max)	0.4300 (0.260-1.400)	0.6000 (0.460-1.240)	-	0.6650 (0.620-0.710)	-	0.6100 (0.260-1.400)

Kidney injury molecule-1 (µg/g)		Cohort 1 100 mg BD (N=5)	Cohort 2 200 mg BD (N=4)	Cohort 3 400 mg BD (N=3)	Cohort 4 250 mg BD (N=7)	Cohort 5 350 mg BD (N=5)	Total (N=24)
Cycle 5 Day 1	N	2	3	0	1	0	6
	Mean (SD)	0.3950 (0.3323)	0.7808 (1.0078)	-	0.5900 (-)	-	0.6204 (0.6814)
	Median (Min-Max)	0.3950 (0.160-0.630)	0.2900 (0.113-1.940)	-	0.5900 (0.590-0.590)	-	0.4400 (0.113-1.940)
Cycle 6 Day 1	N	2	2	0	1	0	5
	Mean (SD)	0.3769 (0.0751)	0.5300 (0.2263)	-	0.1900 (-)	-	0.4008 (0.1843)
	Median (Min-Max)	0.3769 (0.324-0.430)	0.5300 (0.370-0.690)	-	0.1900 (0.190-0.190)	-	0.3700 (0.190-0.690)
End of Treatment	N	3	2	2	4	3	14
	Mean (SD)	0.9633 (0.9782)	0.7150 (0.5445)	1.7000 (1.0889)	2.6200 (4.4019)	5.1167 (3.6345)	2.3964 (3.0776)
	Median (Min-Max)	0.4700 (0.330-2.090)	0.7150 (0.330-1.100)	1.7000 (0.930-2.470)	0.4900 (0.280-9.220)	6.6300 (0.970-7.750)	0.9500 (0.280-9.220)
Follow-Up	N	2	4	2	4	2	14
	Mean (SD)	0.4200 (0.0707)	1.5200 (1.0086)	1.2450 (0.1626)	1.4425 (1.0485)	1.3050 (0.7566)	1.2707 (0.8214)
	Median (Min-Max)	0.4200 (0.370-0.470)	1.4400 (0.490-2.710)	1.2450 (1.130-1.360)	1.3000 (0.320-2.850)	1.3050 (0.770-1.840)	1.1700 (0.320-2.850)

Abbreviations: BD=twice daily; max=maximum; min=minimum; N=number of patients; SD=standard deviation
Source: Table 14.3.2.6

Module 1, Part B

Urine KIM-1 values over time are summarised for Module 1, Part B in Table 12-18.

At Baseline, in total, mean KIM-1 was 2.6479 µg/g (SD: 2.0383 µg/g), with baseline mean creatinine of 1.9411 µg/g (SD: 1.2221 µg/g) in Cohort 1 and 3.9200 µg/g (SD: 2.7147 µg/g) in Cohort 2.

Mean KIM-1 was lower than baseline for all timepoints measured throughout the study for patients in Cohorts 2 (ranging from 23.8% decrease from baseline to 31.2% decrease from baseline). Mean KIM-1 was lower than baseline for all timepoints measured up to Cycle 1, Day 15 and at Cycle 6, Day 1 for patients in Cohort 1 but was generally higher than baseline at the majority of timepoints (ranging from 4.8% increase from baseline to 41.7% increase from baseline).

At end-of-treatment, in total, mean KIM-1 was 3.3714 µg/g (SD: 1.9299 µg/g). An increase in mean KIM-1 was recorded for both cohorts at end-of-treatment, with 3.0200 µg/g (SD: 2.1250 µg/g) in Cohort 1 and 4.2500 µg/g (SD: 1.4566 µg/g) in Cohort 2.

Table 12-18 Summary of Laboratory Parameters: Urine Renal Markers – Kidney Injury Molecule-1; Module 1, Part B (Safety Set)

Kidney injury molecule-1 (µg/g)		Cohort 1 MET/EXON Expansion (N=10)	Cohort 2 MET other Basket (N=5)	Total (N=15)
Baseline	N	9	5	14
	Mean (SD)	1.9411 (1.2221)	3.9200 (2.7147)	2.6479 (2.0383)
	Median (Min-Max)	1.3800 (0.660-4.420)	3.3000 (1.450-8.550)	2.1100 (0.660-8.550)
Cycle 1 Day 1	N	1	0	1
	Mean (SD)	0.7800 (-)	-	0.7800 (-)
	Median (Min-Max)	0.7800 (0.780-0.780)	-	0.7800 (0.780-0.780)
Cycle 1 Day 8	N	9	3	12
	Mean (SD)	1.4859 (1.4512)	2.6967 (1.1240)	1.7886 (1.4357)
	Median (Min-Max)	0.8300 (0.053-3.760)	2.4300 (1.730-3.930)	1.4600 (0.530-3.930)
Cycle 1 Day 15	N	10	3	13
	Mean (SD)	2.0340 (1.4692)	2.8233 (2.5719)	2.2162 (1.6856)
	Median (Min-Max)	1.7100 (0.530-4.920)	1.6700 (1.030-5.770)	1.7000 (0.530-5.770)
Cycle 2 Day 1	N	10	4	14
	Mean (SD)	2.5400 (2.6451)	2.9875 (0.9841)	2.6679 (2.2608)
	Median (Min-Max)	1.4200 (0.200-7.030)	3.1450 (1.700-3.960)	2.2850 (0.200-7.030)
Cycle 3 Day 1	N	7	0	7
	Mean (SD)	2.1532 (2.9102)	-	2.1532 (2.9102)
	Median (Min-Max)	1.3000 (0.113-8.570)	-	1.3000 (0.113-8.570)
Cycle 4 Day 1	N	7	0	7
	Mean (SD)	2.2900 (1.7488)	-	2.2900 (1.7488)
	Median (Min-Max)	1.9600 (0.180-4.880)	-	1.9600 (0.180-4.880)
Cycle 5 Day 1	N	7	0	7
	Mean (SD)	2.7514 (2.3999)	-	2.7514 (2.3999)
	Median (Min-Max)	1.9500 (1.260-8.060)	-	1.9500 (1.260-8.060)
Cycle 6 Day 1	N	3	0	3
	Mean (SD)	1.6000 (0.5157)	-	1.6000 (0.5157)
	Median (Min-Max)	1.6300 (1.070-2.100)	-	1.6300 (1.070-2.100)
End of Treatment	N	5	2	7
	Mean (SD)	3.0200 (2.1250)	4.2500 (1.4566)	3.3714 (1.9299)
	Median (Min-Max)	2.2600 (1.340-6.730)	4.2500 (3.220-5.280)	2.6000 (1.340-6.730)

Abbreviations: max=maximum; min=minimum; N=number of patients; SD=standard deviation
MET/EXON is any patient with MET EXON 14 mutated NSCLC. MET other basket is any patient with any MET aberration other than MET EXON 14 mutated NSCLC.
Source: Table 14.3.2.6

12.4.2.2 Individual Patient Changes

Clinically significant individual patient changes are described in Section 12.4.2.3.

12.4.2.3 Individual Clinically Significant Abnormalities

It should be noted, that for the individually clinically significant abnormalities section of this report, central renal marker data were used and these data were not assessed by the investigator for clinical significance if abnormal in contrast to the locally assessed data, based on which the AEs were recorded.

Module 1, Part A

Clinically significant blood chemistry abnormalities are summarized in Table 12-19. Clinically significant haematology abnormalities are summarized in Table 12-20. Clinically significant urinalysis abnormalities are summarized in Table 12-21.

The following clinically significant abnormalities were recorded:

- 56 clinically significant blood chemistry abnormalities were recorded for 9 patients;
- 31 clinically significant haematology abnormalities were recorded for 10 patients;
- 7 clinically significant urinalysis abnormalities were recorded for 2 patients.

Clinically significant blood chemistry abnormalities

The distribution of clinically significant blood chemistry abnormalities did not suggest any trend. The majority of events were liver-related (elevated AST, ALT, alkaline phosphatase and bilirubin) and occurred in patients with liver metastases.

Clinically significant haematology abnormalities

The most common clinically significant haematology abnormality was low hemoglobin blood level, a complication that is common in cancer. Out of 7 patients with low hemoglobin levels, 6 patients had hemoglobin levels below normal at screening visit.

Clinically significant urinalysis abnormalities

Clinically significant urinalysis abnormalities occurred in 2 patients and in both cases were related to reported urinary tract infection.

Laboratory-related SAEs

A total of 4 laboratory-related SAEs were recorded for 2 patients (all in Cohort 3; 400 mg BD); 1 event of increased troponin for 1 patient (refer to Section 12.3.1.2) and 1 event each of increased blood bilirubin, increased blood creatinine and increased neutrophil count for 1 patient (refer to Section 12.3.1.2).

Table 12-19 Summary of Clinically Significant Blood Chemistry Abnormalities; Module 1, Part A (Safety Set)

Test	Number of Events	Number of Patients	Cohort 1 100 mg BD (N=5)	Cohort 2 200 mg BD (N=4)	Cohort 3 400 mg BD (N=3)	Cohort 4 250 mg BD (N=7)	Cohort 5 350 mg BD (N=5)
Albumin	6	3	1	1	0	0	1
Alkaline Phosphatase	17	6	0	1	1	0	4
ALT	4	3	0	0	0	1	2
AST	7	3	0	0	0	1	2
C-reactive protein	3	1	0	1	0	0	0
Direct bilirubin	6	1	0	0	0	0	1
Total bilirubin	5	1	0	0	0	0	1
Lactate dehydrogenase	2	2	0	1	0	0	1
Potassium	1	1	0	0	0	0	1
Sodium	3	2	0	1	0	0	1
Urea nitrogen	1	1	0	1	0	0	0
Uric acid	1	1	0	1	0	0	0
Total	**56**	**9**	**1**	**2**	**1**	**1**	**5**

Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; BD=twice daily; N=number of patients.
Source: Listing 16.2.8.1

Table 12-20 Summary of Clinically Significant Haematology Abnormalities; Module 1, Part A (Safety Set)

Test	Number of Events	Number of Patients	Cohort 1 100 mg BD (N=5)	Cohort 2 200 mg BD (N=4)	Cohort 3 400 mg BD (N=3)	Cohort 4 250 mg BD (N=7)	Cohort 5 350 mg BD (N=5)
Activated partial thromboplastin	5	1	0	0	0	0	1
Haemoglobin	21	7	0	2	1	2	2
Lymphocytes	3	2	0	1	0	1	0
Platelet count	1	1	0	0	0	1	0
White blood cell count	1	1	0	1	0	0	0
Total	**31**	**10**	**0**	**3**	**1**	**4**	**2**

Abbreviations: BD=twice daily; N=number of patients.
Source: Listing 16.2.8.2

Table 12-21 Summary of Clinically Significant Urinalysis Abnormalities; Module 1, Part A (Safety Set)

Test	Number of Events	Number of Patients	Cohort 1 100 mg BD (N=5)	Cohort 2 200 mg BD (N=4)	Cohort 3 400 mg BD (N=3)	Cohort 4 250 mg BD (N=7)	Cohort 5 350 mg BD (N=5)
Ketones	1	0	0	0	0	1	0
Leukocytes	1	0	1	0	0	0	0
Nitrite	1	1	1	0	0	0	0
Occult blood	2	2	1	0	0	1	0
Protein	2	2	1	0	0	1	0
Total	**7**	**2**	**1**	**0**	**0**	**1**	**0**

Abbreviations: BD=twice daily; N=number of patients.
Source: Listing 16.2.8.3

Module 1, Part B

Clinically significant blood chemistry abnormalities are summarized in Table 12-22. Clinically significant haematology abnormalities are summarized in Table 12-23.

The following clinically significant abnormalities were recorded:

- 12 clinically significant blood chemistry abnormalities were recorded for 3 patients;
- 29 clinically significant haematology abnormalities were recorded for 6 patients.

Clinically significant blood chemistry abnormalities

The patients with elevated alkaline phosphatase level had bone metastases and the patient with abnormal liver functional tests had liver metastases at screening.

Clinically significant haematology abnormalities

Distribution of clinically significant abnormalities in the haematology panel did not suggest any trends. Of the 6 patients with low haemoglobin levels, 4 patients had haemoglobin levels below normal at screening visit.

In one patient (Patient 3001-001) anaemia was assessed as definitely related to study drug. Low haemoglobin level and prolonged activated partial thromboplastin and prothrombin time were reported in Patient 4002-003 with colorectal cancer and metastases to liver, peritoneum and bones.

Laboratory-related SAEs

One (1) laboratory-related SAE of increased blood creatinine was recorded for 1 patient in Cohort 1 (refer to Section 12.3.1.2).

Table 12-22 Summary of Clinically Significant Blood Chemistry Abnormalities; Module 1, Part B (Safety Set)

Test	Number of Events	Number of Patients	Cohort 1 MET/EXON Expansion (N=10)	Cohort 2 MET other Basket (N=5)
Albumin	1	1	0	1
Alkaline phosphatase	2	2	1	1
ALT	1	1	0	1
AST	1	1	0	1
Direct bilirubin	1	1	0	1
Total bilirubin	3	1	0	1
Potassium	3	1	1	0
Total	**12**	**3**	**2**	**1**

Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; N=number of patients.
MET/EXON is any patient with MET EXON 14 mutated NSCLC. MET other basket is any patient with any MET aberration other than MET EXON 14 mutated NSCLC.
Source: Listing 16.2.8.1

Table 12-23 Summary of Clinically Significant Haematology Abnormalities; Module 1, Part B (Safety Set)

Test	Number of Events	Number of Patients	Cohort 1 MET/EXON Expansion (N=10)	Cohort 2 MET other Basket (N=5)
Activated partial thromboplastin	1	1	0	1
Eosinophils	2	1	0	1
Haemoglobin	13	6	3	3
Haematocrit	4	2	1	1
Lymphocytes	1	1	0	1
Neutrophils	1	1	0	1
Prothrombin time	1	1	0	1
Platelet count	3	1	0	1
Red blood cell count	2	1	1	0
White blood cell count	1	1	0	1
Total	**29**	**6**	**3**	**3**

Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; N=number of patients.
MET/EXON is any patient with MET EXON 14 mutated NSCLC. MET other basket is any patient with any MET aberration other than MET EXON 14 mutated NSCLC.
Source: Listing 16.2.8.2

12.5 Vital Signs, Physical Findings and Other Observations Related to Safety

12.5.1 Vital Signs

There were no notable trends in changes in vital signs recorded over time or by dose (Table 14.3.3).

12.5.2 Physical Examination

Physical examination findings are provided by individual patient in Listing 16.2.8.6.

In total, 76 clinically significant abnormal physical examination findings were recorded for 15 patients in Module 1, Parts A and B. In Module 1, Part B, 2 clinically significant indeterminate physical examination findings were recorded for 2 patients. There were no notable trends in changes in physical examination findings over time or by dose.

12.5.3 Electrocardiogram

Twelve-lead ECG are summarised in Table 14.3.4 and provided by individual patient in Listing 16.2.8.7.

There were no notable trends in changes in 12-lead ECG results recorded over time or by dose.

In total, 5 patients had 6 clinically significant abnormal ECG results. The most commonly recorded clinically significant abnormal ECG result was atrial fibrillation (4 cases recorded for 3 patients):

- Patient 1002-008 (Module 1, Part B; Cohort 1) had atrial fibrillation at Cycle 1, Day 8 and Cycle 1, Day 15;
- Patient 4001-002 (Module 1, Part B; Cohort 1) had atrial fibrillation at an unscheduled visit on 26 November 2018 (Cycle 8, Day 13 [Listing 16.2.1.1]);
- Patient 4001-005 (Module 1, Part B; Cohort 1) had atrial fibrillation at Cycle 1, Day 8.

12.5.4 Eastern Co-operative Oncology Group Performance Status

The ECOG status is summarised for the Safety Set in Table 14.3.5.

Module 1, Part A

At Cycle 1, Day 1, all patients had an ECOG status of either Grade 0 (9/24 patients [37.5%]) or Grade 1 (15/24 patients [62.5%]). At end-of-treatment, the vast majority of patients assessed still had an ECOG status of either Grade 0 (5/21 patients [23.8%]) or Grade 1 (12/21 patients [57.1%]), with ECOG status of Grade 2 reported for 3/21 patients (14.3%) and Grade 3 reported for 1/21 patients (4.8%).

All Grade 2 or 3 ECOG statuses were recorded for patients in the highest dose groups (Cohorts 3, 4 and 5).

Module 1, Part B

At Cycle 1, Day 1, all patients had an ECOG status of either Grade 0 (3 patients [20.0%]) or Grade 1 (12/15 patients [80.0%]). Overall, at end-of-treatment, 3/7 patients (42.9%) had an ECOG status of Grade 1, 1/7 patients (14.3%) had an ECOG status of Grade 2 and 3/7 patients (42.9%) had an ECOG status of Grade 3.

At end-of-treatment, 3 out of 5 (60.0%) MET/EXON patients (Cohort 1) assessed had an ECOG status of Grade 1, while the 2 (100%) MET other basket patients (Cohort 2) assessed had an ECOG status of Grade 3.

12.6 Safety Conclusions

Module 1, Part A

- Overall, the majority of patients had either 1 cycle or 2 cycles of OMO-1 treatment. The mean number of cycles per patient was 3.1 cycles (SD: 2.8 cycles). The mean treatment duration was 8.43 weeks (SD: 9.64 weeks). The extent of exposure was highest in Cohorts 1 and 2, with an apparent reduction in the extent of exposure in the higher dose cohorts.
- A total of 258 TEAEs were recorded for all 24 patients in Module 1, Part A. The vast majority were Grade 1 or Grade 2 in severity.
- Of the 258 TEAEs, 129 events were considered drug related (50.0%). Of the 129 drug-related TEAEs, over half were in the gastrointestinal disorders, investigations and general disorders and administration site conditions SOCs. The most common drug-related TEAEs by PT were vomiting, fatigue, nausea, increased blood creatinine and headache. Most drug-related TEAEs were generally recorded in

similar proportions of patients across treatment cohorts. There were no apparent dose-dependent trends in drug-related TEAEs recorded

- In total, 23 severe TEAEs were recorded for 13 patients (54.2%) and 24 treatment-emergent SAEs were recorded for 11 patients (45.8%; of which, 11 events were considered to be drug-related). More than half of the drug-related SAEs were recorded for 2 patients in the highest dose cohort (Cohort 3; 400 mg BD).
- 18 TEAEs leading to IMP discontinuation were recorded for 9 patients (37.5%). Fatigue, vomiting and nausea were the most common TEAEs leading to IMP discontinuation. The vast majority of TEAEs leading to IMP discontinuation (16/18 TEAEs [88.9%]) were recorded for patients in the 3 highest dose cohorts.
- With the exception of the majority of TEAEs leading to IMP discontinuation being recorded at the higher dose levels, there were no apparent dose-dependent trends in TEAEs recorded across the 5 cohorts.
- Although no DLTs were recorded in Module 1, Part A, the qualitative nature of the AEs reported in the 400mg BD and 350mg BD cohorts, along with the high rate of TEAEs leading to withdrawal resulted in the SRC deciding that these doses were not in keeping with long term dosing; therefore, 250mg BD was chosen as the monotherapy RP2D.
- No patients died in Module 1, Part A.
- Mean serum creatinine was higher than baseline for all cohorts at all timepoints measured throughout the study (ranging from 6.6% increase from baseline to 121.5% increase from baseline); however, throughout the study, overall mean creatinine was within the normal ranges. Changes in mean creatinine over time were lowest in Cohort 1 (100 mg BD).
- Mean serum cystatin C was generally higher than baseline for all cohorts at all timepoints measured throughout the study (ranging from 0.2% increase from baseline to 59.6% increase from baseline), with the exception of Cohort 1 (100 mg BD), where cystatin C was lower than baseline at all timepoints measured (ranging from 9.8% decrease from baseline to 21.7% decrease from baseline).
- Mean urine KIM-1 was higher than baseline at all timepoints measured throughout the study for patients in Cohort 3 (400 mg BD; ranging from 50.0% increase from baseline to 55.7% increase from baseline). Mean KIM-1 was generally lower than baseline at all timepoints measured throughout the study for patients in Cohorts 1, 2, 4 and 5 (ranging from 8.9% decrease from baseline to 85.5% decrease from baseline).
- There was an increase in serum creatinine, which could indicate up to 50% drop in GFR. However, there were no notable trends in the serum cystatin C levels, which is another marker of GFR. Overall serum cystatin C values did not change by more than 20% in Module 1 Part A and this may be within the range of lab test variability.
- There were no notable trends in changes in in vital signs, physical examinations, 12-lead ECG or ECOG performance score recorded over time or by dose.

- Treatment with OMO-1 was associated with a favourable safety profile in Module 1, Part A.

Module 1, Part B

- The highest mean number of cycles (4.5 cycles [SD: 2.0 cycles]) and mean treatment duration (14.50 weeks [SD: 6.68 weeks]) were recorded for MET EXON 14 mutated NSCLC patients (MET/EXON, Cohort 1), which was much higher than for other basket patients with MET aberrations in Cohort 2 (1.8 cycles [SD: 0.4 cycles]; 4.30 weeks [SD: 1.85 weeks]). Extent of exposure was much higher for MET EXON 14 mutated NSCLC patients (MET/EXON, Cohort 1) than for other basket patients with MET aberrations (Cohort 2).
- A total of 178 TEAEs were recorded for all 15 patients (100%) in Module 1, Part B. The majority of TEAEs were considered Grade 1 or Grade 2 in severity.
- Of the 178 TEAEs, 65 events were considered drug related (36.5%). Of the 65 drug-related TEAEs, 23 events were in the gastrointestinal disorders SOC. The most common drug-related TEAEs by PT were nausea and increased blood creatinine. All 10 events of increased blood creatinine were reported in Cohort 1. With the exception of increased blood creatinine, most drug-related TEAEs were generally recorded in similar proportions of patients across both cohorts.
- In total, 23 severe TEAEs were recorded for 11 patients (73.3%) and 14 serious TEAEs were recorded for 9 patients (60.0%; of which 2 events were considered to be drug-related).
- There were no apparent dose-dependent trends in severe TEAEs, SAEs or TEAEs leading to withdrawal recorded across the two dose expansion cohorts in Module 1, Part B.
- In total, 3 patients died following treatment discontinuation due to disease progression. No deaths were considered related to IMP.
- Mean serum creatinine was higher than baseline for both cohorts at all timepoints measured throughout the study from Cycle 1, Day 8 (ranging from 7.4% increase from baseline to 106.3% increase from baseline), with an apparent larger increase in MET EXON patients.
- Mean serum cystatin C was generally higher than baseline for both cohorts at most timepoints measured throughout the study (ranging from 7.0% increase from baseline to 41.7% increase from baseline).
- Mean urine KIM-1 was generally higher than baseline for MET EXON patients at the majority of timepoints (ranging from 4.8% increase from baseline to 41.7% increase from baseline) but lower than baseline in MET other basket patients (ranging from 23.8% decrease from baseline to 31.2% decrease from baseline).
- There was an increase in serum creatinine, which could indicate up to 50% drop in GFR. Also, there was an increase in serum cystatin C levels that could reflect some loss of GFR.

- There were no notable trends in changes in vital signs, physical examinations, 12-lead ECG or ECOG performance score recorded over time or by dose.
- Treatment with OMO-1 was associated with a favourable safety profile in Module 1, Part B.

Interpretation of Renal Marker Data (Module 1, Part A and B; see Appendix 16.1.4)

Serum creatinine is a well-known biomarker of the GFR. But it is also affected by tubular secretion, which can be hindered by injuries of drugs that do not affect the GFR. Serum cystatin C is probably a better marker of the GFR because its excretion only depends on glomerular filtration. If the serum creatinine rises without a change in the serum cystatin C, then one can assume an effect that has influenced the renal secretion of creatinine. KIM-1 is a marker of renal injury, probably the proximal tubule more than any other part of the kidneys. Urinary levels of more than 2 µg/gram of creatinine can be found with acute kidney injuries, i.e., events that damage the tubular epithelium.

Normal serum creatinine is around 90 µmol/L. In this study, we see an up to 50% increase in serum creatinine, which is beyond the range of lab test variability, which could indicate up to 50% drop in GFR. However, when one considers the stability of the serum cystatin C measurements, it probably does not reflect a change in GFR in this study. The overall serum cystatin C values do not change by more than 20% in Part A of Module 1 of the study, this may be within the range of lab test variability, and there is no trend in their levels with time. There may be an upward trend in the serum cystatin C levels in Module 1, part B, however, that could reflect some loss of GFR.

- The most common drug related TEAEs by PT included vomiting, nausea and increased blood creatinine. This suggests that if there were true renal function changes, they were from pre-renal azotemia in most cases.

13 DISCUSSION AND OVERALL CONCLUSIONS

Overall Conclusions

- Overall, multiple BD dosing of OMO-1 in patients with locally advanced, unresectable or metastatic malignancy and patients with MET pathway aberrations was associated with a favourable safety profile.
- No dose-limiting toxicities were observed at any OMO-1 dose level tested.
- In Module 1, Part A, the extent of exposure was highest in Cohorts 1 (100 mg BD) and 2 (200 mg BD), with an apparent reduction in the extent of exposure in the higher dose cohorts. In Module 1, Part B, the extent of exposure was much higher for MET EXON 14 mutated NSCLC patients (MET/EXON, Cohort 1) than for other basket patients with MET aberrations (Cohort 2).
- In Module 1, Part A, the most common drug-related TEAEs by PT were vomiting, fatigue, increased blood creatinine, nausea and headache. Most drug-related TEAEs were generally recorded in similar proportions of patients across treatment cohorts. More than half of the drug-related SAEs were recorded for 2 patients in the highest dose cohort (Cohort 3; 400 mg BD). Fatigue, vomiting and nausea were the most common TEAEs leading to IMP discontinuation. The vast majority of TEAEs leading to IMP discontinuation (16/18 TEAEs [88.9%]) were recorded for patients in the 3 highest dose cohorts. With the exception of the majority of TEAEs leading to IMP discontinuation being recorded at the higher dose levels, there were no apparent dose-dependent trends in TEAEs recorded across all 5 cohorts.
- In Module 1, Part B, the most common drug-related TEAEs by PT were nausea and increased blood creatinine. All 10 events of increased blood creatinine were reported in Cohort 1 (MET EXON 14 mutated NSCLC patients). With the exception of increased blood creatinine, most drug-related TEAEs were generally recorded in similar proportions of patients across both cohorts. There were no apparent trends in severe TEAEs, SAEs or TEAEs leading to withdrawal recorded across the two dose expansion cohorts in Module 1, Part B.
- No DLTs were reported.
- In Module 1, Part A, no patients died. In Module 1, Part B, 3 patients died following treatment discontinuation due to disease progression. No deaths were considered related to IMP.
- In Module 1, Part A and Part B, there was an increase in serum creatinine, which could indicate up to 50% drop in GFR. However, in Module 1 Part A, there were no notable trends in the serum cystatin C levels, which is another marker of GFR. In Module 1 Part B, there was an increase in serum cystatin C levels that could reflect some loss of GFR. The most common drug related TEAEs by PT included vomiting, nausea and increased blood creatinine. This suggests that if there were true renal function changes, they were from pre-renal azotaemia in most cases.

- In both Module 1, Part A and Part B, there were no notable trends in changes in vital signs, physical examinations, 12-lead ECG or ECOG performance score recorded over time or by dose.

14 TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data

14.2 Efficacy Data

14.3 Safety Data

14.3.1 Display of Adverse Events

Table 14.3.1.5	Drug Related Treatment-Emergent Adverse Events, by SOC and PT	Safety Set
Table 14.3.1.6	Serious Drug Related Treatment-Emergent Adverse Events, by SOC and PT	Safety Set
Table 14.3.1.7	Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation, by SOC and PT	Safety Set
Table 14.3.1.8	Non-Treatment-Emergent Adverse Events, by SOC and PT	Safety Set
Table 14.3.1.9	Treatment-Emergent Adverse Events, by SOC and PT, by CTCAE Grade	Safety Set
Table 14.3.1.10	Non-Treatment-Emergent Adverse Events, by SOC and PT, by CTCAE Grade	Safety Set
Table 14.3.1.11	Treatment-Emergent Adverse Events, by SOC and PT, by Worst Grade Per Patient	Safety Set

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

Not applicable.

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

14.3.3.1 Patient 2001-001

SAE TERM(S)	PREFERRED TERM(S)
Dyspnea	Dyspnoea

RELEVANT DEMOGRAPHICS
56-year-old female

RELEVANT MEDICAL HISTORY TERM(S)
None

RELEVANT CONCOMITANT MEDICATION(S)	
Durogesic (fentanyl)	17 July 2019 – Ongoing
Paracetamol	June 2019 – Unknown

OMO-1 ADMINISTRATION

OMO-1 ADMINISTRATION		
Module	Module 1 Part B Expansion with MET/EXON (Cohort 1)	
Study arm		
Dose	500 mg	
First dose	17 July 2019	Study day 1 (C1D1)
Last dose prior to the event(s)	28 August 2019	Unscheduled Visit

SAE NARRATIVE

On Cycle 1 Day 1 (**17 July 2019**), the patient began receiving OMO-1, at 250 mg oral capsule twice daily.

On **28 August 2019** (Unscheduled Visit), the patient received the last dose of OMO-1 prior to the reported event. On Cycle 2 Day 1 (**19 August 2019)**, a pneumo puncture was performed on the patient during a consultation in an hospital.

Thereafter, on **08 September 2019** (Unscheduled Visit), the patient presented to the emergency department in another hospital with dyspnea and pain on the location of the puncture, due to which she was hospitalised on the same day.

On **12 September 2019** (Unscheduled Visit), the patient underwent bronchoscopy, which revealed metastatic pleural invasion and occlusion of the right lower bronchus due to tumor compression.

On **13 September 2019** (Unscheduled Visit), two thorax drains were inserted.

Action taken with the study drug was not applicable since the patient completed the study.

On **18 September 2019** (Unscheduled Visit)**,** the event dyspnea was considered as resolved and the patient was discharged from hospital on the same day. The patient's discharge medications included Movicol (macrogol) 1 sachet orally as laxative and Oxynorm (oxycodone) at a dose of 5 mg orally for pain.

No additional information was expected.

The Investigator assessed dyspnea as serious (hospitalisation), CTCAE grade 3 and not related to OMO-1. The most likely cause of the event was disease under study.

INVESTIGATOR ASSESSMENT OF EVENT(S)		
Dyspnoea	CTCAE grade	3
	Relationship to OMO-1	Not related
	Action taken with OMO-1	Not applicable (patient completed the study)
	Duration	11 Days
	Outcome	Resolved
	Withdrawn from study	No

SPONSOR ASSESSMENT OF EVENT(S)

SPONSOR ASSESSMENT OF EVENT(S)		
Dyspnoea	Relationship to OMO-1	Not related

14.3.3.2 Patient 2001-002

SAE TERM(S)	PREFERRED TERM(S)
Seizure secondary to brain metastases	Seizure

RELEVANT DEMOGRAPHICS

55-year-old female

RELEVANT MEDICAL HISTORY TERM(S)

Brain metastases	Ongoing

RELEVANT CONCOMITANT MEDICATION(S)

None

OMO-1 ADMINISTRATION

Module	Module 2 Part A MET amplified in combination with EGFR-TKI	
Study arm		
Dose	400 mg	
First dose	19 August 2019	Study day 1 (C1D1)
Last dose prior to the event(s)	21 October 2019	Cycle 4 Day 1

SAE NARRATIVE

On Cycle 1 Day 1 (**19 August 2019**), the patient began receiving OMO-1, at 200 mg oral capsule twice daily.

On **10 November 2019** (Unscheduled Visit), the patient presented in the local hospital with visual impairment (light), impairment of good communication and bifrontal headache. the patient was admitted to hospital due to epileptic seizure with cyanosis and clonus involving all 4 limbs. The patient started receiving treatment with Medrol (methylprednisolone) at 32 mg once daily and Keppra (levetiracetam) at 1000 mg twice daily. On the same day, a CT scan was performed which showed brain metastases. It was noted that there was not any radiological progression on CT scan when compared from the brain metastases reported at screening.

On **11 November 2019** (Unscheduled Visit), the patient recovered from the event seizure secondary to brain metastases and was discharged from hospital. It was reported that the patient left hospital in a good condition.

At the time of the report, the treatment with methylprednisolone and levetiracetam was ongoing.

No action was taken with OMO-1 as a result of the event.

No additional information was expected.

The Investigator assessed seizure secondary to brain metastases as serious (hospitalisation), CTCAE

SAE NARRATIVE

grade 2 and not related to OMO-1. The investigator assessed this event as related to the disease under study.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Seizure	CTCAE grade	2
	Relationship to OMO-1	Not related
	Action taken with OMO-1	No action taken
	Duration	2 Days
	Outcome	Resolved
	Withdrawn from study	No

SPONSOR ASSESSMENT OF EVENT(S)

Seizure	Relationship to OMO-1	Not related

14.3.3.3 Patient 3001-001

14.3.3.3.1 Chills

SAE TERM(S)	PREFERRED TERM(S)
Chills	Chills

RELEVANT DEMOGRAPHICS

70-year-old female

RELEVANT MEDICAL HISTORY TERM(S)

Hypothyroidism	2003 - ongoing
Hiatal hernia	2008 - ongoing

RELEVANT CONCOMITANT MEDICATION(S)

Haldol (Haloperidol)	22 October 2018 - Unknown
Mag -2 (Magnesium)	01 October 2018 - Ongoing
Vogalene (Metopimazine)	03 September 2018 - Ongoing
Macrogol	03 September 2018 - 15 October 2018
Diffu K (Pottsium)	27 August 2018 - Ongoing
Zophren (Ondansetron)	20 August 2018 - 07 November 2018
Ranitidine	17 May 2018 - Ongoing
Levothyrox (levothyroxine sodium)	01 January 2018 - Ongoing

OMO-1 ADMINISTRATION

Module	Module 1 Part B Expansion with MET/EXON (Cohort 1)	
Study arm		
Dose	500 mg	
First dose	20 August 2018	Study day 1 (C1D1)
Last dose prior to the event(s)	01 October 2018	Cycle 3 Day 1

SAE NARRATIVE

On Cycle 1 Day 1 (**20 August 2018**), the patient began receiving OMO-1, 250 mg oral capsule twice daily.

SAE NARRATIVE

On Cycle 3 Day 1 (**01 October 2018**), the patient received their last dose of OMO-1 prior to the event.

On **06 November 2018** (Unscheduled Visit), the patient presented with faintness, chills and fever of 38 degrees.

On **07 November 2018** (Unscheduled Visit), the patient was consequently hospitalised due to chills.

On Cycle 4 Day 1 (**09 November 2018**), the patient recovered from the event of chills and was discharged from hospital.

No action was taken with study drug OMO-1 as a result of the event and the patient is still in the trial.

No additional information is expected.

The investigator assessed chills as CTCAE grade 2 and not related to OMO-1 and most likely related to another illness.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Chills	CTCAE grade	2
	Relationship to OMO-1	Not related
	Action taken with OMO-1	No action taken
	Duration	4 Days
	Outcome	Resolved
	Withdrawn from study	No

SPONSOR ASSESSMENT OF EVENT(S)

Chills	Relationship to OMO-1	Not related

14.3.3.3.2 Lung infection

SAE TERM(S)	PREFERRED TERM(S)
Lung infection	Lung infection

RELEVANT DEMOGRAPHICS

70-year-old female

RELEVANT MEDICAL HISTORY TERM(S)

Hypothyroidism	2003
Kidney failure	Unknown
Appendectomy	Unknown
Hiatal hernia	2008

RELEVANT CONCOMITANT MEDICATION(S)

Mag -2 (Magnesium)	01 October 2018 to Ongoing
Vogalene (Metopimazine)	09 November 2018 – Ongoing
Diffu K (Potassium chloride)	27 August 2018 to Ongoing
Levothyrox (Levothyroxine sodium)	01 January 2018 to Ongoing

OMO-1 ADMINISTRATION

Module	Module 1 Part B Expansion with MET/EXON (Cohort 1)	
Study arm		
Dose	500 mg	
First dose	20 August 2018	Study day 1 (C1D1)
Last dose prior to the event(s)	03 December 2018	Cycle 5 Day 1

SAE NARRATIVE

On Cycle 1 Day 1 (**20 August 2018)**, the patient began receiving OMO-1, 250 mg oral capsule twice daily. On the same date, the patient began experiencing palpitations with dyspnoea on exertion.

These symptoms improved on stopping treatment and reappeared on restarting treatment.

On Cycle 3 Day 1 (**01 October 2018)**, the patent experienced grade 1 hypomagnesemia not related to the treatment.

On **22 October 2018** (Unscheduled Visit), the patient developed dyspnoea grade 1 not related to the treatment.

On Cycle 4 Day 18 (**26 November 2018**), the patient experienced bronchitis grade 1, not related to the treatment.

SAE NARRATIVE

On Cycle 5 Day 1 (**03 December 2018),** the patient experienced grade 1 elevated creatinine and grade 3 hypokalaemia both related to the treatment.

The events grade 1 hypomagnesemia, dyspnoea grade 1, bronchitis grade 1, grade 1 elevated creatinine and grade 3 hypokalaemia, mentioned above, were all assessed as non-serious adverse events by the investigator.

On Cycle 5 Day 1 (**03 December 2018)**, the patient received her last dose of OMO-1 prior to the lung infection.

On Cycle 5 Day 4 (**06 December 2018)**, the study drug was stopped.

On Cycle 5 Day 5 (**07 December 2018)**, the patient was hospitalised due to lung infection grade 2 with fever, dyspnoea, sinus tachycardia, hyperleukocytosis and C-reactive protein of 89. A probable bronchial disorder with atypical bacteria was suspected. The patient had significant asthenia with problems eating over the past few days.

Dehydration and skin pallor were also observed. Laboratory tests show inflammatory syndrome with hyperleukocytosis at 17 330/mm^3. Therefore, the patient started receiving treatment with Augmentin (amoxicillin/clavulanic acid) at 1 g, thrice daily. As the inflammatory syndrome was still present in laboratory tests and on the advice of patient's pneumonologist, Rovamycin (spyramicin) was added to the therapy since the patient reported rhino bronchitis for around 2 weeks with clear sputum. The investigator assessed the event rhino-bronchitis as non-serious.

Following treatment with spyramicin, the patient's CRP decreased from 80 to 40 mg/l. Hyperleukocytosis remained, however, stable with the same levels. An estimation of the patient's creatinine clearance using serum creatine was found to be 41 mls/min, this was assessed as a non-serious event by the investigator.

On Cycle 5 Day 10 (**11 December 2018)**, the patient re-started treatment with OMO-1.

On Cycle 5 Day 11 (**12 December 2018)**, the patient started experiencing anemia grade 2 not linked to the treatment requiring transfusion of 2 units of labile blood products (non-serious adverse event).

The patient's general condition and kidney function started to improve with perfusion and hydration. The patient remained afebrile for the duration of her admission.

On Cycle 5 Day 12 (**13 December 2018)**, the treatment with the study drug was stopped, the patient recovered from lung infection and he was discharged from hospital. Medications on discharge included: amoxicillin/clavulanic acid one tablet thrice daily for 4 days, spyramicin one tablet thrice daily for rhino bronchitis for 12 days.

On Cycle 5 Day 15 (**16 December 2018)**, the patient's treatment with amoxicillin/clavulanic acid was stopped.

On **17 December 2018** (End of Treatment), the patient was discontinued from the study due to disease progression.

No additional information is expected.

On **25 December 2018** (Unscheduled Visit), the patient's treatment with spyramicin was stopped.

The Investigator assessed lung infection as serious (hospitalisation), as CTCAE grade 2 and not related to OMO-1.

INVESTIGATOR ASSESSMENT OF EVENT(S)

INVESTIGATOR ASSESSMENT OF EVENT(S)		
Lung infection	CTCAE grade	2
	Relationship to OMO-1	Not related
	Action taken with OMO-1	No action taken
	Duration	7 Days
	Outcome	Resolved
	Withdrawn from study	Yes

SPONSOR ASSESSMENT OF EVENT(S)		
Lung infection	Relationship to OMO-1	Not related

14.3.3.4 Patient 3001-002

SAE TERM(S)	PREFERRED TERM(S)
Vomiting	Vomiting

RELEVANT DEMOGRAPHICS

67-year-old male

RELEVANT MEDICAL HISTORY TERM(S)

Malaria	2006
Prostate adenoma	2012
Sigmoid diverticulosis	2014 to May 2014
Gastroesophageal reflux	June 2017 – Ongoing
Gastroesophageal reflux	04 September 2017 - Ongoing
Maculopapular rash	04 September 2017 - 31 October 2018
Nausea	06 August 2018 - Ongoing
Hiccups	06 August 2018 - 05 November 2018
Nivaquine (chloroquine) allergy	2006 - Ongoing
Tumour pain	06 August 2018 - Ongoing

RELEVANT CONCOMITANT MEDICATION(S)

Pantoprazole	05 June 2017 - 16 November 2018
Tolexine (doxycycline)	04 June 2018 - 31 October 2018
Domperidone	06 August 2018 - 14 November 2018
Haldol (haloperidol)	24 September 2018 - 24 September 2018
Largactil (chlorpromazine)	06 August 2018 - 31 October 2018

OMO-1 ADMINISTRATION

Module	Module 1 Part B Expansion with MET/EXON (Cohort 2)	
Study arm		
Dose	500 mg	
First dose	17 October 2018	Study day 1 (C1D1)
Last dose prior to the event(s)	13 November 2018	Cycle 2 Day 6

SAE NARRATIVE

Since the beginning of this study, the patient had nausea and vomiting that prevented food intake. On Cycle 1 Day 1 (**17 October 2018)**, the patient began receiving OMO-1, 250 mg oral capsule twice daily.

On Cycle 2 Day 6 (**13 November 2018),** the patient began experiencing a severe digestive disorder with disabling vomiting, asthenia and alteration of general state under multi-metastatic progression and was hospitalised. The investigator assessed the events asthenia and alteration of general condition as part of disease progression.

The patient was treated with Zophren (ondansetron) and Vogalene (metopimazine).

The patient's lab tests included White blood cell count (WBC) at 26000 with predominance of neutrophils, Platelets at 99000, Hemoglobin at 8.7 g/l, Albumin 24.2 g/l, c-reactive protein (CRP) at 72.9 mg/l. The study drug was temporarily discontinued as a result of the event vomiting. The event vomiting did not abate after stopping the study drug.

On Cycle 2 Day 8 (**15 November 2018)**, a scan of the chest, abdomen and pelvis was performed which showed liver, lymph node and peritoneal progression. The patient's brain MRI scan was normal.

On **16 November 2018** (End of Treatment), the patient's lab tests showed leukocytes at 30500/mm^3, Hb at 8.3 g/dl, Platelets at 90000/mm^3, Sodium at 132 mmol/l, CRP at 119 mg/l and blood albumin at 23 g/l.

On the same date, the patient was withdrawn from the study.

On **21 November 2018** (Follow-Up Visit), the patient had increased thrombocytopenia with platelet threshold of 52000/mm^3. On this date, the patient recovered from the event vomiting and was discharged from the hospital.

On **26 November 2018** (Unscheduled Visit), the patient was admitted to the department due to the gradual appearance of hyperleukocytosis at 68440/mm^3. An Improvement of thrombocytopenia to 68000/mm^3 was observed. Otherwise, persistence of associated hyponatraemia of 128 mmol/l. The patient's nausea, vomiting and hiccups were under monitoring.

On **26 November 2018** (Unscheduled Visit), the patient's Hb was at 9.1 g/dl, sodium at 129 mmol/l, Albumin at 22.6 g/l, CRP at 103.6 mg/l.

On **29 November 2018** (Unscheduled Visit), the site informed the patient's wife about the unfavourable prognosis in the short term in the circumstances of a rapid neoplastic progression explaining the general condition and a probable paraneoplastic leukemogenic response, crushing the platelet cell line (central thrombocytopenia with the possibility of toxic involvement but more likely paraneoplastic exacerbation), as well as partial intestinal obstruction related to the peritoneal progression with no reasonable possibility of surgery in the context.

A specific treatment (anti-EGFR or immunotherapy) had an unfavourable risk/benefit ratio considering the deterioration of general condition. Platelet transfusion was suggested only in case of signs of bleeding.

On **30 November 2018** (Unscheduled Visit), the patient complained of vomiting 4-5 times the day before and 4 times in the night, which prevented him from sleeping. In the afternoon, the patient started experiencing a feeling of malaise.

Laboratory tests performed on this day showed platelets at 38000 and blood sodium at 123 mM.

SAE NARRATIVE

On **04 December 2018** (Unscheduled Visit), the patient was hypotensive. The dose of chlorpromazine was increased. The patient's platelet count was 19 G/l. The patient experienced cholestatic jaundice, kidney failure and cardiac arrest. In accordance with the therapeutic care plan, resuscitation was not carried out.

On **04 December 2018** at 22:10, the patient died due to a major disease progression (peritoneal carcinosis, liver progression and probable paraneoplastic leukemogenic response). The autopsy was not performed.

Additional information is not expected.

The Investigator assessed vomiting as serious (hospitalisation), CTCAE grade 3, and definitely related to OMO-1. The investigator confirmed that this event was not related to disease progression.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Vomiting	CTCAE grade	3
	Relationship to OMO-1	Definitely related
	Action taken with OMO-1	Drug discontinued
	Duration	9 Days
	Outcome	Resolved
	Withdrawn from study	Yes

SPONSOR ASSESSMENT OF EVENT(S)

Vomiting	Relationship to OMO-1	Possibly related

14.3.3.5 Patient 3001-003

SAE TERM(S)	PREFERRED TERM(S)
Pyelonephritis on ureteral lithiasis left	Pyelonephritis
Pneumopathy	Lung disorder
Urolithiasis	Calculus urinary

RELEVANT DEMOGRAPHICS

63-year-old male

RELEVANT MEDICAL HISTORY TERM(S)

Pulmonary adenocarcinoma with lung and bone metastases	Unknown - Ongoing
Peripheral neuropathy	01 January 2017 - Ongoing
Nivolumab-induced hypothyroidism	2019 - Ongoing
Allergy (skin reaction) to Bactrim (sulfamethoxazole trimethoprim)	Unknown – Ongoing

RELEVANT CONCOMITANT MEDICATION(S)

Movicol (macrogol)	27 May 2019 - Unknown
Levothyrox (levothyroxine sodium)	31 January 2019 - Ongoing
Cortancyl (prednisone)	27 May 2019 - Unknown
Actiskenan (morphine sulphate)	06 May 2019 - Unknown
Lyrica (pregabalin)	27 May 2019 - Unknown
Bactrim Forte (sulfamethoxazole)	27 May 2019 - Unknown
Skenan (morphine sulphate)	27 May 2019 – Unknown
Speciafoldine (folic acid)	27 May 2019 - Unknown
Crizotinib.	01 July 2019 – August 2019

OMO-1 ADMINISTRATION

Module	Module 1 Part B Expansion with MET/EXON (Cohort 1)	
Study arm		
Dose	500 mg	
First dose	11 February 2019	Study day 1 (C1D1)
Last dose prior to the event(s)	09 June 2019	Cycle 6 Day 14

SAE NARRATIVE

On **31 January 2019**, the patient started experiencing anaemia grade 1 and asthenia. These events were assessed as non-serious by the investigator.

On Cycle 1 Day 1 (**11 February 2019)**, the patient began receiving OMO-1, at 250 mg oral capsule twice daily. On this date, patient begun experiencing nausea and fatigue. All these events were assessed as grade 1 and non-serious by the investigator.

Since an unspecified date in **February 2019**, the patient experienced worsening of renal function with baseline creatinine around 150 umol/L (normal reference range 64-104).

On Cycle 1 Day 8 (**18 February 2019)**, the patient begun experiencing increased creatinine Grade 2, assessed as non-serious and linked to OMO-1.

On Cycle 5 Day 1 (**06 May 2019)**, the patient experienced tumour pain, grade 2 which was not linked to the OMO-1. This event was assessed as non-serious by the investigator.

On Cycle 6 Day 14 (**09 June 2019),** the patient was administered the last dose of OMO-I on the study.

On Cycle 6 Day 15 (**10 June 2019)**, the patient was admitted to the emergency department due to fever at 39 degree Celsius, worsening pain on his right shoulder with paraesthesia of his right arm due to spinal epidural abscess at C7 (assessed as non-serious by the investigator), abdominal skin shingles caused by Zoster virus (assessed as grade 2, non-serious and not related to OMO-I) and acute kidney injury (assessed as non-serious by the investigator). The patient was also hospitalised for sepsis with clinical sign of suspected secondary infection of shingles rash and obstructive pyelonephritis. The cause of sepsis was unknown. The patient's creatinine levels were at 230 umol/L. Urinalysis performed showed leukocyturia, haematuria and gram stain was negative. The patient's urine culture reflected clear appearance of the urine, leucocytes at 20000/ml and erythrocytes at 25300/ml. The epithelial cells were absent and the cytobacteriological examination of urine showed presence of enterobacteria at 103 UFC/ml. The patient started receiving Augmentin (amoxicillin, clavulanic acid) for pyelonephritis. During the hospitalisation, the patient experienced gram-negative bacteria-induced pneumopathy causing ventilation-perfusion mismatch. A chest x-ray was performed which showed severe lung disease of the right lower lobe. The patient's fever was probably caused by the urinary infection and a very probable bronchopulmonary superinfection. The patient started receiving oxygen therapy up to 4 l/min.

On Cycle 6 Day 15 (**10 June 2019)**, the patient's C-reactive protein was 149.6 mg/L (normal reference range <5). Chest, abdomen and pelvis computerised tomogram (CT) showed progression of lesions at C7 and pelvicalyceal dilation on the right to 20 mm with ureteral lithiasis at 7mm which was drained on this date with a placement of a double-J stent. The treatment with amoxicillin/clavulanic acid was stopped and switched with Claforan (cefotaxime sodium) for patient's cutaneous and urinary conditions and for pneumopathy. The patient started receiving anti-viral treatment with Zovirax (acyclovir) then oral Zelitrex 1000 (valacyclovir) at 1g two times a day, for abdominal skin shingles. The patient treatment with morphine sulphate pentahydrate LP 10 and morphine sulphate 5 was switched to Patient Controlled Analgesia (PCA) with morphine at 1mg/h, bolus at 2mg as part of palliative radiotherapy for shoulder pain. Due to acute kidney injury with creatinine clearance at 30mL/min and risk of overdose, the morphine PCA was replaced with intravenous fentanyl up to 75 ug/h for scapular pain.

On Cycle 6 Day 17 (**12 June 2019)**, laboratory test showed CRP of 97.4 mg/L and creatinine 197 umol/L.

On Cycle 6 Day 18 (**13 June 2019)**, the patient treatment included aerosols of Pentacarinat (pentamidine) for prophylaxis of pulmonary pneumocystis.

SAE NARRATIVE

On Cycle 6 Day 19 (**14 June 2019)**, in the morning, the auscultation identified severe bilateral bronchial congestion necessitating bronchial drainage by a physiotherapist. The patient's bronchial secretions microscopy and cultures identified several non-specified gram-negative bacteria (polymorph flora). As a result of the pneumopathy, the patient's hospitalisation was prolonged. The patient's radiotherapy at the cervical level was ended on the same day.

On Cycle 6 Day 21 (**16 June 2019)**, antibiotic sensitivity testing was performed which showed resistance to third generation cephalosporin and sensitivity to tazocillin. Therefore, the patient's treatment with cefotaxime sodium was switched to tazocillin, 4 g intravenously thrice daily. The treatment with fentanyl was gradually decreased to 25 ug/h, the patient's symptoms started improving and oxygen therapy was withdrawn. It was noted that there was improvement in CRP and the white cells at 17000 cells/mm^3.

On Cycle 6 Day 22 (**17 June 2019)**, the patient was admitted to the drug development department (DITEP) for emergency follow-up management due to a deterioration in general condition with herpes zoster, lung disease, acute renal failure (assessed as non-serious by the investigator) and pain due to epidural spread of metastases. A physical examination was performed on this date, pulmonary auscultation was clear, no cough or sputum, eupneic in ambient air, no chest pain and healed herpes Zoster of the left hemithorax with no blisters. In the morning, the renal function was improving with urea at 6.9 and creatinine at 110 umol/L. On this date, the patient was withdrawn from the study due to disease progression. The study drug was permanently discontinued, as a result of the events.

On **21 June 2019** (Unscheduled Visit), the patient recovered from the pneumopathy and pyelonephritis and the treatment with tazocillin was stopped. On this date, the patient was discharged from hospital.

On **16 July 2019** (Unscheduled Visit), the patient started experiencing urolithiasis and he was re-hospitalised. On this date, the patient started receiving treatment with 1g Doliprane (paracetamol) for scapular pain.

On an unknown date, the control abdomino-pelvic scan showed the stone in the lumbar ureter stayed intact at 7 mm at the level of the lumbar ureter.

On **17 July 2019** (Unscheduled Visit), right semi-rigid ureteroscopy was performed for ablation of the bladder catheter.

On **18 July 2019** (Unscheduled Visit), the patient's ureteral catheter was removed, and the event urolithiasis was resolved. On this date, the patient was discharged from hospital with prescription of paracetamol at a dose of 1g 4 times a day, and Spasfon (phloroglucinol) at a dose of 80mg 3 times a day for 5 days.

On **28 August 2019** (Unscheduled Visit), the patient's renal function recovered.

No action was applicable to be taken with the study drug following the event urolithiasis since the study drug was permanently discontinued prior to onset of this event.

Additional information is expected.

The investigator assessed pyelonephritis on ureteral lithiasis left and pneumopathy as serious (required hospitalisation and prolonged hospitalisation, respectively), CTCAE grade 3 and not related to OMO-1.

The investigator assessed urolithiasis as serious (required hospitalisation), CTCAE grade 2 and not related to OMO-1. The most likely cause of the events pyelonephritis with ureteral lithiasis left and urolithiasis was other illness.

SAE NARRATIVE

The investigator assessed the infectious pulmonary disease as probably linked to the bronchial drainage especially bronchial drainage on the left side.

The investigator reported that the patient's renal failure was a non-serious event, probably linked to the phase 1 treatment and associated with the initial treatment with fentanyl at 75 ug/h. Furthermore, the obstruction possibly contributed to the worsening of the renal failure.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Pyelonephritis	CTCAE grade	3
	Relationship to OMO-1	Not related
	Action taken with OMO-1	Drug discontinued
	Duration	12 days
	Outcome	Resolved
	Withdrawn from study	Yes
Lung disorder	CTCAE grade	3
	Relationship to OMO-1	Not related
	Action taken with OMO-1	Drug discontinued
	Duration	12 days
	Outcome	Resolved
	Withdrawn from study	Yes
Calculus urinary	CTCAE grade	2
	Relationship to OMO-1	Not related
	Action taken with OMO-1	Not applicable (drug was permanently discontinued prior to onset of event)
	Duration	3 days
	Outcome	Resolved
	Withdrawn from study	Not applicable

SPONSOR ASSESSMENT OF EVENT(S)

Pyelonephritis	Relationship to OMO-1	Not related
Lung disorder	Relationship to OMO-1	Not related
Calculus urinary	Relationship to OMO-1	Not related

14.3.3.6 Patient 1001-001

14.3.3.6.1 Constipation (worsening from baseline)

SAE TERM(S)	PREFERRED TERM(S)
Constipation (worsening from baseline)	Constipation

RELEVANT DEMOGRAPHICS

65-year-old female.

RELEVANT MEDICAL HISTORY TERM(S)

Right lateral unicompartmental replacement	Unknown
Constipation grade 1	April 2017 - Ongoing
Wrist joint painful on movement	Unknown
Elbow joint painful on movement	Unknown
Colorectal cancer (tumour status was noted as being of rapid disease progression with hydronephrosis, hydroureter and increased tumour involvement of sigmoid ascending colon)	Unknown
Knee operation	26 September 2007

RELEVANT CONCOMITANT MEDICATION(S)

Omeprazole	August 2014 - Ongoing
Cyclizine	July 2017 - 15 September 2017
Buscopan (hyoscine butylbromide)	27 July 2017 - 15 September 2017
Codeine	14 August 2017 - 15 September 2017
Macrogol	29 August 2017 - Ongoing
Paracetamol	April 2017 - 15 September 2017
Docusate	27 July 2017 - 29 August 2017

OMO-1 ADMINISTRATION

Module	Module 1 Part A Dose-Escalation (Cohort 1)	
Study arm		
Dose	Patient was not administered study drug prior to the event	
First dose	23 August 2017	Study day 1 (C1D1)
Last dose prior to the event(s)	-	

SAE NARRATIVE

The patient did not receive the study drug OMO-1 prior to the onset of the reported event.

On **19 August 2017**, the patient was admitted to hospital with abdominal pain due to constipation. During admission, she had a CT-Scan of her abdomen and pelvis, which showed no evidence of obstruction but indicated increased peritoneal deposits from her colorectal malignancy and an increased size of right adnexal mass. She was treated with IV fluid, oral laxatives and enema. It was also noted that her potassium level was low at 3.4 mmol/L and she was started on a course of Sando-K (potassium chloride and potassium bicarbonate).

On **20 August 2017**, the patient was discharged from the hospital with codeine and laxatives to manage her condition. The patient remained with grade 1 intermittent constipation and the event was considered to have resolved with sequelae.

No action was taken with the study drug as the event constipation (worsening from baseline) occurred before the first dose of OMO-1.

On Cycle 1 Day 1 (**23 August 2017)**, the patient received her first (cycle 1 day 1) dose of the study drug OMO-1.

On Cycle 1 Day 2 (**24 August 2017)**, the patient was prescribed fentanyl patch for abdominal pain.

On Cycle 1 Day 3 (**25 August 2017)**, the patient began to experience intermittent grade 1 vomiting.

On **29 August 2017** (Unscheduled Visit), the patient was admitted to hospital due to back pain (internal reference number OCT-GB-17-CLI-0173, assessed as unrelated to OMO-1). Therapy with OMO-1 was interrupted on this day.

On Cycle 1 Day 10 (**01 September 2017)**, at 13:30, the patient restarted therapy with OMO-1.

On Cycle 1 Day 11 (**02 September 2017)**, the patient was discharged from hospital.

On Cycle 1 Day 17 (**08 September 2017)**, CT-scan performed showed new minor right hydronephrosis and hydroureter due to ureteric obstruction by the large pelvic mass.

On Cycle 1 Day 19 (**10 September 2017)**, the patient began to experience vomiting and nausea (internal reference number OCT-GB-17-CLI-0175, assessed as related to OMO-1 by the investigator but also possibly related to grade 1 constipation, the concomitant medications of fentanyl and codeine, and the disease under study).

On **11 September 2017** (Unscheduled Visit), the patient received their last dose of OMO-1 and was admitted to hospital on the same day with a 1-day history of nausea and vomiting. The patient was unable to tolerate food and drink and was becoming dehydrated. At admission, the patient was also complaining of abdominal pain. As a result of the event of vomiting OMO-1 was temporarily discontinued.

On **12 September 2017** (Unscheduled Visit), following withdrawal of OMO-1 and treatment with antiemetics and intravenous fluid the patient recovered and was discharged. On the same day, the patient was discontinued from the study due to disease progression.

On **27 September 2017** (Unscheduled Visit), the patient experienced vomiting (internal reference number OCT-GB-17-CLI-0202, assessed as unrelated to OMO-1) again and was hospitalised on the same date.

Additional information is expected.

The investigator assessed constipation (worsening from baseline) as serious (required hospitalisation),

SAE NARRATIVE

CTCAE grade 2 and not related to OMO-1. The most likely cause of this event was reported to be due to the patient's underlying condition of bulky pelvis disease.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Constipation	CTCAE grade	2
	Relationship to OMO-1	Not related
	Action taken with OMO-1	No action (dosage maintained)
	Duration	2 days
	Outcome	Resolved with sequelae
	Withdrawn from study	No

SPONSOR ASSESSMENT OF EVENT(S)

Constipation	Relationship to OMO-1	Not related

14.3.3.6.2 Right sided abdominal pain

SAE TERM(S)	PREFERRED TERM(S)
Right sided abdominal pain	Abdominal pain

RELEVANT DEMOGRAPHICS
65-year-old female

RELEVANT MEDICAL HISTORY TERM(S)	
Back pain	Unknown - Ongoing
Flank pain	April 2017 - Ongoing

RELEVANT CONCOMITANT MEDICATION(S)	
Omeprazole	August 2014 - Ongoing
Cyclizine	July 2017 - 15 September 2017
Buscopan (hyoscine butylbromide)	27 July 2017 - 15 September 2017
Codeine	14 August 2017 - 15 September 2017
Paracetamol	April 2017 - 15 September 2017
Docusate	27 July 2017 - 29 August 2017
Sando-k (Potassium bicarbonate, potassium chloride)	20 August 2017 - Unknown
Laxido sachets	18 August 2017 - Ongoing
Fentanyl	24 August 2017 - Ongoing

OMO-1 ADMINISTRATION		
Module	Module 1 Part A Dose-Escalation (Cohort 1)	
Study arm		
Dose	200 mg	
First dose	23 August 2017	Study day 1 (C1D1)
Last dose prior to the event(s)	25 August 2017	Cycle 1 Day 3

SAE NARRATIVE

On Cycle 1 Day 1 (**23 August 2017)**, the patient started to receive the study drug OMO-1 at a dose of 100 mg twice a day.

On Cycle 1 Day 3 (**25 August 2017)**, the patient received last dose of OMO-1 prior to the SAE.

On **29 August 2017** (Unscheduled Visit), the patient was hospitalised due to right sided abdominal pain which was initially thought to be due to bowel obstruction. The investigator mentioned that in

SAE NARRATIVE

case of possible bowel obstruction all oral drugs were prohibited (nil by mouth) until the condition was excluded and OMO-1 was temporarily discontinued.

The patient received analgesic treatment for right sided abdominal pain. Since a CT scan excluded the bowel obstruction, on Cycle 1 Day 10 (**01 September 2017)**, the study drug was restarted.

On Cycle 1 Day 11 (**02 September 2017)**, the right sided abdominal pain was considered resolved with sequelae as it was continuing as intermittent grade 1. On this date, the patient was discharged from hospital.

After analgesic treatment, right sided abdominal pain did not subsequently recur.

Additional information is not expected.

The investigator assessed right sided abdominal pain as serious (hospitalisation), CTCAE grade 2 in severity, serious (hospitalisation) and not related to OMO-1. The most likely cause of the event was disease under study.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Abdominal pain	CTCAE grade	2
	Relationship to OMO-1	Not related
	Action taken with OMO-1	Dose re-introduced
	Duration	5 days
	Outcome	Resolved with sequelae
	Withdrawn from study	No

SPONSOR ASSESSMENT OF EVENT(S)

Abdominal pain	Relationship to OMO-1	Not related

14.3.3.6.3 Worsening vomiting

SAE TERM(S)	PREFERRED TERM(S)
Worsening vomiting	Vomiting

RELEVANT DEMOGRAPHICS
65-year-old female

RELEVANT MEDICAL HISTORY TERM(S)	
Wrist joint painful on movement	Unknown
Elbow joint painful on movement	Unknown
Colorectal cancer (tumour status was noted as being of rapid disease progression with hydronephrosis, hydroureter and increased tumour involvement of sigmoid ascending colon)	Unknown

RELEVANT CONCOMITANT MEDICATION(S)	
Omeprazole	August 2014 - Ongoing
Cyclizine	July 2017 – 15 September 2017
Buscopan (hyoscine butylbromide)	27 July 2017 – 15 September 2017
Codeine	14 August 2017 – 15 September 2017
Paracetamol	April 2017 – 15 September 2017
Docusate	27 July 2017 – 29 August 2017
Sando-k (Potassium bicarbonate, potassium chloride)	20 August 2017 - 22 August 2017
Laxido sachets	18 August 2017 - Ongoing April 2017 - 17 August 2017
Fentanyl	24 August 2017 – Ongoing
Morphine	29 August 2017 – Ongoing

OMO-1 ADMINISTRATION		
Module	Module 1 Part A Dose-Escalation (Cohort 1)	
Study arm		
Dose	200 mg	
First dose	23 August 2017	Study day 1 (C1D1)
Last dose prior to the event(s)	11 September 2017	Unscheduled Visit

SAE NARRATIVE

On **19 August 2017**, the patient was admitted to hospital with abdominal pain due to constipation (internal reference number OCT-GB-17-CLI-0170, assessed as unrelated to OMO-1). During admission, she had a CT-Scan of her abdomen and pelvis, which showed no evidence of obstruction but indicated increased peritoneal deposits from her colorectal malignancy and an increased size of right adnexal mass. She was treated with intravenous (IV) fluid, oral laxatives and enema. It was also noted that her potassium level was low at 3.4 mmol/L and she was started on a course of Sando-K (potassium chloride and potassium bicarbonate).

On **20 August 2017**, the constipation resolved with sequelae and the patient was discharged from the hospital with codeine and laxatives to manage her condition.

On Cycle 1 Day 1 (**23 August 2017)**, the patient began therapy with OMO-1 at a dose of 100 mg twice a day via the oral route.

On Cycle 1 Day 3 (**25 August 2017)**, the patient began to experience intermittent grade 1 vomiting.

On **29 August 2017** (Unscheduled Visit), the patient was admitted to hospital due to back pain (internal reference number OCT-GB-17-CLI-0173, assessed as unrelated to OMO-1). Therapy with OMO-1 was interrupted on this date.

On Cycle 1 Day 10 (**01 September 2017)**, at 13:30, the patient restarted therapy with OMO-1.

On Cycle 1 Day 11 (**02 September 2017)**, the patient was discharged from hospital.

On Cycle 1 Day 17 (**08 September 2017)**, CT-scan performed showed new minor right hydronephrosis and hydroureter due to ureteric obstruction by the large pelvic mass.

On Cycle 1 Day 19 (**10 September 2017)**, the patient began to experience vomiting (grade 2) and nausea.

On **11 September 2017** (Unscheduled Visit), the patient received her last dose of OMO-1 on this date prior to the start of the event worsening vomiting. She was hospitalised for worsening vomiting. The patient was unable to tolerate food and drink and was becoming dehydrated. At admission, the patient was also complaining of abdominal pain. As a result of the event worsening vomiting, OMO-1 was temporarily discontinued.

On **12 September 2017** (Unscheduled Visit), following withdrawal of OMO-1 and treatment with antiemetics and intravenous fluid the patient recovered from the event with the sequelae of mild nausea (grade 1). On the same day she was discharged from hospital in a stable state and was discontinued from the study due to disease progression.

On **27 September 2017** (Unscheduled Visit), the patient experienced vomiting (internal reference number OCT-GB-17-CLI-0202, assessed as unrelated to OMO-1) again and was hospitalised on the same day.

On **29 September 2017** (Follow-Up Visit), she recovered and was discharged from hospital. The most likely cause of this episode of vomiting was reported by the investigator to be the disease under study and not OMO-1.

Additional information is not expected.

The investigator assessed the event worsening vomiting as serious (hospitalisation), CTCAE Grade 3, and possibly related to OMO-1. The rationale for the causality assessment provided by the investigator was that vomiting stopped as soon as the IMP was discontinued. The investigator stated that other potential causes for the SAE of vomiting were grade 1 constipation, the concomitant medications of fentanyl and codeine, and the disease under study.

INVESTIGATOR ASSESSMENT OF EVENT(S)		
Vomiting	CTCAE grade	3
	Relationship to OMO-1	Possibly related
	Action taken with OMO-1	Dose discontinued
	Duration	2 days
	Outcome	Resolved with sequelae
	Withdrawn from study	Yes

SPONSOR ASSESSMENT OF EVENT(S)		
Vomiting	Relationship to OMO-1	Possibly related

14.3.3.6.4 Vomiting

SAE TERM(S)	PREFERRED TERM(S)
Vomiting	Vomiting

RELEVANT DEMOGRAPHICS

65-year-old female

RELEVANT MEDICAL HISTORY TERM(S)

Wrist joint painful on movement	Unknown
Elbow joint painful on movement	Unknown
Colorectal cancer (tumour status was noted as being of rapid disease progression with hydronephrosis, hydroureter and increased tumour involvement of sigmoid ascending colon)	Unknown
Allergy to morphine	Unknown
Allergy to tramadol	Unknown

RELEVANT CONCOMITANT MEDICATION(S)

Macrogol compound	29 August 2017- Ongoing
Paracetamol	April 2017 - 15 September 2017
Dalteparin	29 August 2017 – Ongoing
Metoclopramide	12 September 2017 – Ongoing
Dexamethasone	28 September 2017 – Unknown
Oramorph (Morphine sulfate pentahydrate)	29 August 2017 - Ongoing
Red Blood cells Transfusion	On 28 September 2017

OMO-1 ADMINISTRATION

Module	Module 1 Part A Dose-Escalation (Cohort 1)	
Study arm		
Dose	200 mg	
First dose	23 August 2017	Study day 1 (C1D1)
Last dose prior to the event(s)	11 September 2017	Unscheduled Visit

SAE NARRATIVE

On Cycle 1 Day 1 (**23 August 2017)**, the patient began therapy with OMO-1 at a dose of 100 mg twice a day via the oral route.

SAE NARRATIVE

On Cycle 1 Day 2 (**25 August 2017)**, the patient began to experience intermittent grade 1 vomiting.

On **29 August 2017** (Unscheduled Visit), the patient was admitted to hospital due to back pain (internal reference number OCT-GB-17-CLI-0173). Therapy with OMO-1 was interrupted on this date.

On Cycle 1 Day 10 (**01 September 2017)**, at 13:30, the patient restarted therapy with OMO-1.

On Cycle 1 Day 11 (**02 September 2017)**, the patient was discharged from hospital.

On **11 September 2017** (Unscheduled Visit), the patient was admitted to hospital with a 1-day history of nausea and vomiting (CTCAE grade 3; internal reference number OCT-GB-17-CLI-0175). As a result of this episode of vomiting, OMO-1 was temporarily discontinued; after receiving her last dose.

On **12 September 2017** (Unscheduled Visit), the patient was discharged from hospital. On the same day, the patient was discontinued from the study due to disease progression.

On **27 September 2017** (Unscheduled Visit), the patient experienced vomiting again and was hospitalised on the same day. The patient was treated with 1 unit of blood due to a haemoglobin result of 74 g/L.

On **29 September 2017** (Follow-Up Visit), the patient recovered and was discharged from hospital to community palliative care team to follow up. The patient was advised to take oramorph and antiemetics as treatment.

No further information is expected.

The investigator assessed vomiting as not related to OMO-1 and CTCAE grade 2. The most likely cause of vomiting was determined by the investigator to be the disease under study.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Vomiting	CTCAE grade	2
	Relationship to OMO-1	Not related
	Action taken with OMO-1	Not applicable (Dose discontinued prior to event onset)
	Duration	3 days
	Outcome	Resolved
	Withdrawn from study	Not applicable

SPONSOR ASSESSMENT OF EVENT(S)

Vomiting	Relationship to OMO-1	Not related

14.3.3.7 Patient 1001-004

SAE TERM(S)	PREFERRED TERM(S)
Worsening right upper quadrant pain	Abdominal pain upper
Nausea	Nausea
Pneumonia	Pneumonia
E.coli UTI	Urinary tract infection

RELEVANT DEMOGRAPHICS

59-year-old male

RELEVANT MEDICAL HISTORY TERM(S)

Indwelling catheter insertion (changed every 3 months)	October 2016 - Ongoing
Previous incision for an indwelling catheter	May 2015
Urinary tract infection	August 2017 - Unknown

RELEVANT CONCOMITANT MEDICATION(S)

Dexamethasone	10 October 2017 - 11 October 2017
	12 October 2017 - Ongoing
Gabapentin	July 2017 - Ongoing
Oxynorm (oxycodone)	28 September 2017 - Ongoing
Paracetamol	28 September 2017 - Ongoing
	10 October 2017 - 11 October 2017
Omeprazole	11 October 2017

OMO-1 ADMINISTRATION

Module	Module 1 Part A Dose-Escalation (Cohort 1)	
Study arm		
Dose	200 mg	
First dose	09 October 2017	Study day 1 (C1D1)
Last dose prior to the event(s)	09 October 2017	Cycle 1 Day 1

SAE NARRATIVE

On Cycle 1 Day 1 (**09 October 2017)**, the patient began receiving OMO-1, 100 mg oral capsules twice daily. The patient's tumour status was T3, N2, M1 with lung metastases at the beginning of the

SAE NARRATIVE

therapy.

On Cycle 1 Day 1 (**09 October 2017)**, the patient began experiencing nausea, pneumonia, and an E.Coli UTI, after the first dosing.

On **10 October 2017** (Unscheduled Visit), the patient began experiencing worsening right upper quadrant pain and was hospitalised. The therapy with OMO-1 was temporarily discontinued. A chest x-ray was undertaken and compared to a chest X-ray in April 2017. A differential diagnosis included: right lower lobe pneumonia versus disease progression from capsular distension of liver metastases. There was a bilateral ill-defined airspace shadowing the milled and lower zones, there was consolidation in the right lower lobe with obscuration of the right hemidiaphragm silhouette. There were also multiple lung nodules in the lower lobes in keeping with known metastatic disease and there was associated right-sided pleural effusion. The patient also underwent an abdominal x-ray which revealed bowel gas pattern which were non-specific and within normal limits. No features of bowel obstruction new or peritoneal. A urine culture grew E.Coli sensitive to amoxicillin. The patient began treatment with nystatin, Co-amoxiclav (amoxicillin and clavulanic acid), cyclizine, gentamycin, metronidazole, paracetamol, oxycodone, dexamethasone, ferrous fumarate, and metoclopramide. Amoxicillin was used to treat UTI and pneumonia.

On **12 October 2017** (End of Treatment), the patient recovered from nausea. The event of upper right quadrant pain was considered to be resolved with sequelae as the pain was still present and was being managed by palliative care team. On this date, the patient was discharged from hospital and the patient was withdrawn from the study due to toxicity to OMO-1 and due to withdrawal of consent.

On **13 October 2017** (Unscheduled Visit), the patient recovered from pneumonia, and E.Coli UTI.

On **12 December 2017**, the patient died.

The reporter confirmed that the patient did not receive any prior treatments which could have caused the events and also confirmed that the nausea was not due to the UTI but it was due to the study drug.

Additional information is not expected.

The investigator assessed the event nausea as CTCAE grade 3, serious (hospitalization) and definitely related to OMO-1.

The investigator assessed upper right quadrant pain as CTCAE grade 3, pneumonia as CTCAE grade 1 and E. Coli UTI as CTCAE grade 3. None of these events were considered to be related to OMO-1 by the investigator. The most likely cause of the upper right quadrant pain was reported to be the disease understudy. The most likely cause for pneumonia and E. coli UTI was reported to be other illness.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Nausea	CTCAE grade	3
	Relationship to OMO-1	Definitely related
	Action taken with OMO-1	No action taken
	Duration	4 Days
	Outcome	Resolved
	Withdrawn from study	Yes
Abdominal pain	CTCAE grade	3

INVESTIGATOR ASSESSMENT OF EVENT(S)		
upper	Relationship to OMO-1	Not Related
	Action taken with OMO-1	Drug discontinued
	Duration	3 Days
	Outcome	Resolved with sequelae
	Withdrawn from study	Yes
Pneumonia	CTCAE grade	1
	Relationship to OMO-1	Not Related
	Action taken with OMO-1	Drug discontinued
	Duration	5 Days
	Outcome	Resolved
	Withdrawn from study	Yes
Urinary tract infection	CTCAE grade	3
	Relationship to OMO-1	Not Related
	Action taken with OMO-1	Drug discontinued
	Duration	5 Days
	Outcome	Resolved
	Withdrawn from study	Yes

SPONSOR ASSESSMENT OF EVENT(S)		
Nausea	Relationship to OMO-1	Related
Abdominal pain upper	Relationship to OMO-1	Not related
Pneumonia	Relationship to OMO-1	Not related
Urinary tract infection	Relationship to OMO-1	Not related

14.3.3.8 Patient 1002-001

SAE TERM(S)	PREFERRED TERM(S)
Rigor	Chills

RELEVANT DEMOGRAPHICS

51-year-old female

RELEVANT MEDICAL HISTORY TERM(S)

Reflux gastritis	2011 - Ongoing
Peripheral neuropathy	October 2015 - Ongoing
Left shoulder pain	October 2017 - Ongoing
Diverticulosis	2014 - Ongoing
Right big toe osteoarthritis	2017 - Ongoing
Left big toe osteoarthritis	2017 - Ongoing

RELEVANT CONCOMITANT MEDICATION(S)

Paracetamol	October 2017 - Ongoing
Metoclopramide	January 2017 - Ongoing
Loperamide	January 2017 - Ongoing

OMO-1 ADMINISTRATION

Module	Module 1 Part A Dose-Escalation (Cohort 2)	
Study arm		
Dose	400 mg	
	Drug restarted at 200 mg	
First dose	05 December 2017	Study day 1 (C1D1)
Last dose prior to the event(s)	28 December 2017	Cycle 2 Day 1

SAE NARRATIVE

On Cycle 1 Day 1 (**05 December 2017)**, the patient began therapy with OMO-1 at a dose of 200 mg twice a day via the oral route.

On Cycle 2 Day 1 (**28 December 2017)**, at 11.20 hrs the patient received the last dose of study drug prior to the event onset. At 12.30 hrs the patient developed a rash and itch which improved with IV Piriton (chlorphenamine). The patient also had a headache which settled with paracetamol. At 13.30 hrs the patient began to experience rigor and was given hydrocortisone. The patient also had coryzal

SAE NARRATIVE

symptoms. The body temperature went up to 37.4 degrees Celsius. The examination was normal and therapy with OMO-1 was temporarily interrupted. On the same day, the event of rigor was resolved.

On **02 January 2018** (Unscheduled Visit), the patient restarted on OMO-01 at a dose of 100 mg twice a day. The event did not recur. The rash and rigor did not recur. The patient had patientive feeling of short lived palpitations and HR of 105, but the patient felt well and ECGs were satisfactory. Palpitations resolved and have not recurred since reintroduction.

No additional information is expected.

The investigator assessed rigor as serious (medically significant/important), CTCAE grade 2 in severity and definitely related to OMO-1.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Chills	CTCAE grade	2
	Relationship to OMO-1	Definitely related
	Action taken with OMO-1	Study drug was temporary stopped and restarted
	Duration	1 day
	Outcome	Resolved
	Withdrawn from study	No

SPONSOR ASSESSMENT OF EVENT(S)

Chills	Relationship to OMO-1	Possibly related

14.3.3.9 Patient 1001-006

SAE TERM(S)	PREFERRED TERM(S)
Colonic obstruction	Large intestinal obstruction

RELEVANT DEMOGRAPHICS

64-year-old male

RELEVANT MEDICAL HISTORY TERM(S)

Abdominal discomfort	10 September 2017 - Ongoing
Constipation	10 September 2017 - Ongoing

RELEVANT CONCOMITANT MEDICATION(S)

Paracetamol	20 September 2017 - Ongoing
Movicol (macrogol)	17 October 2017 - Ongoing
Cetraban (paraffin)	01 January 2018 - Ongoing

OMO-1 ADMINISTRATION

Module	Module 1 Part A Dose-Escalation (Cohort 1)	
Study arm		
Dose	200 mg	
First dose	01 November 2017	Study day 1 (C1D1)
Last dose prior to the event(s)	22 January 2018	Cycle 4 Day 20

SAE NARRATIVE

On Cycle 1 Day 1 (**01 November 2017)**, the patient started to receive the study drug OMO-1 orally at a dose of 100 mg twice a day.

On Cycle 4 Day 19 (**21 January 2018)**, the patient was admitted to the hospital due to abdominal pain, the patient had a colonic obstruction. CT results showed progressive disease. The patient was started on dexamethasone.

On Cycle 4 Day 20 (**22 January 2018)**, the patient received their last dose of the study drug and as a consequence of the event, the study drug was permanently stopped. The patient was withdrawn from the trial due to disease progression.

On **02 February 2018** (Unscheduled Visit), the event of colonic obstruction had resolved with a sequelae of pain, and the patient was discharged to a hospice.

On **05 February 2018** (Unscheduled Visit), it was noted the patient was receiving treatment with subcutaneous morphine and had a nasogastric tube, the start dates for these treatments were not

SAE NARRATIVE

reported.

No additional information is expected.

The investigator assessed colonic obstruction as CTCAE grade 2 in severity and not related to OMO-1. The most likely cause of the event was due to disease under study.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Large intestinal obstruction	CTCAE grade	2
	Relationship to OMO-1	Not related
	Action taken with OMO-1	Drug permanently discontinued
	Duration	13 days
	Outcome	Resolved with sequelae
	Withdrawn from study	Yes

SPONSOR ASSESSMENT OF EVENT(S)

Large intestinal obstruction	Relationship to OMO-1	Not related

14.3.3.10 Patient 1002-002

SAE TERM(S)	PREFERRED TERM(S)
Diarrhoea (Increased stoma output)	Diarrhoea
Upper respiratory tract infection	Upper respiratory tract infection
Increased creatinine	Blood creatinine increased
Increased bilirubin	Blood bilirubin increased
Increased neutrophilia	Neutrophil count increased
Nausea	Nausea

RELEVANT DEMOGRAPHICS

65-year-old male

RELEVANT MEDICAL HISTORY TERM(S)

Superior vena cava thrombosis	November 2016 - Ongoing
Fatigue	Unknown

RELEVANT CONCOMITANT MEDICATION(S)

Enoxaparin	November 2016 - Ongoing
Paracetamol	27 February 2018 - 07 March 2018

OMO-1 ADMINISTRATION

Module	Module 1 Part A Dose-Escalation (Cohort 3)	
Study arm		
Dose	800 mg	
First dose	21 February 2018	Study day 1 (C1D1)
Last dose prior to the event(s)	22 February 2018	Cycle 1 Day 2

SAE NARRATIVE

On Cycle 1 Day 1 (**21 February 2018)**, the patient began therapy with OMO-1 with a twice daily dose of 400 mg via the oral route.

On Cycle 1 Day 2 (**22 February 2018)**, the patient took his dose of OMO-1 at 14:00 pm as it had to be taken 24 hrs after PK. Half an hour later the patient felt shivery. One hour later the patient felt nauseated (at 15:30) and experienced diarrhoea (increased stoma output) (at 15:30) and vomited three times. The diarrhoea began to settle after a while. The patient was therefore advised to take the pm dose between 18:30 – 19:30, which he took at 19.45. This was the last dose of OMO-1. The patient

SAE NARRATIVE

experienced flu-like symptoms 45 minutes (at 20:30) after the second dose of study drug, which were due to upper respiratory tract infection. The patient experienced increased, watery stoma output/loose stools simultaneously, and felt unwell. The patient then contacted Christie hospital hotline and was advised to call the ambulance. He was then admitted to hospital just before midnight. On arrival, the patient had a low temperature, but observations were otherwise stable. He was noted to have grade 1 neutrophillia at 23:22 hours.

On an unknown date, the patient received IV normal saline for treatment for the SAEs.

On Cycle 1 Day 3 (**23 February 2018)**, the patient was noted to have increased creatinine of 161 µmol/L and increased bilirubin of 22 µmol/L. He received a stat dose of IV meropenem and IV fluids. It was considered that symptoms and signs were possibly related to study drug inflammatory reaction rather than infection. The symptoms of nausea and chills settled. On this date, the non-serious AE of fatigue, which had been present prior to the start of the patient's involvement in the trial, became CTCAE grade 2 (non-serious) (was previously CTCAE grade 1). The event of diarrhoea continued along with further worsening of creatinine to 172 µmol/L and bilirubin to 28 µmol/L. The patient continued to receive IV fluids and had a stat dose of meropenem. The patient had emptied the stoma 5-6 times by the time the investigator saw the patient at 10:30am. The patient's vomiting and shivering had stopped. The patient stayed in hospital and therapy with OMO-1 tablets was not restarted.

On **24 February 2018** (Unscheduled Visit), the events of increased neutrophilia and increased bilirubin had resolved.

On **26 February 2018** (Unscheduled Visit), the events of nausea, diarrhoea (increased stoma output) and upper respiratory tract infection had resolved at 09.48 hours (discharge time) and the patient was discharged from hospital. It was reported that nausea, diarrhoea (increased stoma output) and the blood test values were likely study drug induced. It was noted that the patient continued to experience diarrhoea (non-serious) CTCAE grade 1.

On **27 February 2018** (Unscheduled Visit), the patient began experiencing a non-serious AE of grade 1 headache which resolved on the same date.

On **28 February 2018** (Unscheduled Visit), the non-serious AE of diarrhoea CTCAE grade 1 resolved.

On **01 March 2018** (Unscheduled Visit), the non-serious AE of fatigue reduced in severity to CTCAE grade 1.

On **21 March 2018** (End of Treatment), the event of increased creatinine had resolved. The patient's creatinine returned to baseline value at 107umol/L. A formal discontinuation was performed with regards to the study drug being permanently discontinued.

No additional information is expected.

The investigator assessed nausea, increased bilirubin, increased creatinine and increased neutrophilia as CTCAE grade 1 whereas the events diarrhoea (increased stoma output) and upper respiratory tract infection as CTCAE grade 2 in severity. The investigator assessed increased creatinine, increased neutrophilia and increased bilirubin as possibly related whereas nausea and diarrhoea (increased stoma output) as definitely related to OMO-1. The investigator assessed upper respiratory tract infection as not related to OMO-1.

INVESTIGATOR ASSESSMENT OF EVENT(S)

INVESTIGATOR ASSESSMENT OF EVENT(S)		
Diarrhoea	CTCAE grade	2
	Relationship to OMO-1	Definitely related
	Action taken with OMO-1	Drug discontinued
	Duration	5 days
	Outcome	Resolved
	Withdrawn from study	Yes
Upper respiratory tract infection	CTCAE grade	2
	Relationship to OMO-1	Not related
	Action taken with OMO-1	Drug discontinued
	Duration	5 days
	Outcome	Resolved
	Withdrawn from study	Yes
Blood creatinine increased	CTCAE grade	1
	Relationship to OMO-1	Possibly related
	Action taken with OMO-1	Drug discontinued
	Duration	27 days
	Outcome	Resolved
	Withdrawn from study	Yes
Blood bilirubin increased	CTCAE grade	1
	Relationship to OMO-1	Possibly related
	Action taken with OMO-1	Drug discontinued
	Duration	2 days
	Outcome	Resolved
	Withdrawn from study	Yes
Neutrophil count increased	CTCAE grade	1
	Relationship to OMO-1	Possibly related
	Action taken with OMO-1	Drug discontinued
	Duration	3 days
	Outcome	Resolved
	Withdrawn from study	Yes
Nausea	CTCAE grade	1
	Relationship to OMO-1	Definitely related
	Action taken with OMO-1	Drug discontinued

INVESTIGATOR ASSESSMENT OF EVENT(S)		
	Duration	5 days
	Outcome	Resolved
	Withdrawn from study	Yes

SPONSOR ASSESSMENT OF EVENT(S)		
Diarrhoea	Relationship to OMO-1	Possibly related
Upper respiratory tract infection	Relationship to OMO-1	Not related
Blood creatinine increased	Relationship to OMO-1	Possibly related
Blood bilirubin increased	Relationship to OMO-1	Possibly related
Neutrophil count increased	Relationship to OMO-1	Possibly related
Nausea	Relationship to OMO-1	Possibly related

14.3.3.11 Patient 1001-009

SAE TERM(S)	PREFERRED TERM(S)
Flu-like symptoms - Grade 3	Influenza like illness

RELEVANT DEMOGRAPHICS

64-year-old male

RELEVANT MEDICAL HISTORY TERM(S)

Fatigue	25 January 2018 - Ongoing
Right shoulder pain	25 January 2018 - Ongoing
High blood pressure	2013 - Ongoing
Obesity	Unknown - Ongoing

RELEVANT CONCOMITANT MEDICATION(S)

Amlodipine	January 2013 - Ongoing
Ibuprofen	25 January 2018 - Ongoing
Codeine	25 January 2018 - Ongoing

OMO-1 ADMINISTRATION

Module	Module 1 Part A Dose-Escalation (Cohort 3)	
Study arm		
Dose	800 mg	
	Study drug reduced to 400 mg	
First dose	21 February 2018	Study day 1 (C1D1)
Last dose prior to the event(s)	23 February 2018	Cycle 1 Day 3

SAE NARRATIVE

On Cycle 1 Day 1 (**21 February 2018)**, the patient began therapy with OMO-1 capsules with a dose of 400 mg BID via the oral route.

On Cycle 1 Day 3 (**23 February 2018)**, the patient experienced first episode of flu-like symptoms with coryzal and viral symptoms, for preceding 5 days, which was considered as a non-serious event by the investigator. On this date, the treatment with OMO-1 was withheld since the patient's creatinine increased (non-serious adverse event).

It was noted by the reporter that the patient was not immunosuppressed.

On **06 March 2018** (Unscheduled Visit), the patient started experiencing flu-like symptoms and he

SAE NARRATIVE

was admitted to his local hospital. Approximately 60 minutes after taking OMO-1, the patient started shaking and retching. The patient was also quite peripherally shut down (with white extremities) but blood pressure (BP) and heart rate (HR) were normal. He spiked a temperature as well. The patient's symptoms settled after receiving treatment with paracetamol and Piriton (Chlorphenamine).

The patient was initially diagnosed with 'infection (pneumonia)'. The patient received treatment with IV meropenem. The site reported that the initial diagnosis of pneumonia was not supported by test results since no focus of infection and no increase in white cell count and a normal chest x-ray. No other tests or X-ray were performed. The patient was therefore diagnosed with 'flu like symptoms - grade 3' with no respiratory tract infection (RTI) symptoms. The first time this event occurred, the patient attributed it to a "dodgy kebab".

On **07 March 2018** (Unscheduled Visit), therapy with 400 mg of OMO-1 was temporarily interrupted as a result of the event.

On **08 March 2018** (Unscheduled Visit), the patient stopped receiving treatment with IV meropenem.

On **09 March 2018** (Unscheduled Visit), the event of 'flu-like symptoms - grade 3' had resolved and the patient was discharged from hospital.

On **11 March 2018** (Unscheduled Visit), the patient had oral herpes simplex which was assessed as non-serious by the investigator.

On Cycle 2 Day 1 (**21 March 2018)**, the patient was re-started on 200 mg of OMO-1 capsules twice daily. On this date, the patient experienced shaking and retching after 1 hour of the study drug intake. These events were assessed as non-serious, grade 2 and definitely related to OMO-1 by the investigator. The Investigator also stated that the events, shaking and retching were not flu-like symptoms but more a drug reaction. On the same date, the patient recovered from non-serious events shaking and retching. As a result of the event, the treatment with OMO-1 was withdrawn.

On **29 March 2018** and on **26 April 2018**, the patient attended the end of treatment visit and follow-up end of study (EOS) visit, respectively.

No additional information is expected.

The investigator assessed 'flu-like symptoms - grade 3' as CTCAE grade 3 and possibly related to OMO-1.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Influenza like illness	CTCAE grade	3
	Relationship to OMO-1	Possibly related
	Action taken with OMO-1	Drug discontinued
	Duration	4 days
	Outcome	Resolved
	Withdrawn from study	Yes

SPONSOR ASSESSMENT OF EVENT(S)

Influenza like illness	Relationship to OMO-1	Possibly related

14.3.3.12 Patient 1003-002

SAE TERM(S)	PREFERRED TERM(S)
Troponin rise	Troponin increased
Worsening of dyspnoea	Dyspnoea
Superior vena cava obstruction	Superior vena cava occlusion

RELEVANT DEMOGRAPHICS

66-year-old male

RELEVANT MEDICAL HISTORY TERM(S)

Epithelioid mesothelioma	Unknown
Hypertension	2000 - Ongoing
Hypercholesterolemia	1998 - Ongoing
Dyspnoea	January 2016 - 13 March 2018
Neuropathic pain right shoulder and arm	September 2016 - Ongoing
Pain right chest wall - non-cardiac	January 2017 - Ongoing
Anorexia	December 2017 - February 2018
Constipation intermittent	January 2018 - Ongoing
Anaemia	02 February 2018 - 05 March 2018
Raised ALP	December 2016 - Ongoing
COPD (chronic obstructive pulmonary disease)	2013 - Ongoing

RELEVANT CONCOMITANT MEDICATION(S)

Ramipril	June 2011 - 01 March 2018
	02 March 2018 - Ongoing
Lacidipine	June 2011 - 26 February 2018
Aspirin	March 2011 - Ongoing
Atorvastatin	April 2011 - Ongoing
Oxycodone	16 January 2018 - Ongoing
Oxynorm	October 2016 - Ongoing
Gabapentin	11 December 2017 - Ongoing
Prednisolone	15 January 2018 - 02 March 2018
Buprenorphine	October 2017 - Ongoing

RELEVANT CONCOMITANT MEDICATION(S)	
Salbutamol	January 2013 - Ongoing
Tiotropium	January 2014 - Ongoing
Seretide	January 2016 - Ongoing
Dexamethasone	12 March 2018 - Ongoing
Tinzaparin	12 March 2018 - Ongoing
Paracetamol	January 2017 - Ongoing
Senna	January 2018 - Ongoing

OMO-1 ADMINISTRATION		
Module	Module 1 Part A Dose-Escalation (Cohort 3)	
Study arm		
Dose	800 mg	
	Reduced to 400 mg	
First dose	19 February 2018 (800 mg)	Study day 1 (C1D1)
	05 March 2018 (400 mg)	
Last dose prior to the event(s)	05 March 2018	Cycle 1 Day 15

SAE NARRATIVE

On Cycle 1 Day 1 (**19 February 2018)**, the patient began therapy with OMO-1 capsules twice daily with a dose of 400 mg via the oral route.

On Cycle 1 Day 8 (**26 February 2018)**, therapy with OMO-1 was withheld due to serum creatinine increase.

On Cycle 1 Day 15 (**05 March 2018)**, the patient re-started therapy with OMO-1 capsules via the oral route with a reduced dose from 400 mg twice a day to 200 mg twice a day for cycle 1 Day 15. On this date, the patient took the last dose of OMO-1 prior to the event.

On Cycle 2 Day 1 (**12 March 2018)**, therapy with OMO-1 was temporarily interrupted as a consequence of the event superior vena cava (SVC) obstruction, related to mesothelioma. As a result of the superior vena cava obstruction, the patient was hospitalised.

On **13 March 2018** (Unscheduled Visit), a CT pulmonary angiogram ruled out pulmonary embolism. On this date, a stent placement was performed for superior vena cava obstruction and the patient recovered from this event.

On **14 March 2018** (Unscheduled Visit), the patient began to experience serum troponin rise and worsening of dyspnoea. Facial and neck swelling as well as on-going tachycardia was reported. On this date, troponin had increased to 229 IU. It was noted that troponin rise could be secondary to left ventricular impairment. The reporter stated that the dyspnoea was likely due to a combination of mesothelioma and a possible cardiac event. The patient began treatment with tinzaparin, aspirin and

SAE NARRATIVE

bisoprolol. The reporter also stated that dyspnoea was present before the onset of superior vena cava obstruction, although this may have worsened the dyspnoea.

On **15 March 2018** (Unscheduled Visit), the patient was discharged from hospital and the outcome of the events of troponin rise and worsening of dyspnoea were reported as recovering.

The patient had an ECG. The reporter stated that on the basis of the ECG and troponin test the patient probably had an entreo lateral non-q wave myocardial infarction. An echo showed no abnormality.

On **21 March 2018** (Unscheduled Visit), the patient was withdrawn from the study due to troponin rise and worsening of dyspnoea.

On **20 April 2018**, the patient died, and the events of troponin rise and worsening of dyspnoea were considered not resolved. The cause of death was believed to be epithelioid mesothelioma.

Additional information was not expected.

The investigator assessed superior vena cava obstruction, troponin rise and worsening of dyspnoea as not related to OMO-1. The most likely cause was other illness. The events of troponin rise, and superior vena cava obstruction were considered to be CTCAE grade 3 and the event of worsening of dyspnoea was considered to be CTCAE grade 2.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Troponin increased	CTCAE grade	3
	Relationship to OMO-1	Not related
	Action taken with OMO-1	No action taken (End of Treatment rationale: Confirmed Disease Progression; [source: L.16.2.1.3.1])
	Duration	Unknown
	Outcome	Not resolved
	Withdrawn from study	Yes
Dyspnoea	CTCAE grade	2
	Relationship to OMO-1	Not related
	Action taken with OMO-1	No action taken (End of Treatment rationale: Confirmed Disease Progression; [source: L.16.2.1.3.1])
	Duration	Unknown
	Outcome	Not resolved
	Withdrawn from study	Yes
Superior vena cava occlusion	CTCAE grade	3
	Relationship to OMO-1	Not related
	Action taken with OMO-1	No action taken (End of Treatment rationale: Confirmed Disease Progression; [source: L.16.2.1.3.1])

INVESTIGATOR ASSESSMENT OF EVENT(S)		
	Duration	2 Days
	Outcome	Resolved
	Withdrawn from study	No

SPONSOR ASSESSMENT OF EVENT(S)		
Troponin increased	Relationship to OMO-1	Not related
Dyspnoea	Relationship to OMO-1	Not related
Superior vena cava occlusion	Relationship to OMO-1	Not related

14.3.3.13 Patient 1003-005

SAE TERM(S)	PREFERRED TERM(S)
Type 2 Respiratory failure	Respiratory failure

RELEVANT DEMOGRAPHICS

69-year-old male

RELEVANT MEDICAL HISTORY TERM(S)

Dyspnoea	October 2016 – Ongoing
Dry cough	October 2016 – Ongoing
Left arm swelling	April 2018 – Ongoing
Left upper limb pain (radiate to front of chest)	November 2017 – Ongoing
Anaemia	23 February 2018 – Ongoing
Acne rosacea	1982 – Ongoing
Paraesthesia	February 2018 – Ongoing
Left leg swelling	May 2018 – Ongoing
Hypertension	13 July 2016 – Ongoing
Hypercholesterolaemia	2008 – Ongoing

RELEVANT CONCOMITANT MEDICATION(S)

Zomorph (morphine)	April 2018 - Unknown
Oramorph (morphine)	June 2017 - Unknown
Omeprazole	October 2016 - Unknown
Atorvastatin	January 2015 - Unknown
Gabapentin	15 May 2018 - Unknown
Paracetamol	June 2017 - Unknown
Ibuprofen	May 2018 - Unknown
Oxytetracycline	January 1982 - Unknown
Dexamethasone	13 May 2018 - Unknown
Movicol (macrogol)	April 2018 - Unknown
Diazepam	17 May 2018 - Unknown

OMO-1 ADMINISTRATION

OMO-1 ADMINISTRATION		
Module		
Study arm		
Dose	The patient never received the study drug.	
First dose	Not applicable	Study day 1 (C1D1)
Last dose prior to the event(s)	Not applicable	

SAE NARRATIVE

On **15 May 2018**, the patient signed the informed consent. The patient never received the study drug.

On **31 May 2018**, the patient began experiencing shortness of breath and swelling of the left arm that became gradually worse.

On **03 June 2018**, the patient was admitted to hospital due to shortness of breath (later diagnosed as type 2 respiratory failure). The patient was also experiencing an intermittent, non-productive cough, haemoptysis and additional face swelling. The patient was treated with oxygen after decreased oxygen saturation was noted.

On **04 June 2018**, the patient had a popular rash on the left arm and a right lung pleural effusion. The patient also noted that he had been experiencing hallucinations over the last couple of days. The patient had swollen feet and distended neck veins but remained mobile. The patient was treated with dexamethasone and a CT scan was performed which showed progression of mesothelioma.

On **05 June 2018**, the patient had deteriorated overnight and had trouble breathing without a bag ventilator. The patient could still move all limbs but not respond to the doctor's comments. The doctor believed that the deterioration was due to worsening infection in pleural fluid and limited lung function due to the patient's rapidly progressive biphase mesothelioma. The patient was placed on palliative care and died due to type 2 respiratory failure at 13:40.

No action was applicable with OMO-1 as the patient never received OMO-1.

No additional information is expected.

The investigator assessed the event type 2 respiratory failure as serious (hospitalization, death), CTCAE Grade 5 and not related to OMO-1. The most likely cause was deemed to be the disease under study.

INVESTIGATOR ASSESSMENT OF EVENT(S)		
Respiratory failure	CTCAE grade	5
	Relationship to OMO-1	Not related
	Action taken with OMO-1	Not applicable as the patient never received the study drug
	Duration	3 days
	Outcome	Fatal
	Withdrawn from study	Not applicable

SPONSOR ASSESSMENT OF EVENT(S)		
Respiratory failure	Relationship to OMO-1	Not related

14.3.3.14 Patient 1005-002

SAE TERM(S)	PREFERRED TERM(S)
Metastatic spinal cord compression	Spinal cord compression

RELEVANT DEMOGRAPHICS

44-Year-old male

RELEVANT MEDICAL HISTORY TERM(S)

Gastroesophageal reflux disease	April 2017 - Ongoing
Pulmonary embolism	January 2018 – Ongoing

RELEVANT CONCOMITANT MEDICATION(S)

Enoxaparin	January 2018 - Ongoing
Bisoprolol	April 2017 - Ongoing
Morphine sulfate	April 2017 - Ongoing
Paracetamol	April 2017 - Ongoing
Pregabalin	January 2018 - Ongoing
Omeprazole	April 2017 - Ongoing
Sevredol (morphine)	April 2017 - Ongoing

OMO-1 ADMINISTRATION

Module	Module 1 Part B Expansion with MET/EXON (Cohort 2)	
Study arm		
Dose	400 mg	
First dose	10 May 2018	Study day 1 (C1D1)
Last dose prior to the event(s)	06 June 2018	Unscheduled visit

SAE NARRATIVE

On Cycle 1 Day 1 (**10 May 2018)**, the patient began receiving OMO-1 at a dose of 200 mg orally twice daily.

On **04 June 2018** (Unscheduled Visit), the patient noticed back pain and leg weakness and attended hospital. It was noted that at the patient's last review on 31 May 2018, he was able to mobilise. The patient was treated with dexamethasone.

On **06 June 2018** (Unscheduled Visit), the patient received his last dose of OMO-1 prior to the event. On this date, the patient underwent a spinal MRI. The patient was diagnosed with metastatic spinal

SAE NARRATIVE

cord compression. Surgical input was not possible in light of patient's disease. Therefore, the study drug was withheld and the patient was commenced on palliative care.

On **07 June 2018** (Unscheduled Visit), as a result of the event metastatic spinal cord compression, the study drug was permanently discontinued and never re-started.

On **19 June 2018** (Unscheduled Visit), the event metastatic spinal cord compression was reported to have resolved with the sequelae of loss of lower limb power. On this date, the patient was discharged home with persisted symptoms of spinal cord compression caused by disease progression to be managed by supportive care only.

On **11 July 2018**, the patient died. The cause of death was reported as cardiac arrest thought to be disease related. Autopsy was not performed.

No additional information is expected.

The investigator assessed the event metastatic spinal cord compression as serious (hospitalisation), CTCAE Grade 3 and not related to OMO-1. The most likely cause was deemed to be the disease under study.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Spinal cord compression	CTCAE grade	3
	Relationship to OMO-1	Not related
	Action taken with OMO-1	Drug discontinued
	Duration	14 days
	Outcome	Resolved with sequelae
	Withdrawn from study	Yes

SPONSOR ASSESSMENT OF EVENT(S)

Spinal cord compression	Relationship to OMO-1	Not related

14.3.3.15 Patient 1002-004

SAE TERM(S)	PREFERRED TERM(S)
Nausea	Nausea
Worsening SVCO	Superior vena cava occlusion

RELEVANT DEMOGRAPHICS

75-year-old female

RELEVANT MEDICAL HISTORY TERM(S)

None

RELEVANT CONCOMITANT MEDICATION(S)

Levothyroxine	April 2017 - Ongoing
Esomeprazole	January 2015 - Ongoing
Oramorph (morphine sufate pentahydrate)	December 2017 - Ongoing
Zomorph (morphine sufate)	February 2018 - Ongoing
Amitriptyline	2012 - 15 June 2018
Alendronic acid	January 2011 - Ongoing
Paracetamol	December 2017 - Ongoing
Magnaspartate (magnesium aspartate)	13 June 2018 - Ongoing
Zopiclone	15 June 2018 - Ongoing
Domperidone	17 June 2018 - 20 June 2018
Ondansetron	20 June 2018 - Ongoing
Metoclopramide	20 June 2018 - Ongoing

OMO-1 ADMINISTRATION

Module	Module 1 Part A Dose-Escalation (Cohort 4)	
Study arm		
Dose	500 mg	
First dose	19 June 2018	Study day 1 (C1D1)
Last dose prior to the event(s)	21 June 2018	Cycle 1 Day 3

SAE NARRATIVE

SAE NARRATIVE

From **23 May 2018**, the patient had grade 1 nausea which was believed to be opiate induced.

On Cycle 1 Day 1 (**19 June 2018)**, the patient began therapy (cycle 1, day 1) with OMO-1 with a twice daily dose of 250 mg via the oral route. The patient suffered from grade 1 nausea after the very first dose of study drug. The patient received metoclopramide and ondansetron as antiemetics.

On Cycle 1 Day 2 (**20 June 2018)**, the patient had grade 2 nausea when dosing with OMO-1. The patient received treatment with oral metoclopramide at 10 mg three times daily and oral ondansetron at 8 mg as required.

On Cycle 1 Day 4 (**22 June 2018)**, the site contacted the patient. She informed the site that she had severe nausea and could not eat or drink and was feeling very tired. The patient was admitted to the hospital. The plan was to temporarily hold the study drug and commence cyclizine infusion, intravenous fluids and blood tests.

On Cycle 1 Day 6 (**24 June 2019)**, the patient received treatment with Movicol (macrogol), 2 sachets, twice daily for constipation.

On Cycle 1 Day 8 (**26 June 2018)**, the patient begun treatment with oral hyoscine butyl bromide at 20 mg twice daily, for the event nausea.

On Cycle 1 Day 10 (**28 June 2018)**, a CT pulmonary angiogram was performed for a possible pulmonary embolism. This test did not show a pulmonary embolism but a significant SVCO and an increase in size of the right sided pleural effusion and a new small volume left basal pleural effusion. The event pleural effusion was assessed as non-serious by the investigator. As a result of the worsening of SVCO, the patient hospitalisation was prolonged. The patient started receiving treatment with oral dexamethasone at 12 mg twice daily.

On Cycle 1 Day 12 (**30 June 2018)**, the patient received treatment with oral levopromazine, 6 mg as required for nausea.

On Cycle 1 Day 13 (**01 July 2018)**, the patient received the last dose of OMO-1. On the same day, the patient received co-amoxiclav (amoxicillin/clavulanic acid) for lung infection.

On Cycle 1 Day 14 (**04 July 2018)**, the patient was discharged from hospital. Whilst in hospital the patient deteriorated with disease progression and worsening of SVCO.

On **10 July 2018** (End of Treatment), the patient received treatment with oral docusate at 100 mg twice daily, for constipation. On the same date, the patient was withdrawn from the study. The oral treatment with dexamethasone was decreased to 10, 8, 6, 4, 2 and 1 mg, once daily, on 11 July 2018, 16 July 2018, 21 July 2018, 26 July 2018, 31 July 2018 and on 05 August 2018, respectively.

On **18 August 2018**, the patient died due to metastatic lung cancer with superior vena cava obstruction.

The outcome for the events nausea and worsening SVCO was reported as not recovered. The investigator reported that the SAEs were on-going at the time of death.

No additional information is expected.

The investigator assessed nausea, as serious (required hospitalisation) CTCAE grade 2 in severity and definitely related to OMO-1. The investigator assessed worsening SVCO, as serious (prolonged hospitalisation) CTCAE grade 2 in severity and not related to OMO-1 and most likely caused by disease under study.

INVESTIGATOR ASSESSMENT OF EVENT(S)		
Nausea	CTCAE grade	2
	Relationship to OMO-1	Definitely related
	Action taken with OMO-1	No action taken (End of Treatment rationale: Symptomatic Progression; [source: L.16.2.1.3.1])
	Duration	Unknown
	Outcome	Not resolved
	Withdrawn from study	Yes
Superior vena cava occlusion	CTCAE grade	2
	Relationship to OMO-1	Not related
	Action taken with OMO-1	Drug discontinued
	Duration	Unknown
	Outcome	Not resolved
	Withdrawn from study	Yes

SPONSOR ASSESSMENT OF EVENT(S)		
Nausea	Relationship to OMO-1	Related
Superior vena cava occlusion	Relationship to OMO-1	Not related

14.3.3.16 Patient 1005-003

14.3.3.16.1 Fever and Tachycardia

SAE TERM(S)	PREFERRED TERM(S)
Fever	Pyrexia
Tachycardia	Tachycardia

RELEVANT DEMOGRAPHICS

62-year-old male

RELEVANT MEDICAL HISTORY TERM(S)

Biliary stent	Unknown
Varicose vein	2016 – Ongoing
Pulmonary embolism	June 2018

RELEVANT CONCOMITANT MEDICATION(S)

None

OMO-1 ADMINISTRATION

Module	Module 1 Part B Expansion with MET/EXON (Cohort 2)	
Study arm		
Dose	500 mg	
First dose	26 July 2018	Study day 1 (C1D1)
Last dose prior to the event(s)	5 August 2018	Cycle 1 Day 11

SAE NARRATIVE

On Cycle 1 Day 1 (**26 July 2018)**, the patient began receiving OMO-1, 250 mg oral capsule BD.

On Cycle 1 Day 11 (**05 August 2018)**, the patient took their last dose of OMO-1 prior to experiencing fever and tachycardia. On the same date, the patient attended Accident and Emergency (A&E) late in the evening with general weakness and it was decided to admit him based on elevated temperature and tachycardia with suspected sepsis later diagnosed as fever (no temperature data provided, reported as "high fever"). The reported events were considered serious due to hospitalisation. As a consequence of these events, dosing was interrupted on 05 August 2018.

On Cycle 1 Day 12 (**06 August 2018)**, the patient was treated with intravenous (IV) meropenem and IV fluid. The patient had a blood culture taken. The events resolved on this date.

On Cycle 1 Day 16 (**10 August 2018)**, the patient was discharged from hospital as the blood cultures

SAE NARRATIVE

were negative and the patient was asymptomatic of infection. The patient completed the course of IV antibiotics and was started on a 5 day oral antibiotic course.

The study drug was discontinued as a result of the reported events fever and tachycardia. It was noted that the biliary stent was not removed.

Additional information is not expected.

The Investigator assessed fever as CTCAE grade 3 whereas the event tachycardia assessed as CTCAE grade 1. The investigator assessed fever and tachycardia as not related to OMO-1 and instead most likely related to another medical condition (biliary stent) due to the patient's worsening jaundice on admission.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Pyrexia	CTCAE grade	3
	Relationship to OMO-1	Not related
	Action taken with OMO-1	Drug discontinued
	Duration	2 days
	Outcome	Resolved
	Withdrawn from study	Yes
Tachycardia	CTCAE grade	1
	Relationship to OMO-1	Not related
	Action taken with OMO-1	Drug discontinued
	Duration	2 days
	Outcome	Resolved
	Withdrawn from study	Yes

SPONSOR ASSESSMENT OF EVENT(S)

Pyrexia	Relationship to OMO-1	Not related
Tachycardia	Relationship to OMO-1	Not related

14.3.3.16.2 Primary occluded stent

SAE TERM(S)	PREFERRED TERM(S)
Primary occluded stent	Device occlusion

RELEVANT DEMOGRAPHICS

62-year-old male

RELEVANT MEDICAL HISTORY TERM(S)

Biliary stent	Unknown
Varicose vein	2016 – Ongoing
Pulmonary embolism	June 2018

RELEVANT CONCOMITANT MEDICATION(S)

None

OMO-1 ADMINISTRATION

Module	Module 1 Part B Expansion with MET/EXON (Cohort 2)	
Study arm		
Dose	500 mg	
First dose	26 July 2018	Study day 1 (C1D1)
Last dose prior to the event(s)	5 August 2018	Cycle 1 Day 11

SAE NARRATIVE

On Cycle 1 Day 1 (**26 July 2018)**, the patient began receiving OMO-1, 250 mg oral capsule twice daily.

On Cycle 1 Day 11 (**05 August 2018)**, the patient received the last dose of OMO-1 prior to the SAEs. On the same date, the patient attended Accident and Emergency (A&E) late in the evening with general weakness and it was decided to admit him based on elevated temperature and tachycardia with suspected sepsis which was later diagnosed as fever (Case OCT-GB-18-CLI-0096). Dosing was consequently interrupted on 05 August 2018.

On Cycle 1 Day 12 (**06 August 2018)**, the patient was treated with intravenous (IV) antibiotics and IV fluid. The patient had a blood culture taken. The events of fever and tachycardia resolved on this date.

On Cycle 1 Day 16 (**10 August 2018)**, the patient was discharged from hospital as the blood cultures were negative and the patient was asymptomatic. The patient completed the course of IV antibiotics

SAE NARRATIVE

and was started on a 5 day oral antibiotic course.

On **15 August 2018** (Unscheduled Visit), blood test result showed total bilirubin 41 µmol/L, conjugated bilirubin 41 µmol/L, alkaline phosphatase (ALP) 1756 IU/L and alanine aminotransferase (ALT) 231 IU/L.

On **16 August 2018** (Unscheduled Visit), the patient was pyrexial at home and presented to hospital. The patient was afebrile but was admitted due to deranged liver function tests (blood bilirubin increased, alkaline phosphatase increased, and alanine aminotransferase increased). The patient was treated with IV meropenem to treat cholangitis and it was reported the patient will be reimaged in case the stent is blocked.

Thereafter, a successful endoscopic retrograde cholangiopancreatography (ERCP) was performed and the patient was diagnosed with primary occluded stent. The patient consequently had the stent removed and a new stent inserted. The SAE of primary occluded stent was considered to be resolved with sequelae (stent removed).

On **28 August 2018** (Unscheduled Visit), the patient was discharged from hospital.

Additional information is not expected.

The Investigator assessed primary occluded stent as CTCAE grade 3 and not related to OMO-1 and instead related to the disease under study.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Device occlusion	CTCAE grade	3
	Relationship to OMO-1	Not related
	Action taken with OMO-1	Not applicable (Drug was discontinued prior to the event onset)
	Duration	8 days
	Outcome	Resolved with sequelae
	Withdrawn from study	Yes

SPONSOR ASSESSMENT OF EVENT(S)

Device occlusion	Relationship to OMO-1	Not related

14.3.3.17 Patient 1003-008

SAE TERM(S)	PREFERRED TERM(S)
Vomiting	Vomiting

RELEVANT DEMOGRAPHICS

74-year-old male

RELEVANT MEDICAL HISTORY TERM(S)

Peripheral sensory neuropathy	March 2017 - Ongoing
Anemia	October 2018 - Ongoing

RELEVANT CONCOMITANT MEDICATION(S)

None

OMO-1 ADMINISTRATION

Module	Module 1 Part A Dose-Escalation (Cohort 5)	
Study arm		
Dose	700 mg	
First dose	24 October 2018	Study day 1 (C1D1)
Last dose prior to the event(s)	27 October 2018	Cycle 1 Day 4

SAE NARRATIVE

On **16 October 2018**, the patient's creatinine was at 82 umol/L and urea was at 5.1 mmol/L.

On **23 October 2018**, prior to dosing, the patient's creatinine level and urea level were at 82 umol/L and 5.1 mmol/L, respectively.

On Cycle 1 Day 1 (**24 October 2018)**, the patient began receiving OMO-1, 350 mg oral capsule twice daily.

On Cycle 1 Day 3 (**26 October 2018)**, it was noted that the patient began to experience tachycardia but had felt better that afternoon.

On Cycle 1 Day 4 (**27 October 2018)**, the patient received their last dose of OMO-1. As the patient was admitted to the local Accident and Emergency (A+E), creatinine levels result during study drug treatment and blood urea nitrogen results both during study drug treatment and when creatinine peaked were not available.

SAE NARRATIVE

On Cycle 1 Day 4 (**27 October 2018)**, in the morning, the patient experienced fatigue and a racing pulse. The patient then began experiencing vomiting and was hospitalised after 7 pm. The patient was treated with IV fluid hydration. No abdominal pain was reported. On the same day, the study drug was withdrawn and never re-started.

On Cycle 1 Day 5 (**28 October 2018)**, the patient was found to have creatinine between 1.5 to 1.9 times baseline (acute kidney injury, non-serious AE). The patient underwent an ECG which revealed sinus tachycardia. The event of vomiting resolved on this date and the patient was discharged from hospital.

On **30 October 2018** (End of Treatment and Study), the patient arrived at the unit and did not want to continue with OMO-1.

Additional information is not expected.

The investigator assessed vomiting as CTCAE grade 2 and definitely related to OMO-1.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Vomiting	CTCAE grade	2
	Relationship to OMO-1	Definitely related
	Action taken with OMO-1	Drug discontinued
	Duration	2 days
	Outcome	Resolved
	Withdrawn from study	Yes

SPONSOR ASSESSMENT OF EVENT(S)

Vomiting	Relationship to OMO-1	Definitely related

14.3.3.18 Patient 1002-005

SAE TERM(S)	PREFERRED TERM(S)
Brain metastasis	Metastases to central nervous system

RELEVANT DEMOGRAPHICS

57-year-old male

RELEVANT MEDICAL HISTORY TERM(S)

None

RELEVANT CONCOMITANT MEDICATION(S)

Pregabalin	January 2014 - Ongoing
Metoclopramide	18 September 2018 - Ongoing

OMO-1 ADMINISTRATION

Module	Module 1 Part A Dose-Escalation (Cohort 5)	
Study arm		
Dose	700 mg	
First dose	18 September 2018	Study day 1 (C1D1)
Last dose prior to the event(s)	29 October 2018	Cycle 2 Day 21

SAE NARRATIVE

On Cycle 1 Day 1 (**18 September 2018)**, the patient began receiving OMO-1 (batch number: 1271/1272), 350 mg oral capsule twice a day, for metastatic solid malignancy and completed two cycles of treatment prior to the onset of the events.

On Cycle 2 Day 20 (**28 October 2018)**, the patient began experiencing CTCAE grade 2 vomiting.

On **30 October 2018** (Unscheduled Visit), a CT scan showed disease progression and therapy with OMO-1 was permanently discontinued.

On **04 November 2018** (Unscheduled Visit), the patient experienced grade 3 vomiting. On the same day, the patient underwent the following laboratory tests: Sodium (result: 140 mmol/L), Potassium (result: 3.5 mmol/L), Urea (4.3 mmol/L), creatinine (result: 75 umol/L) and estimated GFR (CKD-EPI) (result > 90 mL/min/1.73m^2). No further relevant investigations were required.

On **04 November 2018** (Unscheduled Visit), the patient was admitted to the local hospital for

SAE NARRATIVE

vomiting.

On **05 November 2018** (Unscheduled Visit), the patient was discharged from hospital.

On **06 November 2018** (End of Treatment), the patient was admitted to hospital with grade 3 dizziness, grade 2 vomiting, fatigue and ataxia. The patient was treated with intravenous (IV) fluids and antiemetics. The patient began treatment with oral dexamethasone at 8 mg once daily for brain metastasis and oral omeprazole at 20 mg daily for gastric prophylaxis. All the events vomiting, ataxia, fatigue and dizziness improved with this treatment.

On the same day, the patient was withdrawn from the study due to disease progression.

On **07 November 2018** (Unscheduled Visit), the patient underwent a head MRI with contrast which found multiple cerebellar metastases and oedema. The final diagnosis of the event was reported as brain metastasis. On the same date, the patient recovered from the (symptoms of the) event brain metastasis.

On **10 November 2018** (Unscheduled Visit), the patient was discharged from hospital.

At the time of this report, the event brain metastasis was ongoing.

Additional information is expected.

The investigator assessed brain metastasis as serious (required hospitalisation) CTCAE grade 3 and not related to OMO-1.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Metastases to central nervous system	CTCAE grade	3
	Relationship to OMO-1	Not related
	Action taken with OMO-1	Drug discontinued
	Duration	Unknown
	Outcome	Not resolved
	Withdrawn from study	Yes

SPONSOR ASSESSMENT OF EVENT(S)

Metastases to central nervous system	Relationship to OMO-1	Not related

14.3.3.19 Patient 1001-012

SAE TERM(S)	PREFERRED TERM(S)
Brain metastasis	Metastases to central nervous system

RELEVANT DEMOGRAPHICS

58-year-old male

RELEVANT MEDICAL HISTORY TERM(S)

Metastatic duodenal cancer	January 2017 - Unknown
Diabetes	March 2017 - Ongoing

RELEVANT CONCOMITANT MEDICATION(S)

Amlodipine	March 2017 - Ongoing
Creon (pancreatin tablets)	March 2017 - Ongoing
Bisoprolol	March 2017 - Ongoing
Lansoprazole	March 2017 - Ongoing
Insulin Humalog (Insulin lispro)	March 2017 - Ongoing

OMO-1 ADMINISTRATION

Module	Module 1 Part A Dose-Escalation (Cohort 5)	
Study arm		
Dose	700 mg	
First dose	14 August 2018	Study day 1 (C1D1)
Last dose prior to the event(s)	14 August 2018	Cycle 1 Day 1

SAE NARRATIVE

On Cycle 1 Day 1 (**14 August 2018)**, the patient began receiving OMO-1, 350 mg oral capsule twice daily.

On Cycle 1 Day 2 (**15 August 2018)**, the patient was withdrawn from the trial and the reason for withdrawal was provided as "not eligible".

On **21 August 2018** (End of Treatment), the patient started experiencing brain metastasis. On this date, a CT head scan was performed which showed brain metastasis.

SAE NARRATIVE

On **02 September 2018** (Unscheduled Visit), a preoperative magnetic resonance imaging (MRI) head scan was performed confirming the CT findings.

On **08 September 2018** (Unscheduled Visit), the patient was admitted for electric craniotomy surgery. On the same day, the patient recovered from the event brain metastasis.

On **10 September 2018** (Unscheduled Visit), the patient was discharged from the hospital.

Although the patient recovered from this event, on **19 February 2019**, the patient died due to disease progression (extra-cranial). No autopsy was performed.

Action taken with the study drug due to the event was not applicable.

No additional information is expected.

The Investigator assessed brain metastasis as serious (hospitalisation), CTCAE grade 3 and not related to OMO-1. The most likely cause of this event was disease progression of colorectal cancer.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Metastases to central nervous system	CTCAE grade	3
	Relationship to OMO-1	Not related
	Action taken with OMO-1	Not applicable
	Duration	19 days
	Outcome	Resolved
	Withdrawn from study	Yes

SPONSOR ASSESSMENT OF EVENT(S)

Metastases to central nervous system	Relationship to OMO-1	Not related

14.3.3.20 Patient 1002-008

SAE TERM(S)	PREFERRED TERM(S)
Atrial fibrillation	Atrial fibrillation

RELEVANT DEMOGRAPHICS

72-year-old male

RELEVANT MEDICAL HISTORY TERM(S)

Gastrooesophageal reflux disease (GORD)	2000 - Ongoing
Back pain	1980 - Ongoing
Actinic keratosis	2016 - Ongoing

RELEVANT CONCOMITANT MEDICATION(S)

Simvastatin	January 2006 - Ongoing
Omeprazole	January 2006 - Ongoing
Co-codamol (codeine phosphate, paracetamol)	January 2006 - Ongoing
Metoclopramide	01 October 2019 - Ongoing

OMO-1 ADMINISTRATION

Module	Module 1 Part B Expansion with MET/EXON (Cohort 1)	
Study arm		
Dose	500 mg	
First dose	17 September 2019	Study day 1 (C1D1)
Last dose prior to the event(s)	01 October 2019	Cycle 1 Day 15

SAE NARRATIVE

On Cycle 1 Day 1 (**17 September 2019)**, the patient began receiving OMO-1, at 250 mg oral capsule twice daily.

On Cycle 1 Day 15 (**01 October 2019),** the patient received his last dose prior to onset of the event.

On Cycle 1 Day 16 (**02 October 2019)**, the patient was admitted to hospital for elective ultrasound guided pleural drain. The patient remained hospitalised to monitor the pleural drain.

SAE NARRATIVE

On Cycle 1 Day 19 (**05 October 2019)**, the patient's hospitalisation was prolonged due to atrial fibrillation. The patient was not known to have atrial fibrillation, however, the patient experienced intermittent atrial fibrillation on previous electrocardiography (ECG) which were thought to be secondary to pleural effusion. The investigator assessed pleural effusion as a non-serious adverse event which was present at diagnosis and before enrolment.

On Cycle 1 Day 20 (**06 October 2019)**, the patient started receiving treatment with bisoprolol at 2.5 mg for atrial fibrillation. On this date, the patient's drain was removed.

On Cycle 1 Day 21 (**07 October 2019)**, the patient was discharged from hospital. At the time of this report, the treatment with bisoprolol was ongoing and the patient recovered with sequelae due to ongoing non-serious atrial fibrillation.

No action was taken with OMO-1 as a result of the event.

Additional information is not expected.

The Investigator assessed atrial fibrillation as serious (prolonged hospitalisation), CTCAE grade 2 and not related to OMO-1. The investigator assessed this event as related to the mass effect of the known pleural effusion.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Atrial fibrillation	CTCAE grade	2
	Relationship to OMO-1	Not related
	Action taken with OMO-1	Dosage maintained
	Duration	3 days
	Outcome	Resolved with sequelae
	Withdrawn from study	No

SPONSOR ASSESSMENT OF EVENT(S)

Atrial fibrillation	Relationship to OMO-1	Not related

14.3.3.21 Patient 4001-002

SAE TERM(S)	PREFERRED TERM(S)
Pneumosepsis	Pulmonary sepsis

RELEVANT DEMOGRAPHICS

72-year-old male

RELEVANT MEDICAL HISTORY TERM(S)

Dyspnoea	2010 - Ongoing
Fatigue	2018 - Ongoing
Cough	2017 - Ongoing
Tinnitus	2017 - Ongoing
Thromboembolic event	June 2017 - 2017
Right lung cancer	Unknown - Ongoing

RELEVANT CONCOMITANT MEDICATION(S)

Salmeterol	January 2017 - Ongoing
Rivaroxaban	January 2018 - Ongoing
Pantoprazole	07 December 2017 - Ongoing
Metoclopramide	26 June 2018 - 03 July 2018
Paracetamol	30 May 2018 - Ongoing

OMO-1 ADMINISTRATION

Module	Module 1 Part B Expansion with MET/EXON (Cohort 1)	
Study arm		
Dose	400 mg	
First dose	13 June 2018	Study day 1 (C1D1)
Last dose prior to the event(s)	20 June 2018	Cycle 1 Day 8

SAE NARRATIVE

On Cycle 1 Day 1 (**13 June 2018)**, the patient began receiving OMO-1, 200 mg oral capsule twice

SAE NARRATIVE

daily.

On Cycle 1 Day 8 (**20 June 2018)**, the patient received the last dose of OMO-1 prior to the reported event.

On Cycle 1 Day 14 (**26 June 2018)**, the patient began experiencing abdominal pain, nausea, vomiting, fever with dyspnoea. Nausea and vomiting were considered to be prodrome to pneumonia.

On Cycle 1 Day 15 (**27 June 2018)**, the patient presented to hospital and was admitted with a suspected pneumosepsis in the right lung. The same lung as the localisation of the patient's cancer. The patient underwent a chest X-ray which showed increased infiltrate. The combination of increased infiltrate and dyspnoea with fever were considered to be sufficient evidence for diagnosis of pneumonia. There was no evidence of pneumococcal infection, no positive culture and no pneumococcal antigen was found. Therefore, a diagnosis of pneumonia/pneumosepsis was made. On this date, OMO-1 was temporarily discontinued. The patient was treated with oral amoxicillin/clavulanic acid and sodium chloride.

On Cycle 1 Day 18 (**30 June 2018**,) the patient was treated with paracetamol due to pain.

On Cycle 1 Day 21 (**03 July 2018)**, the patient recovered from the event and was discharged from hospital. The patient's treatment with amoxicillin/clavulanic acid continued as home medication.

On Cycle 2 Day 1 (**11 July 2018)**, the patient re-started receiving therapy with OMO-1.

On **29 November 2018** (Unscheduled Visit), the patient's treatment with amoxicillin/clavulanic acid was stopped.

No additional information is expected.

The Investigator assessed pneumosepsis as CTCAE grade 3 and not related to OMO-1. The most likely cause of this event was unknown. The investigator also noted that the patient did not have any signs of disease progression.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Pulmonary sepsis	CTCAE grade	3
	Relationship to OMO-1	Not related
	Action taken with OMO-1	Dose temporarily discontinued and re-introduced
	Duration	7 days
	Outcome	Resolved
	Withdrawn from study	No

SPONSOR ASSESSMENT OF EVENT(S)

Pulmonary sepsis	Relationship to OMO-1	Not related

14.3.3.22 Patient 4002-003

SAE TERM(S)	PREFERRED TERM(S)
Viral airway infection	Respiratory tract infection viral

RELEVANT DEMOGRAPHICS

57-year-old male

RELEVANT MEDICAL HISTORY TERM(S)

Rectal carcinoma with liver metastases	November 2016 - Unknown
Progressive disease	November 2017 - Unknown
Progressive disease	June 2018 - Unknown
Progressive disease	September 2018 - Unknown
Previous hospitalisation due to fever and elevated infection parameters related to the progressive disease.	10 October 2018 - Unknown

RELEVANT CONCOMITANT MEDICATION(S)

None

OMO-1 ADMINISTRATION

Module	Module 1 Part B Expansion with MET/EXON (Cohort 2)	
Study arm		
Dose	Patient did not receive study drug prior to the event	
First dose	06 November 2018	Study day 1 (C1D1)
Last dose prior to the event(s)	Not applicable	

SAE NARRATIVE

The patient had not yet begun therapy with OMO-1, prior to the event.

On **26 October 2018**, the patient began experiencing viral airway infection and was hospitalised. The patient reported symptoms of fever (up to 39 degrees C), chills, and darker urine production for a few days prior to admission. On the same date, laboratory test showed C-reactive protein (CRP) of 230. It was noted that at screening the patient's CT scan revealed dilated intrahepatic bile duct.

An initial diagnosis of cholangitis was made and the patient began treatment with Augmentin

SAE NARRATIVE

(amoxicillin/clavulanic acid). However, following extensive examination with daily chemistry and haematology lab, blood cultures, abdominal echography, and clinical observation the diagnosis of cholangitis was not proven. Since admission, the patient had no measured fever, nor complaints or signs of cholangitis were observed. As other members of the family complained of signs of common cold, and as a single measurement of fever with elevated CRP and clinical signs of common cold were observed, a final diagnosis of viral airway infection was made.

On **28 October 2018**, the patient was discharged after a rapid recovery. The event of viral airway infection was considered resolved.

No action was applicable to be taken with the study drug.

No additional information is expected.

The investigator assessed viral airway infection as CTCAE grade 1 and not related to OMO-1.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Respiratory tract infection viral	CTCAE grade	1
	Relationship to OMO-1	Not related
	Action taken with OMO-1	No action taken
	Duration	3 days
	Outcome	Resolved
	Withdrawn from study	No

SPONSOR ASSESSMENT OF EVENT(S)

Respiratory tract infection viral	Relationship to OMO-1	Not related

14.3.3.23 Patient 4001-006

SAE TERM(S)	PREFERRED TERM(S)
Creatinine increased	Blood creatinine increased

RELEVANT DEMOGRAPHICS

72-year-old female

RELEVANT MEDICAL HISTORY TERM(S)

Nausea	23 October 2018 to 30 October 2018
Vomiting	16 October 2018 to 30 October 2018
Diarrhoea	22 October 2018 to 30 October 2018
Anorexia	18 October 2018 to Ongoing

RELEVANT CONCOMITANT MEDICATION(S)

None

OMO-1 ADMINISTRATION

Module	Module 1 Part B Expansion with MET/EXON (Cohort 1)	
Study arm		
Dose	500 mg	
First dose	15 October 2018	Study day 1 (C1D1)
Last dose prior to the event(s)	22 October 2018	Cycle 1 Day 8

SAE NARRATIVE

On Cycle 1 Day 1 (**15 October 2018)**, the patient began receiving OMO-1, 250 mg oral capsule twice daily.

On Cycle 1 Day 15 (**29 October 2018)**, the patient came to hospital for C1D15 and was found to have increased creatinine. Laboratory results showed increased creatinine grade 4, 590 umol/L (normal range 55-90 umol/L) and increased cystatin C, 3.29 mg/L (normal range 0.68-1.36 mg/L). The patient was noted to also be suffering from nausea, vomiting, diarrhoea, and anorexia. The

SAE NARRATIVE

patient was then hospitalised for rehydration. An ultrasound was performed on the patient's kidneys and urinary tract which revealed no post-renal cause of renal insufficiency. The patient received treatment with omeprazole, ipratropium aerosol, loperamide, MetaRelax (magnesium amino acid chelate), metoclopramide, glucose/natrium chloride and kalium chloride.

On **30 October 2018** (Unscheduled Visit), the patient experienced a second instance of creatinine increased (514 umol/L) and as a result their hospitalisation was prolonged. On this date, the patient's cystatin C level was, 2.79 mg/L.

On **01 November 2018** (Unscheduled Visit), the patient's cystatin C level was, 2.48 mg/L.

On **04 November 2018** (Unscheduled Visit), the patient recovered from the event of creatinine increased. On this date, the patient was discharged from hospital in good condition.

As a consequence of the event creatinine increased, therapy with OMO-1 was temporarily interrupted. OMO-1 therapy is due to restart on 13 December 2018 if the patient's creatinine is stable.

Additional information is not expected.

The Investigator assessed creatinine increased as serious (required hospitalisation), CTCAE grade 4 and possibly related to OMO-1.

INVESTIGATOR ASSESSMENT OF EVENT(S)

Blood creatinine increased	CTCAE grade	4
	Relationship to OMO-1	Possibly related
	Action taken with OMO-1	Drug temporarily interrupted
	Duration	7 days
	Outcome	Resolved
	Withdrawn from study	No

SPONSOR ASSESSMENT OF EVENT(S)

Blood creatinine increased	Relationship to OMO-1	Possibly related

14.3.3.24 Patient 1002-009

RELEVANT DEMOGRAPHICS

62-year old Caucasian female

40kg; 1.62m

RELEVANT DISEASE HISTORY

Lung adenocarcinoma

- Diagnosis: 28 May 2019 - Stage IV; T4N0M1b; lung and bone metastases MET exon 14 splice site (6,6%) (3028+2T>G)
- Study screening: 23 October 2019 - Stage IV; T4N0M1a; lung and bone metastases

Prior cancer treatment: 1 line:

- Carboplatin and pemetraxol (NK July 2019 – 10 September 2019); best response: stable disease

Prior cancer surgery: None

Prior radiotherapy: 1 treatment:

- Palliative – T7 (21 June 2019); best response: not evaluable

RELEVANT MEDICAL HISTORY	
Pulmonary embolism (Grade 2)	July 2019 - ongoing
Tachycardia (Grade 1)	July 2019 - ongoing
Right lower chest discomfort (Grade 1)	July 2019 – ongoing
Gastro oesophageal reflux disease (Grade 1)	July 2019 – ongoing
Constipation (Grade 1)	July 2019 – ongoing
Shortness of breath (Grade 1)	July 2019 – ongoing
Reduced sleep (Grade 1)	July 2019 – ongoing
Intermittent nausea (Grade 1)	July 2019 – ongoing
Anaemia (Grade 1)	August 2019 - ongoing
Increase alkaline phosphatase (Grade 1)	August 2019 - ongoing

RELEVANT CONCOMITANT MEDICATION(S)		
Amitriptyline	Reduced sleep	Pre-existing condition

RELEVANT CONCOMITANT MEDICATION(S)		
Dalteparin	Pulmonary embolism	Pre-existing condition
Dexamethasone	Fatigue; right chest pain	Adverse events
Dexamethasone	Pulmonary embolism	Pre-existing condition
Docusate	Constipation	Pre-existing condition
Doxycycline hyclate	Bronchial infection; lung infection	Adverse events
Folic acid	Pemetrexed	Prophylaxis
Lidocaine 5% patch	Right chest pain	Adverse event
Menthol 1% aqueous cream	Right chest pain	Adverse event
Metoclopramide	Nausea	Pre-existing condition
Morphine	Right lower chest pain	Pre-existing condition
Naproxen	Right chest pain; pain	Adverse events
Omeprazole	Gastro oesophageal reflux disease	Pre-existing condition
Oxycodone	Right chest pain	Adverse event
Oxycodone hydrochloride	Right chest pain	Adverse event
Paracetamol	Right lower chest pain	Pre-existing condition
Pregabalin	Right chest pain	Adverse event
Pregabalin	Right lower chest pain	Pre-existing condition

OMO-1 ADMINISTRATION			
Study cohort	Part B Module 1		
Dose	250 mg BD		
First dose	06 November 2019	C1D1	Study day 1
Last dose	16 April 2020	C8D17	Study day 163
Dose modification	None		
Dose interruption 1 (Cycle 1)	16 November 2019 to 25 November 2019 Study days 11 to 20 Reason: Central laboratory renal monitoring trigger		
Dose interruption 2 (Cycle 7)	10 March 2020 to 12 March 2020 Study days 126 to 128 Reason: Hospital admission due to hypotension		

OMO-1 ADMINISTRATION	
Primary reason for treatment discontinuation	16 April 2020 Study day 163 Reason: Clinical evidence of disease progression

PATIENT NARRATIVE

During Cycle 1, the patient experienced the following Grade 1 events considered related to OMO-1: Fatigue, polydipsia, visual disturbance, and light-headedness (postural) (all events from study day 8). She also experienced intermittent elevated glucose in serum (Grade 1; unrelated to OMO-1; from study day 1).

Following Cycle 1, the patient experienced a worsening of anaemia (Grade 2; study days 28 to 42), worsening right lower chest pain (Grade 2; study days 45 to 189), bronchial infection (Grade 2; from study day 62) and peripheral oedema (Grade 1; from study day 105) – these events were considered unrelated to OMO-1.

On study day 126, the patient experienced the following serious adverse events (SAEs) which were considered unrelated to OMO-1: Hypotension (Grade 3), and lower respiratory tract infection (Grade 2). Both events resolved after 1 day.

Following this, the patient experienced the following events: Lung infection (Grade 2; study days 127 to 133), proteinuria (Grade 1; study days 147 to 168), swelling right thigh (Grade 1; from study day 161), increased aspartate aminotransferase (AST) (Grade 1; study days 169 to 177) and worsening right lower chest pain (Grade 3; from study day 189) – all these events with the exception of proteinuria, were considered unrelated to OMO-1.

Pre-treatment (C1D1) central laboratory measurements showed normal serum creatinine, normal cystatin C and normal blood urea nitrogen (BUN). All other blood and urine markers (secondary parameters) were also normal except for FE_{urea} <35%, indicating potential volume depletion (dehydration). After 7 days of OMO-1 treatment, serum creatinine, cystatin C and BUN remained unchanged; other secondary markers also remained normal, but FE_{urea} remained <35%, enforcing a temporary pause of OMO-1 administration. Thus, despite a clear lack of safety concerns, due to the Renal Management Plan, OCTIMET took the treatment decision to temporarily pause OMO-1 treatment.

On study day 15 (4 days of OMO-1 interruption), central laboratory results showed normal serum creatinine, cystatin C and BUN. All other blood and urine markers (secondary parameters) were also normal except for FE_{urea} which was 34.92. The Principle Investigator (PI) proposed to regard FE_{urea} as normal (in combination with the proposed protocol amendment) and this was presented to the Safety Review Committee (SRC) who, considering that the temporary pause was not enforced by any safety signal related to OMO-1, agreed to restart OMO-1 at 250 mg BD.

On study day 21, the patient commenced Cycle 2. Her FE_{urea} remained <35% on this day. At the start of Cycle 3 (study day 42), her FE_{urea} was >35% and remained so until study day 168 when it was 22.73%. At this point, the patient had already discontinued OMO-1.

PATIENT NARRATIVE

The patient continued on the study from Cycle 3 to Cycle 7 without any safety concerns. Central laboratory measurements showed that her creatinine remained within range from pre-treatment till the start of Cycle 7. At C7D1 (study day 126), the patient's BUN showed a 50% increase from baseline and her creatinine was 1.1 mg/dL (0.63-1.04 mg/dL). This same day, the patient was admitted to the hospital for treatment of the above-mentioned SAEs. The patient recommenced OMO-1 treatment on study day 129.

As per the Renal Management Plan, OMO 1 treatment was stopped as the patient's central laboratory measurements met the stopping criteria on study day 163; however, due to laboratory reporting delays, these results were only made available for review on study day 161. In addition to this, the site confirmed on study day 163 that the patient did not attend the hospital for the C8D1 visit due to COVID-19 pandemic. The next available results at C9D1 (study day 168) showed a BUN with a 50% increase from baseline and a FE_{urea} <35% (which met the stopping criteria) as well as an elevated cystatin C and beta-2-microglobulin. The site confirmed that the patient remained clinically stable, albeit a bit dehydrated.

Central laboratory measurements on study day 177 continued to meet the stopping criteria (as per the Renal Management Plan): BUN with a 50% increase from baseline and a FE_{urea} >70%. The patient's potassium, inorganic phosphorus and urea were elevated.

The patient's central laboratory measurements on study day 183 continued to meet the stopping criteria with a FE_{urea} <35%. The patient's BUN, cystatin C and beta-2-microglobulin results were elevated.

KIM-1 analysis showed an overall decrease in results from the screening (9.377 ng/mL) to study day 126 (0.818 ng/mL).

Overall assessment of tumour response showed stable disease on the following study days: 42 (Cycle 3), 85 (Cycle 5), 126 (Cycle 7) and 168 (Cycle 9). The target lesion (lung) decrease in size (longest diameter from 44 mm to 42 mm in Cycle 7, but then to 45 mm in Cycle 9; the 3 non-target lesions remained present.

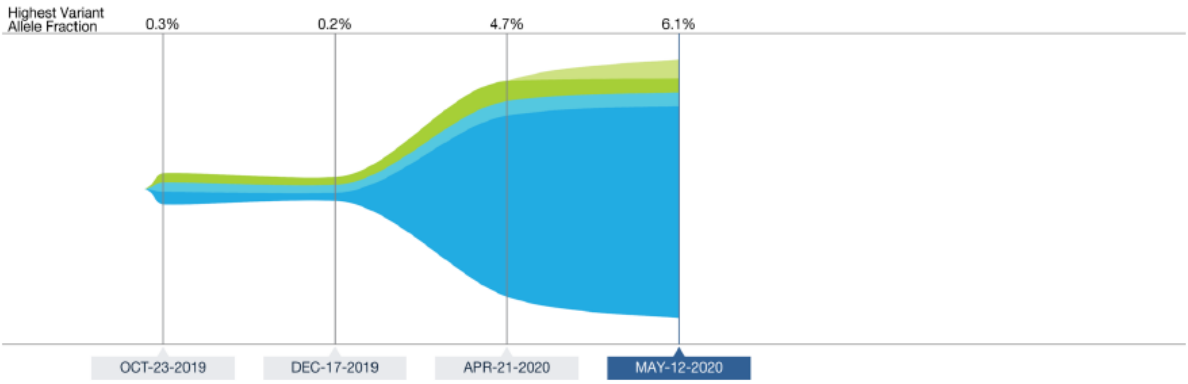
Guardant Health analysis of the liquid biopsy showed MET exon 14 Skipping variant allele frequency (VAF) was 0.3% (see Figure 1) in the screening sample (23 October 2019). The patient first started OMO-1 dosing on 06 November 2019 and had a treatment interruption from 16 to 25 November 2019. The first sampling on treatment after the treatment interruption (17 December 2019) showed that the MET exon 14 VAF had dropped to 0.2%. The next on treatment sampling was taken on 21 April 2020, at which time point the MET exon 14 VAF had risen to 4.7%. There was a concomitant evidence for the emergence of an EGFR amplification (plasma copy number [PCN] 2.3%) that had not been seen before indicating the outgrowth of an alternative driver oncogene that represents a resistance clone. The final sampling (12 May 2020) showed that both the MET exon 14 skipping mutation and EGFR amplification remained elevated at VAF 6.1 and PCN 2.3%, in line with the reported clinical evidence of disease progression.

Figure 1: Gardant360 Tumor Response Map: Patient 1002-009

PATIENT NARRATIVE

Guardant360 Tumor Response Map

The Guardant360 Tumor Response Map illustrates the variant allele fraction (% cfDNA) of observed somatic variants at each sample submission time point. Amplifications are not plotted, and only the first and last five test dates are plotted. Please see the Physician Portal (portal.guardanthealth.com) for the Tumor Response Map with all test dates.



Alteration	% cfDNA or Amp	Alteration Trend
MET Exon 14 Skipping SNV	6.1%	0.3% 0.2% 4.7% 6.1%
APC I1987V	0.3%	ND ND ND 0.3%
APC A2121S	0.2%	0.2% 0.2% 0.2% 0.2%

We evaluated 74 genes, including the following guideline-recommended genes for NSCLC:

EGFR (T790M and others)	*ALK*	*ROS1*	*BRAF*	*MET*	*ERBB2* (HER2)	*RET*

Alteration	% cfDNA or Amp	Alteration Trend
MYC Y324Y	0.2%	0.2% 0.2% 0.3% 0.2%
EGFR Amplification Amplifications not graphed above	Low (+)	ND ND 2.3 2.3 Plasma copy number

The table above annotates the variant allele fraction (% cfDNA) detected in this sample, listed in descending order.

The patient completed the study on study day 189 (EOS visit). The study follow-up assessments were

PATIENT NARRATIVE

not performed.

14.3.3.25 Patient 3001-005

RELEVANT DEMOGRAPHICS

64-year old male

75kg; 1.75m

RELEVANT DISEASE HISTORY

Bronchial adenocarcinoma

- Diagnosis: 18 September 2014 – Stage T1aN0M0; MET exon 14 mutation on historical biopsy (December 2017): c.3028+2T>G (32%)
- Study screening: 05 November 2019 - Stage IV; T1aN1M1b

Prior cancer treatment: 1 line:

- Cisplatin-ALIMTA (NK January 2018 – 08 March 2018); best response: not evaluable

Prior cancer surgery:

- Left-upper lobectomy (NK September 2014)

Prior radiotherapy: 5 treatments:

- Conformational radiotherapy with intensity modulation – mediastinum (09 April 2018 – 29 May 2018); best response: not evaluable
- Conformal radiotherapy palliative analgesic – deltoid (27 June 2018 – 17 July 2018); best response: not evaluable
- Steriotaxic radiotherapy - occipital, cerebellar and temporal lesions (01 - NK February 2019); best response: not evaluable
- Steriotaxic radiotherapy - cerebellar lesion (04 – 09 September 2019); best response: not evaluable
- Steriotaxic radiotherapy - frontal lesion (05 September 2019); best response: not evaluable

RELEVANT MEDICAL HISTORY

Constipation (unknown grade)	October 2019 - ongoing
Tumour pain (Grade 2)	October 2019 - ongoing
Fatigue (Grade 1)	October 2019 - ongoing

RELEVANT CONCOMITANT MEDICATION(S)

Amitriptyline hydrochloride	Tumour pain	Pre-existing condition

RELEVANT CONCOMITANT MEDICATION(S)		
Clonazepam	Tumour pain	Pre-existing condition
Ketamine	Tumour pain	Pre-existing condition
Methylprednisolone sodium succinate	Tumour pain	Pre-existing condition
Movicol	Constipation	Pre-existing condition
Oxycodone hydrochloride	Tumour pain	Pre-existing condition
Paracetamol	Tumour pain	Pre-existing condition
PCA of Morphine	Tumour pain	Pre-existing condition
Pregabalin	Tumour pain	Pre-existing condition

OMO-1 ADMINISTRATION			
Study cohort	Part B Module 1		
Dose	250 mg BD		
First dose	28 November 2019	C1D1	Study day 1
Last dose	13 May 2020	C8D21	Study day 168
Dose modification	None		
Dose interruptions	None		
Primary reason for treatment discontinuation	14 May 2020 Study day 169 Reason: Confirmed disease progression by RECIST 1.1		

PATIENT NARRATIVE

During Cycle 1, the patient experienced the following Grade 1 events which were considered unrelated to OMO-1: Diarrhoea (on study day 3) , episodes of blurred vision with a feeling of "white veil" lasting less than 5 minutes (on study day 21), and asthenia (from study day 21). The site confirmed that the episode of blurred vision was a one-off event and did not re-occur; hence not linked to brain metastases activity.

Following Cycle 1, the patient experienced sleepiness (Grade 2; from study day 23), paraesthesia of the right upper member (Grade 1; study day 23 to 50), balance disorder (Grade 1; from study day 51), peripheral neuropathy upper limbs (Grade 2; from study day 51) and cough (Grade 1; from study day 51) - these events were considered unrelated to OMO-1. The site confirmed that the balance disorder was most likely non-neurological in nature and caused by oxycodone intake. He also experienced the following 2 events considered related to OMO-1: dry skin and memory disturbances

PATIENT NARRATIVE

(both Grade 1; from study day 51).

On study day 162, the patient experienced a serious adverse event (SAE) of uncontrolled pain of the deltoid tumour mass (Grade 3) which was considered unrelated to OMO-1 and resolved after 21 days.

Pre-treatment central laboratory measurements showed an elevated cystatin C and beta-2-microglobulin which remained elevated for the duration of the study. The patient's FE_{urea} was <35% at Screening and Cycle 1 Day 1 only. The patient's central laboratory creatinine level was slightly elevated on study day 22 and on study days 64 to 127 but did not meet the stopping criteria as per the Renal Management Plan.

The patient's KIM-1 results fluctuated from screening (0.868 ng/mL) to study day 106 (0.786 ng/mL). The lowest result (0.24 ng/mL) was recorded at study day 43; the highest result (1.287 ng/mL) was recorded at study day 85.

Overall assessment of tumour response showed stable disease on the following study days: 48 (Cycle 3 Day 1), 58 (Cycle 3 Day 14), and 83 (Cycle 5 Day 1). Disease progression was documented at Cycle 7 Day 1 (study day 125) and confirmed on study day 169 (End of Treatment).

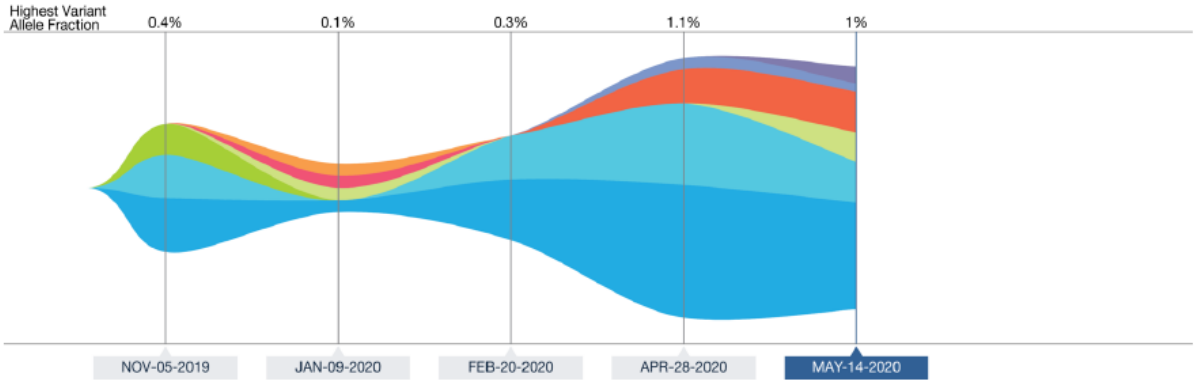
Guardant Health analysis of the liquid biopsy showed MET exon 14 Skipping variant allele frequency (VAF) dropped from 0.3% at screening (5 November 2019) to undetectable levels at the first on treatment analysis (09 January 2020) (see Figure 1). The first dose of OMO-1 was given on 28 November 2019. MET exon14 VAF went up to 0.2% on 20 February 2020 and then rose to 0.6% on 28 April 200 before dropping back to 0.3% on 14 May 2020. The low MET exon 14 VAF % would suggest that MET exon 14 was unlikely to be the primary driver in this patient.

Figure 1: Gardant360 Tumor Response Map: Patient 3001-005

PATIENT NARRATIVE

Guardant360 Tumor Response Map

The Guardant360 Tumor Response Map illustrates the variant allele fraction (% cfDNA) of observed somatic variants at each sample submission time point. Amplifications are not plotted, and only the first and last five test dates are plotted. Please see the Physician Portal (portal.guardanthealth.com) for the Tumor Response Map with all test dates.

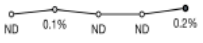
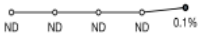
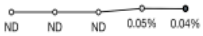
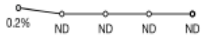
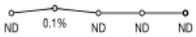
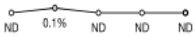


Alteration	% cfDNA or Amp	Alteration Trend
BRCA2 K2909fs	1.0%	0.4% 0.1% 0.3% 1.1% 1%
MET Exon 14 Skipping SNV	0.3%	0.3% ND 0.2% 0.6% 0.3%
BRCA1 G394C	0.3%	ND ND ND 0.2% 0.3%

We evaluated 74 genes, including the following guideline-recommended genes for NSCLC:

EGFR (T790M and others)	*ALK*	*ROS1*	*BRAF*	*MET*	*ERBB2* (HER2)	*RET*

PATIENT NARRATIVE

Alteration	% cfDNA or Amp	Alteration Trend
ATM K1728fs	0.2%	
STK11 P315L	0.1%	
EGFR G719D	0.04%	
FGFR2 R165W	ND	
RB1 R621H	ND	
AR S215P	ND	

The table above annotates the variant allele fraction (% cfDNA) detected in this sample, listed in descending order.

The patient completed the study on study day 180 (EOS visit). The study follow-up assessments were not performed as the follow up visit was completed via phone contact.

14.3.3.26 Patient 2001-002

RELEVANT DEMOGRAPHICS

55-year old female

68.3kg; 1.62m

RELEVANT DISEASE HISTORY

Non-small-cell lung adenocarcinoma

- Diagnosis: NK May 2018 – Stage IV; TxNxM1c; EGFR exon 21 mutation (72%) + 9.36 fold MET amplification
- Study screening: 07 August 2019 - Stage IV; TxN3M1c

Prior cancer treatment: 1 line:

- EGFR inhibitor (Gefitinib; 250 mg) (07 June 2018 – ongoing); best response: partial response (NK September 2018)

Prior cancer surgery: None

Prior radiotherapy: 2 treatments:

- Antalgic - sacrum and ileum bilateral (NK Jun 2019 – NK Jun 2019); best response: not evaluable
- Stereotactic – brain (16-23 July 2019); best response: not evaluable

RELEVANT MEDICAL HISTORY

Maligne SS melanoma (Grade NA)	NK 1994
Adenoma in sigmoid (Grade NA)	NK 1998
Adenoma in colon ascendens (Grade NA)	NK 1998
Acute appendicitis (Grade 3)	NK 2008
Intraductal papillary mucinous neoplasm, stable since diagnosis (Grade NA)	NK 2010 - ongoing
Hypertension (Grade 2)	NK 2011 - ongoing
Spondylosis (Grade 1)	NK 2011 – ongoing
Haematuria (Grade 1)	NK 2014 - ongoing
Depression (Grade 1)	NK 2018 - ongoing

RELEVANT CONCOMITANT MEDICATION(S)

RELEVANT CONCOMITANT MEDICATION(S)		
Alizapride	Nausea	Adverse event
Colecalciferol	Bone metastases	Pre-existing condition
Denosumab	Bone metastases	Pre-existing condition
Domperidone	Nausea	Adverse event
Escitalopram oxalate	Depression	Pre-existing condition
Herbal extract NOS	Nausea	Adverse event
Loperamide hydrochloride	Diarrhoea intermittent	Adverse event
Lekovit Ca	Bone metastases	Pre-existing condition
Levetiracetam	Epilepsy	Adverse event
Methylprednisolone acetate	Epilepsy	Adverse event

OMO-1 ADMINISTRATION			
Study cohort	Part A Module 2		
Dose	200 mg BD*		
First dose	19 August 2019	C1D1	Study day 1
Last dose	28 January 2020	C6D22	Study day 163
Dose interruption	24 October 2019 to 16 December 2019		
	Study days 67 to 120		
	Reason: Renal toxicity		
Dose modification	From 17 December 2019		
	From study day 121		
	*Dose decreased to 100 mg BD from C5		
Primary reason for treatment discontinuation	29 January 2020		
	Study day 164		
	Reason: Confirmed disease progression by RECIST 1.1		

PATIENT NARRATIVE

During Cycle 1, the patient experienced the following Grade 1 events which were considered related to OMO-1: nausea (study days 1 to 43) and intermittent diarrhoea (study days 8 to 48).

On study day 56, following Cycle 1, the patient experienced vomiting which was considered related

PATIENT NARRATIVE

to OMO-1. On study day 84, the patient experienced a serious adverse event (SAE) seizure secondary to brain metastases (Grade 2) which was considered unrelated to OMO-1 and resolved the next day.

Pre-treatment central laboratory measurements showed an elevated creatinine and beta2microglobulin which remained elevated for most of the study, with the creatinine levels within range on study day 121 (Cycle 5 Day 1) only and the beta2microglobulin levels within range on study days 95 and 112 only. The patient's central laboratory cystatin C level was elevated from study day 22 (Cycle 1 Day 15) for the remaining duration of the study. From study day 64, the patient's serum cystatin C increased to >1.5 fold from baseline. This was considered related to OMO-1 and resulted in a temporary interruption of OMO-1 dosing as per the Renal Management Plan. On study day 121 the patient's elevated cystatin C was <25% above the baseline value and OMO-1 treatment was resumed. The patient's FE_{urea} was <71.30% at the end of therapy visit (study day 164). The patient's KIM-1 results fluctuated from screening (0.304 ng/mL) to study day 164 (<0.156 ng/mL). The lowest result (<0.156 ng/mL) was recorded from study days 113 to 164; the highest result (2.062 ng/mL) was recorded at study day 86.

Overall local assessment of tumour response showed stable disease on the following study days: 40 (Cycle 3 Day 1) and 82 (Cycle 5 Day 1). The target lesion (lung) decrease in size (longest diameter from 43 mm to 38 mm on study day 40. However, according to the conclusion from the assessment by the central reader expert of the CT scans, the primary tumor is difficult to delineate, the difference between atelectasis and tumor cannot be made on these scans (Appendix 16.1.4).The 4 non-target lesions remained present. Disease progression was documented at the end of therapy on study day 162.

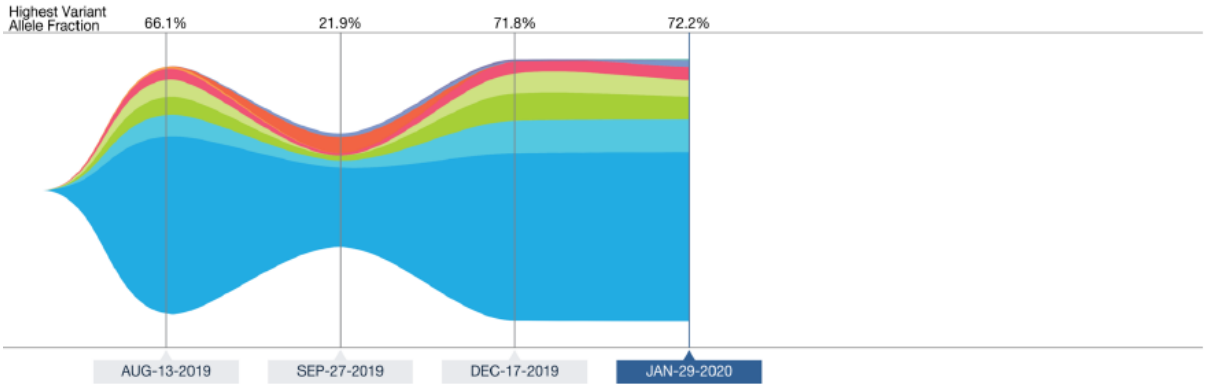
Guardant Health analysis of the liquid biopsy showed that at screening this patient had clear evidence of EGFR L858R mutation variant allele frequency (VAF) of 66.1%. In addition, there was clear evidence for EGFR (plasma copy number [PCN] 5.6), MET (PCN 13.1) and CDK4 (PCN 9.2) gene amplification. All these three genes are known to be located on the same arm of Chromosome 7 (see Figure 1). At the first sampling on treatment (27 September 2019) with OMO-1, the EGFR L858R VAF dropped to 21.9% along with a concomitant drop in amplification to EGFR PCN 2.5, MET PCN 5.5 and CDK4 PCN 3. This represents a dramatic tumour biomarker response on treatment with OMO-1 and is in line with the reduction in lesion size that was observed in 6 nodes as assessed by the central reader expert of the CT scan (Appendix 16.1.4). The biomarkers all increased (EGFR L858R VAF 71.8%, EGFR PCN 7.5, MET PCN 19.5 and CDK4 PCN 13.3) at the next analysis on 17 December 2019. This sampling was preceded by a long period of treatment interruption from 24 October 2019 to 16 December 2019 during which time it is apparent that the tumour burden, as indicated by the circulating DNA, increased. At the final analysis on 29 January 2020, these values still remained at similar elevated levels (EGFR L858R VAF 72.2%, EGFR PCN 7.7, MET PCN 22.8 and CDK4 PCN 12.8) despite the restart of OMO-1 at a lower dose level of 100 mg BD.

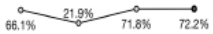
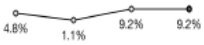
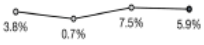
Figure 1: Gardant360 Tumor Response Map: Patient 2001-002

PATIENT NARRATIVE

Guardant360 Tumor Response Map

The Guardant360 Tumor Response Map illustrates the variant allele fraction (% cfDNA) of observed somatic variants at each sample submission time point. Amplifications are not plotted, and only the first and last five test dates are plotted. Please see the Physician Portal (portal.guardanthealth.com) for the Tumor Response Map with all test dates.

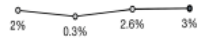
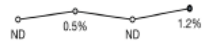
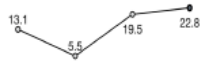
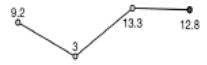
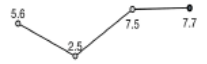
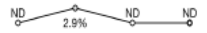
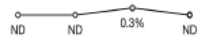


Alteration	% cfDNA or Amp	Alteration Trend
EGFR L858R	72.2%	
BRCA2 S755F	9.2%	
PDGFRA T474T	5.9%	

We evaluated 74 genes, including the following guideline-recommended genes for NSCLC:

EGFR (T790M and others)	*ALK*	*ROS1*	*BRAF*	*MET*	*ERBB2* (HER2)	*RET*

PATIENT NARRATIVE

Alteration	% cfDNA or Amp	Alteration Trend
NF1 I417I	3.9%	
KIT Splice Site SNV	3.0%	
EGFR L11L	1.2%	
AR P724P	0.2%	
MET Amplification Amplifications not graphed above	High (+++)	 Plasma copy number
CDK4 Amplification Amplifications not graphed above	High (+++)	 Plasma copy number
EGFR Amplification Amplifications not graphed above	High (+++)	 Plasma copy number
ALK I1250T	ND	
TP53 I251L	ND	
MET R1203I	ND	

The table above annotates the variant allele fraction (% cfDNA) detected in this sample, listed in descending order.

The patient completed the study on study day 164 (EOS). The study follow-up assessments were not performed as the patient had commenced a new treatment therapy.

14.3.4 Abnormal Laboratory Value Listing (each patient)

Not applicable.

14.3.5 Clinical Laboratory, Haematology, Urinalysis and Other Safety Data

Table 14.3.2.1.1	Summary of Laboratory Parameters: Haematology	Safety Set
Table 14.3.2.1.2	Summary of Percentage Change from Baseline for Laboratory Parameters: Haematology	Safety Set
Table 14.3.2.1.3	Summary of L Toxicities by CTC-grade	Safety Set
Table 14.3.2.2.1	Summary of Laboratory Parameters: Coagulation	Safety Set
Table 14.3.2.2.2	Summary of Percentage Change from Baseline for Laboratory Parameters: Coagulation	Safety Set
Table 14.3.2.3.1	Summary of Laboratory Parameters: Clinical Chemistry	Safety Set
Table 14.3.2.3.2	Summary of Percentage Change from Baseline for Laboratory Parameters: Clinical Chemistry	Safety Set
Table 14.3.2.4	Summary of Laboratory Parameters: Urinalysis	Safety Set
Table 14.3.2.5	Summary of Laboratory Parameters: Tumour Markers	Safety Set
Table 14.3.2.6	Summary of Laboratory Parameters: Renal Markers	Safety Set
Table 14.3.3	Vital Signs including Weight	Safety Set
Table 14.3.4	12-lead Electrocardiogram	Safety Set
Table 14.3.5	ECOG Status	Safety Set

14.3.6 Prior Medications and Concomitant Medications

Table 14.3.6.1	Prior Medications	Safety Set
Table 14.3.6.2	Concomitant Medications	Safety Set
Table 14.3.7	Prior Cancer Medications	Safety Set

14.3.7 Study Drug Exposure

Table 14.3.8	Study Drug Exposure	Safety Set

14.4 Pharmacokinetics

15 REFERENCES

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16 APPENDICES