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Full title: A Sequential Phase I study of MEK1/2 inhibitors PD-0325901 or Binimetinib combined with cMET inhibitor PF-02341066 in Patients with RAS Mutant and RAS Wild Type (with aberrant c-MET) Colorectal Cancer

Short title: MEK and MET Inhibition in Colorectal Cancer

# Statistical Analysis Plan

Version number 1.0

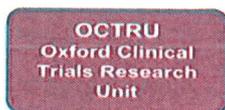
Date: 09 June 2016

Based on protocol version "MErCuRIC1 protocol V5.0 13Apr2016"

APPROVAL HISTORY				
	Name	Role	Signature	Date
Author	Corran Roberts	Trial Statistician		09 June 16
Reviewer	Sharon Love	Senior Statistician		9 Jun 2016
Approver	Prof. Mark Middleton	Chief Investigator		6 Sep 2016

Sponsored by the University of Oxford

Funder: European Commission's Seventh Framework Program (FP7)





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**1. INTRODUCTION**

This document details the proposed presentation and analysis for the main paper(s) reporting results from the sequential Phase I study of MEK1/2 inhibitors PD-0325901 or Binimetinib combined with cMET inhibitor PF-02341066 in patients with *RAS* Mutant and *RAS* Wild Type (with aberrant c-MET) colorectal cancer, funded by the European Commission's Seventh Framework Program (FP7) and sponsored by the University of Oxford. The results reported in these papers should follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis should be carried out by an identified, appropriately qualified and experienced statistician, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

**Note:** Throughout this Statistical Analysis Plan, MErCuRIC1 objectives not covered by this Statistical Analysis Plan (not relevant here) are written in grey.

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## 2. BACKGROUND INFORMATION

The overall MErCuRIC project is a multicentre investigator driven treatment trial to combat and prevent metastases in patients with solid cancer. The project will employ novel stratified treatment regimes and will study the effectiveness of a targeted combination therapy to combat metastasis, improve survival, and change current clinical practice for CRC patients with RAS mutant type (MT) and RAS wild type (WT) (with aberrant c-MET) tumours.

The MErCuRIC1 trial covered by this statistical analysis plan is the first component of the overall MErCuRIC programme. This phase 1 study will evaluate MTD, safety, toxicity, and anti-tumour activity of the combination of PD-0325901 with PF-02341066, as well as the combination of Binimetinib with PF-02341066. The outputs from this trial will inform a further study to compare the effect of combined MEKi/METi treatment (experimental arm) with standard chemotherapy (FOLFOX /XELOX or FOLFIRI, the control arm) in two mCRC patient cohorts, namely the RASMT and RASWT/c-MET+ subgroups.

### Aims of the Trial

To discover the Maximum Tolerated Dose (MTD) of the combined MEK/MET inhibitor treatment (PD-0325901/PF-02341066), and then of the combination Binimetinib and PF-02341066, and investigate if it is well tolerated (assessing the safety and toxicity profile) in patients with KRASMT CRC and KRASWT CRC with aberrant c-MET signalling (overexpression, amplification or mutation; KRASWT/c-MET+).

### 2.1.1 Primary aims

The **primary aims** are to:

Perform a dose escalation phase:

- (1) To assess the safety and toxicity profile of PD-0325901/PF-02341066 or Binimetinib/PF-02341066 combinations in patients with advanced solid tumours using the NCI CTCAE V4.03, and determine the maximum tolerated dose (MTD).

Perform a dose expansion cohort phase:

- (2) To investigate the response to treatment with RPII dose of PF-02341066 in combination with PD-0325901 or Binimetinib in patients with *RASMT* and *RASWT/c-MET+* CRC.

### 2.1.2 Secondary aims

The **secondary aims** are to:

Perform a dose escalation phase:

- (3) To define the recommended phase II (RPII) dose and schedule of PD-0325901 or Binimetinib in combination with PF-02341066.
- (4) To investigate the pharmacokinetics (PK) of PD-0325901 or Binimetinib with PF-02341066 when administered in combination.
- (5) To investigate pharmacodynamic (PD) biomarkers of PD-0325901 or Binimetinib with PF-02341066 in paired skin biopsies, tumour biopsies (where possible), in serum and PBMCs.
- (6) To preliminarily assess the efficacy of RPII dose of PF-02341066 in combination with PD-0325901 or Binimetinib with respect to objective response, progression free survival (PFS) and overall survival (OS).

Perform a dose expansion cohort phase:

- (7) To assess the efficacy of RPII dose of PF-02341066 in combination with PD-0325901 or Binimetinib in patients with *RASMT* and *RASWT/c-MET* CRC with respect to object response, progression free survival (PFS) and overall survival (OS).
- (8) To further investigate the safety and toxicity profile/tolerability of PD-0325901/PF-02341066 or Binimetinib/ PF-02341066 combinations.
- (9) To investigate pharmacokinetic (PK) biomarkers of PF-02341066, PD-0325901 and Binimetinib in blood.
- (10) To measure pharmacodynamic (PD) effect of PF-02341066 in combination with PD-0325901 or Binimetinib in paired skin biopsies, tumour biopsies (where possible), plasma and PBMCs.

### Tertiary and Exploratory Objectives

- (11) To identify molecular signatures of response and resistance to combined PD-0325901 /PF-02341066 or Binimetinib/ PF-02341066 treatment.
- (12) To develop a liquid biopsy platform for routine assessment of therapeutic efficacy.

<b>Table 1: Objectives and Endpoints</b>	
<b>Primary Objective (Dose Escalation)</b>	<b>Endpoints or Outcome Measures</b>
To assess the safety and toxicity profile of PD-0325901/PF-02341066 or Binimetinib/PF-02341066 combinations in patients with advanced solid tumours using the NCI CTCAE V4.03, and determine the maximum tolerated dose (MTD).	Maximal tolerated dose (MTD) of PD-0325901 or Binimetinib with PF-02341066 according to toxicities graded by NCI CTCAE V4.03 in cycle 1 of treatment.
<b>Primary Objective (Dose Expansion)</b>	
(To investigate the response to treatment with RPII dose of PF-02341066 in combination with PD-0325901 or Binimetinib in patients with RASMT and RASWT/c-MET+ CRC.	Clinical and radiological response to PD-0325901 or Binimetinib with PF-02341066 as defined by stable, partially or completely responding disease using RECIST version 1.1.
<b>Secondary Objectives (Dose Escalation)</b>	
To define the recommended phase II (RPII) dose and schedule of PD-0325901 or Binimetinib in combination with PF-02341066.	Recommended phase II (RPII) dose and schedule, guided by safety, PK and PD data.
To investigate the pharmacokinetics (PK) of PD-0325901 or Binimetinib with PF-02341066 when administrated in combination.	Determine plasma Cmax, Cmin, AUC, oral clearance and t1/2 etc. for PF-02341066, PD-0325901 (and its metabolite) and Binimetinib.
To investigate pharmacodynamic (PD) biomarkers of PD-0325901 or Binimetinib with PF-02341066 in paired skin biopsies, tumour biopsies (where possible), in serum and PBMCs.	ELISA for soluble c-MET and HGF in plasma; ERK phosphorylation (pERK) in PBMC; Immunohistochemistry (IHC) for pERK1/2, c-METY1234/1235 in (mandatory) skin and (optional) tumour biopsies.
To preliminarily assess the efficacy of RPII dose of PF-02341066 in combination with PD-0325901 or Binimetinib.	Objective response using CT scan and modified RECIST version 1.1 and progression free and overall survival.
<b>Secondary Objectives (Dose Expansion)</b>	
To assess the efficacy of RPII dose of PF-02341066 in combination with PD-0325901 or Binimetinib in patients with RASMT and RASWT/c-MET CRC.	Objective response using CT scan and modified RECIST version 1.1, and progression free and overall survival.
To further investigate the safety and toxicity profile/tolerability of PD-0325901/PF-02341066 or Binimetinib/PF-02341066 combinations.	Determine plasma Cmax, Cmin, AUC, oral clearance and t1/2 etc. for PF-02341066, Binimetinib, and PD-0325901 (and its metabolite).
To investigate pharmacokinetic (PK) biomarkers of PF-02341066, PD-0325901 and Binimetinib in blood.	Determine plasma Cmax, Cmin, AUC, oral clearance and t1/2 etc for PF-02341066 and PD-0325901 and its metabolite.

To measure pharmacodynamic (PD) effect of PF-02341066 in combination with PD-0325901 or Binimetinib in paired skin biopsies, tumour biopsies (where possible), plasma and PBMCs..	ELISA for soluble c-MET and HGF in plasma; ERK phosphorylation (pERK) in PBMC; Immunohistochemistry (IHC) for pERK1/2, c-MET <sup>Y1234/1235</sup> in skin and tumour biopsies.
<b>Tertiary and Exploratory Objectives</b>	
To identify molecular signatures of response and resistance to combined PD-0325901 /PF-02341066 or Binimetinib/ PF-02341066 treatment.	Whole exome sequencing and miRNA profiling on tumour biopsies taken prior to treatment and upon resistance to PF-02341066 and PD-0325901 or Binimetinib treatment.
(12) Develop a liquid biopsy platform for routine assessment of therapeutic efficacy	Gene sequencing outputs from ctDNA in serially collected plasma samples from mCRC patients in the dose expansion phase

\* Objectives written in grey are those not covered by this Statistical Analysis Plan.

## Study Design

This will be a multicentre, open label, single arm phase I combination study of a MET inhibitor (PF-02341066) and a MEK inhibitor (PD-0325901 or Binimetinib). There was an initial dose escalation phase using patients with advanced solid tumours receiving the combined study treatment of PF-02341066 with PD-0325901. A second escalation phase using patients with advanced solid tumours will involve patients receiving the combined study treatment of PF-02341066 with Binimetinib. This will be followed by a dose expansion phase recruiting patients with *RASMT* and *RASWT/cMET* over-expressing metastatic colorectal cancer who will receive the combined study treatment of PF-02341066 with Binimetinib.

In the dose expansion phase, additional biopsy and blood samples will be obtained to define mechanisms of response/resistance to PF-02341066/Binimetinib therapy.

### 1a . Dose escalation phase of the study using the combination of PF-02341066 with PD-0325901.

For this dose escalation phase, a rolling six design has been chosen. Dose level assignment will be based on the number of patients currently enrolled in the cohort, the number of dose limiting toxicities (DLTs) observed, and the number of patients at risk for developing a DLT (i.e. patients enrolled but who are not yet evaluable for toxicity). Once the MTD has been exceeded the cohort at the next lowest dose level will be expanded to six patients. If the MTD is not defined at the highest dose level to be explored (Dose Level 4, Figure 3), then this dose level will be defined as the RPII dose. If two out of up to six patients at the same dose level experience a DLT in the first cycle of PF-02341066 in combination with PD-0325901, the Maximum Tolerated Dose (MTD) will be determined as the dose level below this. This dose will be determined following discussion of all the relevant toxicity data between OCTO and the TMG. Once the MTD has been defined, dosing at a higher dose must not occur. With the introduction of Binimetinib as the alternative MEKi to PD-0325901, the data accrued from the initial dose escalation phase will not now be used for determining the phase II recommended dose.

### 1b. Dose escalation phase of the study using the combination of PF-02341066 with Binimetinib.

A similar design to 1a, (combination of PF-02341066 with PD-0325901), will be used to determine the dose level to be defined as the RPII dose. There will be flexibility to explore alternate dosing schedules of Binimetinib, as the dosing schedule will be started as continuous dosing but reduced to dosing with a 7 day off treatment period every 28 days with a dosing schedule on days 1-21 every 28 days if continuous dosing is not well tolerated. If two out of up to six patients at the same dose level experience a DLT in the first cycle of PF-02341066 in combination with Binimetinib, the Maximum Tolerated Dose (MTD) will be determined as the dose level below this. This dose will be determined following discussion of all the relevant toxicity data between OCTO and the TMG. Once the MTD has been defined, dosing at a higher dose must not occur. The PF-02341066 and Binimetinib recommended phase II dose to be used in the expansion phase and subsequent phase II/III evaluation will be determined based on the MTD, observed safety profile, PK and pharmacodynamic data, but may include drug-related toxicities experienced in sustained dosing after cycle 1 after discussion with the TMG.

## 2. Dose expansion phase of study

Once the RPII dose and schedule have been identified, 12 patients with *RASMT* and 24 with *RASWT/cMET* CRC will be enrolled in the RPII dose expansion phase so that there are at least 12 evaluable patients in each category further to study the safety, PK, PD and treatment response. The larger *RASWT* cohort will include c-MET high expressors, c-MET super-expressors and c-MET amplified patient groups. In the dose expansion phase, patients will undergo an image-guided biopsy of representative metastases for c-MET testing and further mutational analysis and pharmacodynamic (PD) endpoints (including pERK1/2 and

pMET<sup>Y1234/1235</sup>) before and after combination treatment. Other PD endpoints include sMET, sHGF in plasma, pERK1/2 in PBMCs, and IHC for pERK1/2 and pMET<sup>Y1234/1235</sup> in skin biopsies before and after combination treatment. CT imaging to assess disease status will be performed every 8 weeks (2 cycles) during the study until subjects withdraw, cannot tolerate therapy or have progression of disease. At this time, patients who have given consent will undergo an optional USS or CT-guided metastasis biopsy for further mutational analysis. Blood samples for detection of ctDNA will be obtained every 4 weeks together with safety bloods until progression of disease.

Dose levels:

Dose levels in the first escalation phase of the study are summarised in the table below, and may include an intermediate dose level dependent on the emergent clinical data and dose limiting toxicities. Dose levels 2a and 3a may only be investigated if either dose level 2 or dose level 3 respectively is determined to be the MTD.

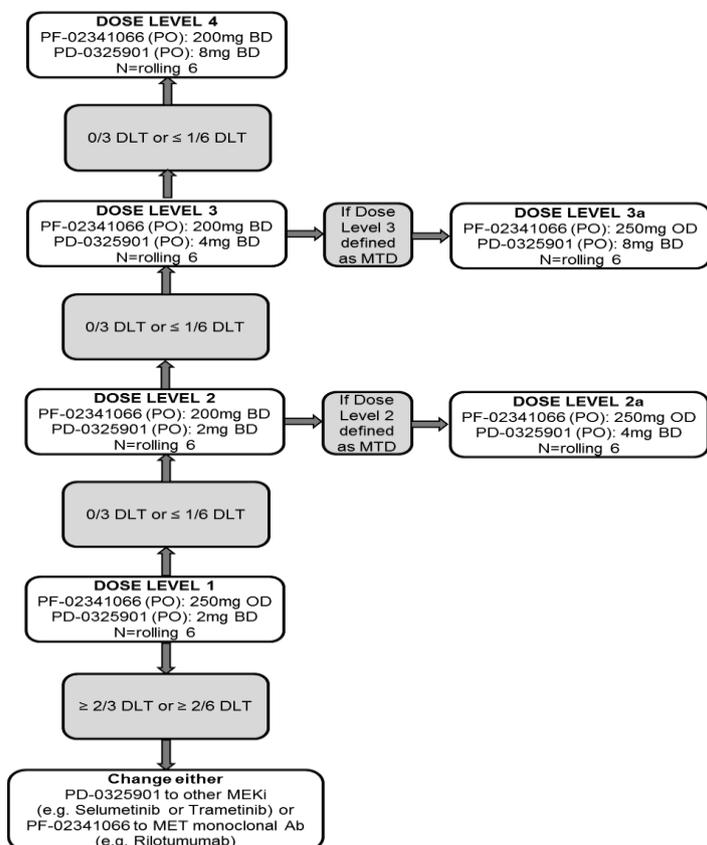
Dose Level	PD-0325901	PF-02341066
1	2mg BD	250mg OD
2	2mg BD	200mg BD
2a	4mg BD	250mg OD
3	4mg BD	200mg BD
3a	8mg BD	250mg OD
4	8mg BD	200mg BD

Dose levels in the second dose escalation phase of the study are summarised in the table below. PF-02341066 250mg BD is the recommended dose level and dose level 7 has been included in this dose escalation phase as we wish to extend dosing to that level if the toxicity profile permits. Dose levels 5a and 6a may be explored if BD dosing of the combination drug treatment is not well tolerated. There may also be a requirement to reduce the frequency of the Binimetinib dosing schedule from continuous dosing throughout the study period to days 1 to 21 every 28 days dependent on emergent clinical data.

Dose Level	Binimetinib	PF-02341066
5	30mg BD	200mg BD
5a	30mg BD	250mg OD
6	45mg BD	200mg BD
6a	45mg BD	250mg OD
7	45mg BD	250mg BD

Dose level assignment will be based on the number of patients currently enrolled in the cohort, the number of dose limiting toxicities (DLTs) observed, and the number of patients at risk for developing a DLT (i.e. patients enrolled but who are not yet evaluable for toxicity). For example, when three patients are enrolled onto a dose cohort, if toxicity data are available for all three when the fourth patient enters and there are no DLTs, the dose will be escalated and the fourth patient will be enrolled to the subsequent dose level. If data are not yet available for one or more of the first three patients, or if one DLT has been observed, the new patient will be entered at the same dose level. Lastly, if two or more DLTs have been observed, the dose level will be de-escalated. The process will be repeated for patients five and six. When patients are non-evaluable for toxicity, they will be replaced with the next available patient if escalation or de-escalation rules have not been fulfilled at the time the next available patient enrolls in the study. Once the maximum tolerated dose (MTD) has been exceeded the cohort at the next lowest

dose level will be expanded to six patients. If the MTD is not defined at the highest dose level to be explored, then this dose level will be defined as the RPII dose.



**Figure 1: Schema for dose levels in the escalation phase using PF-02341066 in combination with PD-0325901**

Date of expected start of recruitment: November 2014 OXFORD. (1<sup>st</sup> Escalation)  
 July 2016 OXFORD (2<sup>nd</sup> Escalation)  
 September 2016 OXFORD (Expansion)

Other sites to follow shortly after.

Date of expected end of recruitment:  
 Dose escalation phase (1<sup>st</sup>): expected to be 9 months from first escalation patient recruited  
 Dose escalation phase (2<sup>nd</sup>): expected to be 3 months from first escalation patient recruited  
 Dose expansion phase: expected to be 6 months from first expansion patient recruited

Target number of subjects: In the initial dose escalation study using PF-02341066 with PD-0325901, 12- 24 patients will be recruited. In the further dose escalation study using PF-02340166 in combination with Binimetinib, between 12-18 patients will be recruited. Once the RPII dose has been identified, patients with biopsiable RASMT or RASWT/cMET CRC will be enrolled in the dose expansion phase to further evaluate the safety, PK, PD and treatment response. We plan to recruit at least 12 evaluable patients in the RASMT CRC category and up to 24 in the RASWT/cMET CR category. Therefore in the dose expansion phase an

additional 36 patients will be recruited, bringing the expected total patient number for the trial to between 60 and 78, not counting any replacements.

**Participating Centres:** 4 EU centres; 2 UK centres (OXFORD and Belfast (BHSCT)); 1 centre in Belgium (UZA) and 1 centre in Spain (VHIO). This will be increased to 8 centres for the dose expansion phase.

## Eligibility

Written informed consent must be obtained before any study specific procedures are performed. The Investigator will determine patient eligibility based on the following criteria.

**Dose escalation:** Adult patients with pathologically proven advanced solid tumours. This will include patients with any solid tumour for whom the drug combination is considered a reasonable treatment option in the opinion of the clinical investigator.

**Dose expansion:** Adult patients with pathologically proven colorectal cancer with *RASMT* or *RASWT* with aberrant c-MET expression (overexpression, amplification or mutation) in a metastatic lesion. This will include CRC patients who received prior lines of cytotoxic drug treatment or targeted therapies.

Subjects must meet all the inclusion/exclusion criteria listed below.

## Inclusion Criteria:

A patient will be eligible for inclusion in this study if all of the following criteria apply.

### All patients:

- Age  $\geq$  16 years
- ECOG performance status 0-1 (Appendix 1)
- Adequate respiratory function on clinical assessment.
- Left ventricular ejection fraction (LVEF)  $\geq$  50% as determined by a multigated acquisition (MUGA) scan or echocardiogram.
- Able to give informed consent prior to any screening procedures being performed and be capable of complying with the protocol and its requirements.
- Haematological and biochemical indices within the ranges shown below:
  - Haemoglobin (Hb)  $\geq$ 9g/dl (transfusion to achieve this allowed),
  - Neutrophils  $\geq$  1,500/ $\mu$ l,
  - Platelet count  $\geq$  100,000/ $\mu$ l,
  - AST or ALT  $\leq$  2.5 x ULN, patient with liver metastases  $\leq$  5 ULN, Alkaline phosphatase  $\leq$  2 x ULN,
  - Serum Bilirubin  $\leq$  1.5 x ULN,
  - Creatinine Clearance  $\geq$  50ml/min (Calculated by Cockcroft Gault equation, or by EDTA) (Appendix 2)
- Able to swallow oral medication
- Life expectancy of at least 3 months.

### Dose escalation phase: combination of PF-02341066 with PD-0325901

- Patients with any advanced solid tumours

- Patients for whom the combination of PF-02341066 with PD-0325901 is a reasonable option.

Dose escalation phase: combination of PF-02341066 with Binimetinib

- Patients with any advanced solid tumours
- Patients for whom the combination of PF-02341066 with Binimetinib is a reasonable option.

Dose expansion phase:

Patients will be eligible for pre-screening for MErCuRIC provided that:

- They have given informed consent to screening.
- They are willing to undergo a biopsy for assessment of tumour RAS mutation status and c-MET assessment.
- The Investigator anticipates that they are likely to satisfy the eligibility criteria for the trial. Formal screening should not be performed until the tumour pre-screening result is known.

Eligibility for the trial, in patients passing pre-screening, requires:

- Histologically confirmed colorectal adenocarcinoma that is *RAS*MT (codon 12, 13, 61 mutations) or *RAS*WT/*c-MET*+, with progressive disease on or within 6 months of completion of adjuvant therapy or after chemotherapy/targeted therapies for metastatic disease.
- No evidence for a mutation in *BRAF* at codon600
- Metastases accessible for biopsy on 2-3 occasions
- At least one other measurable lesion (according to RECIST v1.1).
- Unsuitable for potential curative resection.

**†For non-UK territories: if ECHO cannot be performed, a MUGA scan may be performed in compliance with local policy, applicable national legislation and relevant approvals. Cardiac ejection fraction must be determined as measured by echocardiogram (ECHO) in the UK.**

## **Exclusion criteria:**

All patients:

- Unstable ischemic heart disease, cardiac dysrhythmias, coronary/peripheral artery bypass graft or cerebrovascular accident within 6 months prior to starting treatment.
- Uncontrolled arterial hypertension despite medical treatment.
- Ongoing congestive heart failure or cardiac dysrhythmias of NCI CTCAE Grade  $\geq 2$  or uncontrolled atrial fibrillation.
- History of extensive disseminated/bilateral or known presence of Grade 3 or 4 interstitial fibrosis or interstitial lung disease, including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease (ILD), obliterative bronchiolitis, and pulmonary fibrosis. A history of prior radiation pneumonitis is allowed.
- Any active central nervous system (CNS) lesion (i.e., those with radiographically unstable, symptomatic lesions) and/or leptomeningeal metastases. However, patients treated with stereotactic radiotherapy or surgery are eligible if the patient remained without evidence of CNS disease progression  $\geq 3$  months. Patients must be off corticosteroid therapy for  $\geq 3$  week
- Patients who have neuromuscular disorders that are associated with elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy);
- Patients who are planning on embarking on a new strenuous exercise regimen after first dose of study treatment. NB: Muscular activities, such as strenuous exercise, that can result in significant increases in plasma CK levels should be avoided while on Binimetinib treatment

- Spinal cord compression unless treated with the patient attaining good pain control and stable or recovered neurologic function.
- Carcinomatous meningitis or leptomeningeal disease.
- History of hypoalbuminaemia, or patients with peritoneal disease or pleural disease, where there is a requirement for ascitic or pleural taps.
- History of retinal vein occlusion, intraocular pressure > 21 mmHg or patient considered at risk of retinal vein thrombosis (e.g. history of hyperviscosity or hypercoagulability syndromes).
- History of retinal degenerative disease.
- History of Gilbert's syndrome.
- Active infections (including chronic hepatitis type B or C and HIV infection if status known), severe immunologic defect, compromised bone marrow function
- Other severe acute or chronic medical (including severe gastro-intestinal disorders eg. partial bowel obstruction, malabsorption, active inflammatory bowel disease) or psychiatric conditions or laboratory abnormalities that the investigator considers would make the patient a poor trial candidate, would impart excess risk associated with study participation or drug administration or could interfere with protocol compliance or the interpretation of trial results.
- Use of drugs or foods that are known potent CYP3A4 inhibitors or inducers or are CYP3A4 substrates with narrow therapeutic indices (see Appendix 5)
- Radiotherapy (except for palliative reasons), endocrine therapy, immunotherapy or chemotherapy during the previous four weeks (six weeks for nitrosoureas, Mitomycin-C) and four weeks for investigational medicinal products before treatment. Patients with prostate cancer may continue to receive endocrine therapy to maintain castrate levels of androgens.
- Resting ECG with QTc >480msec at 2 or more time points within a 24h period (using Fredericia correction).
- Requirement for medication known to prolong QT interval (see appendix 5).
- History of other malignancy less than 3 years before the diagnosis of current cancer, EXCLUDING the following: Non-melanoma skin cancer, in situ carcinoma of the cervix treated surgically with curative intent, other malignant tumours that have been treated curatively and patient is deemed disease-free.
- Women with the ability to become pregnant (or already pregnant or lactating). However, those female patients who have a negative serum or urine pregnancy test before enrolment and agree to use two highly effective forms of contraception (oral, injected or implanted hormonal contraception and condom plus spermicide, have an intra-uterine device and condom plus spermicide, diaphragm with spermicidal gel and condom plus spermicide) for four weeks before entering the trial, during the trial and for six months afterwards are considered eligible.
- Male patients with partners of child-bearing potential (unless they agree to take measures not to father children by using any two forms of highly effective contraception including: oral, injected or implanted hormonal contraception and condom plus spermicide, have an intra-uterine device and condom plus spermicide, during the trial and for six months afterwards). Men with pregnant or lactating partners should be advised to use barrier method contraception (condom plus spermicidal gel) during the trial and for six months afterwards to prevent exposure to the foetus or neonate.
- Prior exposure to any of a HGF, cMET or a MEK inhibitor.

### **Protocol deviations and waivers to entry criteria**

Investigators should not deviate from the protocol for the management of enrolled subjects deliberately, unless essential to protect the rights or safety of the individual. It may be necessary to withdraw the patient from further study. All waivers and deviations should be fully documented/ justified and reported to the trial office without delay.

### 2.1.3 Re-screening if patient does not meet criteria first time round

If a patient does not meet the list of key inclusion/exclusion criteria first time round, he/she can be re-screened, as long as dose escalation or dose expansion phase is recruiting. Patients who fail at rescreening are ineligible and may not be rescreened further.

#### Treatment Interventions

In this non-randomised study, patients with advanced solid tumours will be recruited where no potentially curative surgery is planned.

##### Dose escalation phase: PF-02341066 in combination with PD-0325901

PF-02341066 (Crizotinib): 250mg orally, once a day or 200mg orally, twice a day continuously.  
PD-0325901: 2mg orally, twice a day to 8mg orally twice a day. Run-in day -7 to day -1, then days 1 to 21 every 28 days.

Patients who successfully complete the screening will receive PD-0325901 orally continuously as monotherapy for one week (day minus 7 to day minus 1). Thereafter combination dosing of both agents will begin. The dose levels are defined in Figure 1.

Oral PD-0325901 will be administered on days 1 - 21 of each 28 day cycle (after the one week run-in of monotherapy). The dose of PD-0325901 will not be escalated beyond 8mg BD. PF-02341066 tablets will be taken orally, once or twice daily on a continuous schedule.

##### Dose escalation phase: PF-02341066 in combination with Binimetinib

PF-02341066 (Crizotinib): 250mg orally, once a day or 200mg orally, twice a day continuously.  
Binimetinib: 30mg orally, twice a day or 45mg orally twice a day continuously or for 1 to 21 days every 28 days.

Patients who successfully complete the screening will receive the oral combined therapy of PF-02341066 and Binimetinib. Binimetinib tablets will be administered twice daily from Day 1 continuously throughout the study treatment period or on days 1 – 21 of each 28 day cycle if continuous dosing is not well tolerated. PF-02341066 capsules will be administered either once or twice daily on a continuous schedule. The dose of Binimetinib will not be escalated beyond 45mg BD.

##### Dose expansion phase:

In the dose expansion cohort, patients with advanced RASMT and RASWT/ c-MET CRC tumours will be recruited.

PF-02341066 (Crizotinib) at recommended phase II dose continuously.  
Binimetinib at recommended phase II dose either continuously or for 1- 21 days every 28 days.

#### Management of drug administration:

##### Dose escalation phase: PF-02341066 in combination with PD-0325901

Patients will receive the morning dose of PF-02341066 and/or PD-0325901 without regard to meals. Patients should take the capsules at approximately the same time each day. For BD evening dosing PF-02341066 will be administered approximately 12 hours following the morning dosing.

In case of BD administration, doses of PF-02341066 and PD-0325901 should be taken approximately 12 hours apart. Wherever possible doses should not be missed but if a dose is missed then the next dose should be taken at the allotted time and the missed dose should not be made up. If the patient vomits shortly after taking PF-02341066 or PD-0325901, the dose should be replaced only if the vomited capsules can actually be seen and counted. Compliance

with PF-02341066 and PD-0325901 dosing will be evaluated by capsule count during scheduled visits to the trial site by pharmacy staff.

Dose escalation phase and dose expansion phase using PF-02341066 in combination with Binimetinib:

Patients will receive the morning dose of PF-02341066 and Binimetinib. In case of BD administration, doses of PF-02341066 and Binimetinib should be taken approximately 12 hours apart and, wherever possible, at approximately the same time every day, without regard to meals. Doses should not be missed, but, if a dose is missed, then the next dose should be taken at the allotted time and the missed dose should not be made up. If the patient vomits shortly after taking PF-02341066 or Binimetinib, the dose should be replaced only if the vomited capsules or tablets can actually be seen and counted. Compliance with PF-02341066 and Binimetinib dosing will be evaluated by capsule/tablet count during scheduled visits to the trial site by pharmacy staff.

#### **Duration of treatment:**

Treatment will be given continuously until

- Disease progression
- Intercurrent illness that in the judgment of the investigator would affect patient safety, the ability to deliver treatment or the primary study endpoints.
- In case of unacceptable toxicity
- At the patient's request.
- Physician's decision for any other reasons (which should be clearly justified or documented)

It is estimated that the median time to progression in the expansion cohort will be 6 months. Patients may receive further standard treatment, treatment within another clinical trial or palliative and supportive care as appropriate and all will have long-term follow-up for further disease progression and overall survival.

#### **Sample Size**

##### ***Phase I dose escalation using PF-02341066 in combination with PD-0325901***

Between 12 and 24 patients will be recruited to this phase I dose escalation part of the trial in a rolling 6 design to establish an MTD as explained in the protocol. The dose escalation is agreed between the CI's at the four recruiting centres based on the definitions in this protocol.

##### ***Phase I dose escalation using PF-02341066 in combination with Binimetinib***

Between 12 and 18 patients will be recruited to this phase I dose escalation part of the trial in a rolling 6 design to establish an MTD as explained earlier. The dose escalation is agreed between the CI's at the four recruiting centres based on the definitions in this protocol.

#### **Dose expansion**

Based on the data obtained over the last 12 months by the MErCuRIC consortium on c-MET as biomarker in CRC, and on data coming from phase III studies with c-MET inhibitors in other solid tumours, the MErCuRIC consortium recently decided to expand the RASWT/c-MET group, in order that the effect of combined PF-02341066/Binimetinib treatment can not only be evaluated in c-MET high expressors (2-3+, defined by Immunohistochemistry, IHC), but also in c-MET "superexpressor" (10% high 3+ by RNA scope and IHC) and potentially a c-MET amplified case. The c-MET high "superexpressor" and amplified patients are most likely the patients with dependency on c-MET and would benefit from treatment. With this amendment, we would be more confident to have a clear positive signal at the end of our phase I study, that will inform further patient selection in the phase II component of the study. Therefore 36 patients with biopsiable CRC will be recruited at the RPII dose, at least 12 evaluable patients in the RASMT CRC category and up to 24 in the RASWT/cMET CR category.

This sample size is based on TMG discussion.

### **Randomisation**

This is a non-randomised phase I combination study.

**Outcomes Assessment Schedule**

Dose escalation phase for PF-02341066 with PD-0325901:

Visit Description	Screening	Cycle 1											Cycle 2				Cycle 3				Cycle 4				Cycle 5 onwards	End of Treatment °	Post end of treatment
		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24			
Visit No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24			
Day	-28 to -1	-7	-6	-1	1	2	8	15	16	21	22	28	29±3	36	43	49	57±3	64	71	78	85±3	92	99	105		D 28-30 after last dose	
Informed Consent	X																										
Demographics & History	X																										
Concomitant medication	X	X			X		X	X		X	X		X	X	X		X	X	X	X	X	X	X	X		X	
ECOG	X	X			X		X	X		X	X		X	X	X		X	X	X	X	X	X	X	X		X	
Physical examination <sup>a</sup>	X	X			X		X	X		X	X		X	X	X		X	X	X	X	X	X	X	X		X	
Tumour Assessment <sup>b</sup>	X																X									X	
Vital signs	X	X			X		X	X		X	X		X	X	X		X	X	X	X	X	X	X	X		X	
Height & Weight <sup>c</sup>	X	X			X		X	X		X	X						X				X					X	
Ophthalmic Exam <sup>d</sup>	X									X																X	
Haem & Clin Chem Bloods <sup>e</sup>	X	X			X			X			X						X				X					X	
Pregnancy test	X																										
12 lead ECG	X	X			X			X			X						X				X					X	
Echocardiography <sup>f</sup>	X																										
Inclusion/exclusion criteria	X																										
CEA <sup>g</sup>		X									X						X									X	
PK 24 hours profile <sup>h</sup>				X	X					X	X	X	X														
PK trough <sup>i</sup>															X									X			
PD PBMC/plasma <sup>l</sup>		X	X		X	X		X	X																		
AE review		X			X		X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X
PD-0325901 administration <sup>k</sup>		X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X			
PF-02341066 administration													Continuous administration														
Survival data (PFS and OS)																											X
Biomarker studies																											
Archival tumour sample	X																										
Blood sample germline DNA	X																										
PD skin biopsy <sup>l</sup>	X							X																			
PD tumour biopsy <sup>m</sup>	X							X																			
Plasma soluble biomarkers <sup>n</sup>		X			X			X					X	X			X				X						

- <sup>a</sup> To include vital signs (pulse and systolic/diastolic blood pressure, body temperature) and neurological examination.
- <sup>b</sup> CT includes chest, abdomen and pelvis. Measurements using modified RECIST 1.1. At screening and after 2nd, 4th, 6th cycle, and every 2 cycles thereafter until intolerable toxicity or progressive disease.
- <sup>c</sup> Height to measured only at screening.
- <sup>d</sup> Ophthalmic exam on Cycle 1 Day 21 time window of +/- 2 days
- <sup>e</sup> To include FBC with differential and platelets, Na, K, Ca, phosphate, urea, creatinine, total protein, albumin, bilirubin, alk phos, AST and /or ALT, LDH, coagulation screen, APTT, PT (validity period of bloods is 3 days).
- <sup>f</sup> ECHO will only be repeated as clinically indicated.
- <sup>g</sup> At same time as CT scan (optional at every cycle) plus Cycle 1 Day 28.
- <sup>h</sup> Serum PK measurements will be taken as specified in the protocol (section 7.3).
- <sup>i</sup> PK trough sample pre-dose (morning) and 2 hours post dose day 21 of cycles 2, 4, 6, 8, 10 and 12.
- <sup>j</sup> PD PBMC/Plasma samples will be taken as specified in the protocol (section 7.4)
- <sup>k</sup> Run-in day -7 to day -1 then days 1-21 of each 28 day cycle.
- <sup>l</sup> Day 15 +/- 7 days.
- <sup>m</sup> At Screening and Day 15 +/- 7 days. Optional biopsy if separate consent obtained.
- <sup>n</sup> At each sampling point 4ml of plasma obtained.
- <sup>o</sup> Disease progression, intolerance or withdrawal.

Dose expansion phase for PF-02341066 with PD-0325901:

Visit Description	Pre-Screening	Screening	Cycle 1							Cycle 2				Cycle 3				Cycle 4				Cycle 5 onwards	End of treatment <sup>h</sup>	Post-treatment follow-up			
			0	1	2	2	3	4	5	6	7	8	9	10	11	CT/MRI	12	13	14	15	16				17	18	19
Visit No	0	1	2	2	3	4	5	6	7	8	9	10	11	CT/MRI	12	13	14	15	16	17	18	19	CT/MRI				
Day		-28 to -1	-7	1	2	8	15	16	22	29±3	36	43	50		57±3	64	71	78	85±3	92	99	106			14d post last dose		
Informed Consent	X <sup>d</sup>	X																									
Demographics & History	X	X																									
Inclusion/exclusion criteria		X																									
Physical Exam <sup>a</sup>		X	X	X			X			X					X				X							X	
Height & Weight		X	X	X						X					X				X							X	
Pregnancy Test		X	X																							X	
Ophthalmic Exam		X							X																	X	
12 Lead ECG		X		X						X					X				X							X	
Echo <sup>b</sup>		X																								X	
WHO PS		X	X	X						X					X				X							X	
Haem & Clin Chem Bloods <sup>c</sup>		X		X			X			X					X				X							X	
Tumour Assessment <sup>d</sup>		X	X											X									X			X	
CEA			X	X										X									X			X	
PK 24 hours profile <sup>e</sup>				X	X																						
PK trough <sup>f</sup>			X				X			X									X			X					
PD PBMC/plasma			X	X	X		X	X																			
Archival tumour sample	X <sup>d</sup>																										
AE review			X	X		X	X		X	X	X	X	X		X	X	X	X	X	X	X	X				X	X
Concomitant medication		X	X	X		X	X		X	X	X	X	X		X	X	X	X	X	X	X	X				X	X
PD-0325901 administration			X	X		X	X		X	X	X	X	X		X	X	X	X	X	X	X	X					
PF-02341066 administration			X	X		X	X		X	X	X	X	X		X	X	X	X	X	X	X	X					
Survival data (PFS and OS)																											
Special biomarker studies																											
PD skin biopsy		X				X																					
PD tumour biopsy		X																								X	
Tumour	X <sup>d</sup>																									X	
Plasma soluble biomarkers <sup>g</sup>																											
Plasma sample for ctDNA <sup>k</sup>				X						X					X				X							X	
germline DNA		X																									

Repeat cycle 3 and 4

- a. To include vital signs (pulse and systolic/diastolic blood pressure, body temperature) and neurological examination
- b. ECHO will only be repeated as clinically indicated.
- c. To include FBC with differential, Ur, Cr, Na, K, Alb, Ca, ALP, ALT or AST, Bili
- d. CT includes chest, abdomen and pelvis. Measurements using modified RECIST 1.1.
- e. Serum PK measurements will be taken as per protocol.
- f. PK trough sample cycle 2, cycle 4 and cycle 6 day 1 and day 15 before PF-02341066 and PD-0325901 dosing.
- g. At each sampling time point, 4ml of plasma is required.
- h. Disease progression, intolerance or withdrawal.
- i. Skin and tumour biopsy pre-dosing cycle 1 and day 8 4-6 hours following dosing. Tumour biopsy for PK is optional.
- j. Pre-trial screening for c-MET and KRAS status

k. Blood samples for the detection of ctDNA will be obtained every 4 weeks until disease progression or withdrawal.

**Dose escalation phase for PF-02341066 and Binimetinib:**

Visit Description	Screening	Cycle 1						Cycle 2				Cycle 3				Cycle 4				Cycle 5 onwards	End of Treatment °	Post end of treatment follow-up			
		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19						
Visit No	1																								
Day	-28 to -1	D1	D8	D15	D16	D21	D22	D1 (±3)	D8	D15	D21	D1 (±3)	D8	D15	D21	D1 (±3)	D8	D15	D21					D 28-30 after last dose	
Informed Consent	X																								
Demographics & History	X																								
Concomitant medication	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X					X	
ECOG	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X					X	
Physical examination <sup>a</sup>	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X					X	
Tumour Assessment <sup>b</sup>	X											X													
Vital signs <sup>c</sup>	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X					X	
Height & Weight <sup>d</sup>	X	X	X	X		X		X				X				X									
Ophthalmic Exam <sup>e</sup>	X										X											X			
Haem & Clin Chem Bloods <sup>f</sup>	X	X		X				X				X				X								X	
Urinalysis	X	X		X				X				X				X								X	
Pregnancy test	X	X						X				X				X								X	
12 lead ECG	X	X		X				X				X				X								X	
Echocardiography/MUGA <sup>fg</sup>	X							X							X										
Inclusion/exclusion criteria	X											X													
Tumour marker <sup>h</sup>	X											X												X	
PK 24 hours profile <sup>i</sup>						X	X																		
PK trough <sup>j</sup>											X											X			
PD PBMC/plasma <sup>k</sup>		X		X	X																				
AE review		X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X					X	X
Binimetinib administration		Continuous administration or Days 1-21 every 28 days																							
PF-02341066 administration		Continuous administration																							
Survival data (PFS and OS)																									X
Biomarker studies																									
Archival tumour sample	X																								
Blood sample germline DNA	X																								
PD skin biopsy <sup>l</sup>	X			X																					
PD tumour biopsy <sup>m</sup>	X			X																					
Plasma soluble biomarkers <sup>n</sup>		X		X						X		X				X									

- <sup>a</sup> To include neurological examination.
- <sup>b</sup> CT includes chest, abdomen and pelvis. Measurements using modified RECIST 1.1. At screening and after 2nd, 4th, 6th cycle, and every 2 cycles thereafter until intolerable toxicity or progressive disease.
- <sup>c</sup> To include pulse and systolic/diastolic blood pressure, body temperature. Blood pressure to be measured after resting for 5 minutes in a sitting position.
- <sup>d</sup> Height to be measured only at screening.
- <sup>e</sup> Ophthalmic exam at baseline, and end of cycles 2, 4, 6 and 9 and every third cycle (12 weekly) after this and also as clinically indicated. Time window for examination allowable +/- 2 days
- <sup>f</sup> To include FBC with differential and platelets, Na, K, Ca, phosphate, urea, creatinine, total protein, albumin, bilirubin, alk phos, AST and /or ALT, LDH, coagulation screen, APTT, PT (validity period of bloods is 3 days).
- <sup>g</sup> Echo or MUGA at baseline and at end of cycles, 1, 3, 5, 8 and every third cycle (12 weeks) afterwards and also repeated as clinically indicated. For non-UK territories: if ECHO cannot be performed, a MUGA scan may be performed in compliance with local policy, applicable national legislation and relevant approvals. Cardiac ejection fraction must be determined as measured by echocardiogram (ECHO) in the UK.
- <sup>h</sup> For patients with relevant tumour types, tumour marker (CEA, CA-125, PSA or CA19-9 as relevant) will be checked during screening and after 2nd, 4th, 6th cycle, and every 2 cycles thereafter
- <sup>i</sup> Serum PK measurements will be taken as specified in the protocol (section 7.3).
- <sup>j</sup> PK trough sample pre-dose (morning) and 2 hours post dose day 21 of cycles 2, 4, 6, 8, 10 and 12.
- <sup>k</sup> PD PBMC/Plasma samples will be taken as specified in the protocol (section 7.4)
- <sup>l</sup> Day 15 +/- 7 days.
- <sup>m</sup> At Screening and Day 15 +/- 7 days. Optional biopsy if separate consent obtained.
- <sup>n</sup> At each sampling point 4ml of plasma obtained.
- <sup>o</sup> Disease progression, intolerance or withdrawal.

Dose expansion phase for PF-02341066 and Binimetinib:

Visit Description	Screening	Cycle 1						Cycle 2				Cycle 3				Cycle 4				Cycle 5 onwards	End of Treatment <sup>a</sup>	Post end of treatment follow-up
		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19			
Visit No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19			
Day	-28 to -1	D1	D8	D15	D16	D21	D22	D1 (29±3)	D8	D15	D21	D1 (57±3)	D8	D15	D21	D1 (85±3)	D8	D15	D21		D 28-30 after last dose	
Informed Consent	X																					
Demographics & History	X																					
Concomitant medication	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination <sup>a</sup>	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tumour Assessment <sup>b</sup>	X											X									X	
Vital signs <sup>c</sup>	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height & Weight <sup>d</sup>	X	X	X	X		X		X				X				X					X	
Ophthalmic Exam <sup>e</sup>	X										X									X		
Haem & Clin Chem Bloods <sup>f</sup>	X	X		X				X				X				X					X	
Urinalysis	X	X		X				X				X				X					X	
Pregnancy test <sup>g</sup>	X	X						X				X				X					X	
12 lead ECG	X	X		X				X				X				X					X	
Echocardiography/MUGA <sup>h</sup>	X							X							X							
Inclusion/exclusion criteria	X																					
Tumour marker <sup>i</sup>	X											X									X	
PK 24 hours profile <sup>j</sup>						X	X															
PK trough <sup>k</sup>											X										X	
PD PBMC/plasma <sup>l</sup>		X		X	X																	
AE review		X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Binimetinib administration		Continuous administration or Days1-21 every 28 days																				
PF-02341066 administration		Continuous administration																				
Survival data (PFS and OS)																						X
Biomarker studies																						



## Data Management Responsibility

Data management will be performed via a web-based, bespoke trial database (OpenClinica). OpenClinica is a dedicated and validated clinical trials database designed for electronic data capture. See: <http://www.openclinica.org>.

The Chief Investigators will act as Data Custodians for the trial. A guide explaining how to use OpenClinica will be provided to every site. Relevant OCTO staff will have overview of all entered data.

### 2.1.4 Case Report Forms (CRFs)

The Investigator and study site staff will ensure that data collected on each subject is recorded in the CRFs within OpenClinica as accurately and completely as possible. The CRFs will not contain any source data. All appropriate laboratory data, summary reports and Investigator observations will be transcribed into the CRFs from the relevant medical record(s). Sites need to ensure that:

- the relevant CRFs are completed.
- all CRF data are verifiable in the source documentation or the discrepancies must be explained.
- CRF sections are completed in a timely fashion, as close to the visit or event being recorded as possible.
- Data queries are resolved and documented by authorised study staff, giving a reason for the change or correction where appropriate.

The above considerations also apply to patients who are withdrawn early. If a patient withdraws from the study, the reason must be noted on the appropriate form and the patient must be followed-up as per protocol.

### 2.1.5 Accounting for missing, unused or spurious data

Missing data found will be chased up and supplemented where possible after consultation with the investigator. The reason for missing data (consent withdrawn, lost to FU, removed from study due to serious side effects, death) will be indicated. Unused data will be retained as for used data.

Patients will continue on study (with appropriate dose modification if necessary) until disease progression, intolerable side effects or they choose to withdraw.

## Patient replacement

In the dose escalation phase if a patient comes off treatment due to a DLT they will not be replaced. If however, they withdraw for reasons other than safety before completing the first treatment cycle they will need to be replaced. Patients withdrawing will not receive further PF-02341066 or PD-0325901, in the initial dose escalation phase, nor will they receive any further PF-02341066 or Binimetinib in the further dose escalation phase. These patients will be followed up for progression free and overall survival unless they withdraw their consent to do so. If the protocol mandated skin and tumour biopsies in the dose escalation and expansion phases cannot be completed for whatever reason, then the patient will be replaced.

In the dose expansion phase patients who are non-evaluable for the primary end-point of response to treatment will be replaced. This does not include patients who progress early on

treatment so as to be unable to undergo cross-sectional imaging, who will be classified as progressing on treatment.

### 3. **QUALITY CONTROL AND DATA VALIDATION**

The study will undergo a risk assessment prior to study start to determine the extent and nature of site monitoring. Risk assessments will be performed throughout the duration of the study on an ad hoc need basis and in line with any substantial amendments and any significant findings that might change the risk/benefit balance of the study. Monitoring plans will be amended accordingly. Monitoring will be performed according to the plan and OCTO SOPs.

#### **On-Site Monitoring**

Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Monitoring visits reports will be sent to the site in a timely fashion.

#### **Central Monitoring**

Study sites will be monitored centrally by both programmed validation within the data collection database and manual checking of incoming data for compliance with the protocol, data consistency, missing data and timing. All changes to data that could influence the outcome will be queried with and approved by the study site in a timely manner. For all other data, where there is no doubt about the source of any errors, clear changes to data will be made internally by OCTO staff without referring back to the study site.

#### **Audit and Regulatory Inspection**

All aspects of the study conduct may be subject to internal or external quality assurance audit to ensure compliance with the protocol, GCP requirements and other applicable regulation or standards. It may also be subject to a regulatory inspection. Such audits or inspections may occur at any time during or after the completion of the study. Investigators and their host Institution(s) should understand that it is necessary to allow auditors/inspectors direct access to all relevant documents, study facilities and to allocate their time and the time of their staff to facilitate the audit or inspection visit. Anyone receiving notification of a Regulatory Inspection that will (or is likely to) involve this trial must inform the trial office without delay.

### 4. **TRIAL COMMITTEES AND INTERIM ANALYSES**

#### **Trial Management Group (TMG)**

The Chief Investigator will chair a TMG with responsibility for overseeing the successful conduct and publication of the trial in accordance with the protocol. The TMG will review safety and dose escalations with advice from the Independent Early Phase Trial Oversight Committee (IEPTOC). It will provide regular progress reports as required by the applicable steering committees and governance bodies. Members of the TMG will include:

- Chief Investigator
- Trial management staff from OCTO
- Trial Statistician(s)
- Principal Investigators from participating sites

#### **Data and Safety Monitoring**

There is no Data and Safety Monitoring Committee. IEPTOC will be in place to monitor the safety and progress of the trial.

### **Trial Steering Committee**

The role of the Trial Steering Committee will be fulfilled by the IEPTOC.

### **Interim Analysis**

No interim analyses of primary or secondary endpoints are planned beyond those inherent in the rolling 6 design.

## **5. DESCRIPTIVE ANALYSES**

### **Representativeness of Study Sample and Patient Throughput**

CONSORT Diagram for Dose Escalation Phase: PF-02341066 with PD-0325901.

**Enrolment**

Assessed for eligibility (N= )

Excluded (n= )

- Not meeting inclusion criteria (n= )

**Allocation**

Eligible and recruited N =

Entered into trial (N= )

- Received full first cycle as per protocol (n= )
- Did not receive full first cycle as per protocol (n= )
  - (give reasons) (n= )

Dose level 1  
 PD-032590: 2mg BD  
 PF-02341066: 250mg OD  
 N =

Dose level 2  
 PD-032590: 2mg BD  
 PF-02341066: 200mg BD  
 N =

Dose level 3  
 PD-032590: 4mg BD  
 PF-02341066: 200mg BD  
 N =

Dose level 4  
 PD-032590: 8mg BD  
 PF-02341066: 200mg BD  
 N =

**Analysis**

Evaluable for dose escalation N =  
 DLTs experienced  
 Evaluable for safety analysis N =

Evaluable for dose escalation N =  
 DLTs experienced  
 Evaluable for safety analysis N =

Evaluable for dose escalation N =  
 DLTs experienced  
 Evaluable for safety analysis N =

Evaluable for dose escalation N =  
 DLTs experienced  
 Evaluable for safety analysis N =

*Dose escalate*

*Dose escalate*

*Dose escalate*

CONSORT Diagram for Dose Escalation Phase: PF-02341066 with Binimetinib

**Enrolment**

Assessed for eligibility (N= )

Excluded (n= )

- Not meeting inclusion criteria (n= )

**Allocation**

Eligible and recruited N =

Entered into trial (N= )

- Received full first cycle as per protocol (n= )
- Did not receive full first cycle as per protocol (n= )
  - (give reasons) (n= )

Dose level 1  
Binimetinib: 30mg BD  
PF-02341066: 200mg BD  
N =

Dose level 2  
Binimetinib: 45mg BD  
PF-02341066: 200mg BD  
N =

Dose level 3  
Binimetinib: 30mg BD  
PF-02341066: 250mg OD  
N =

**Analysis**

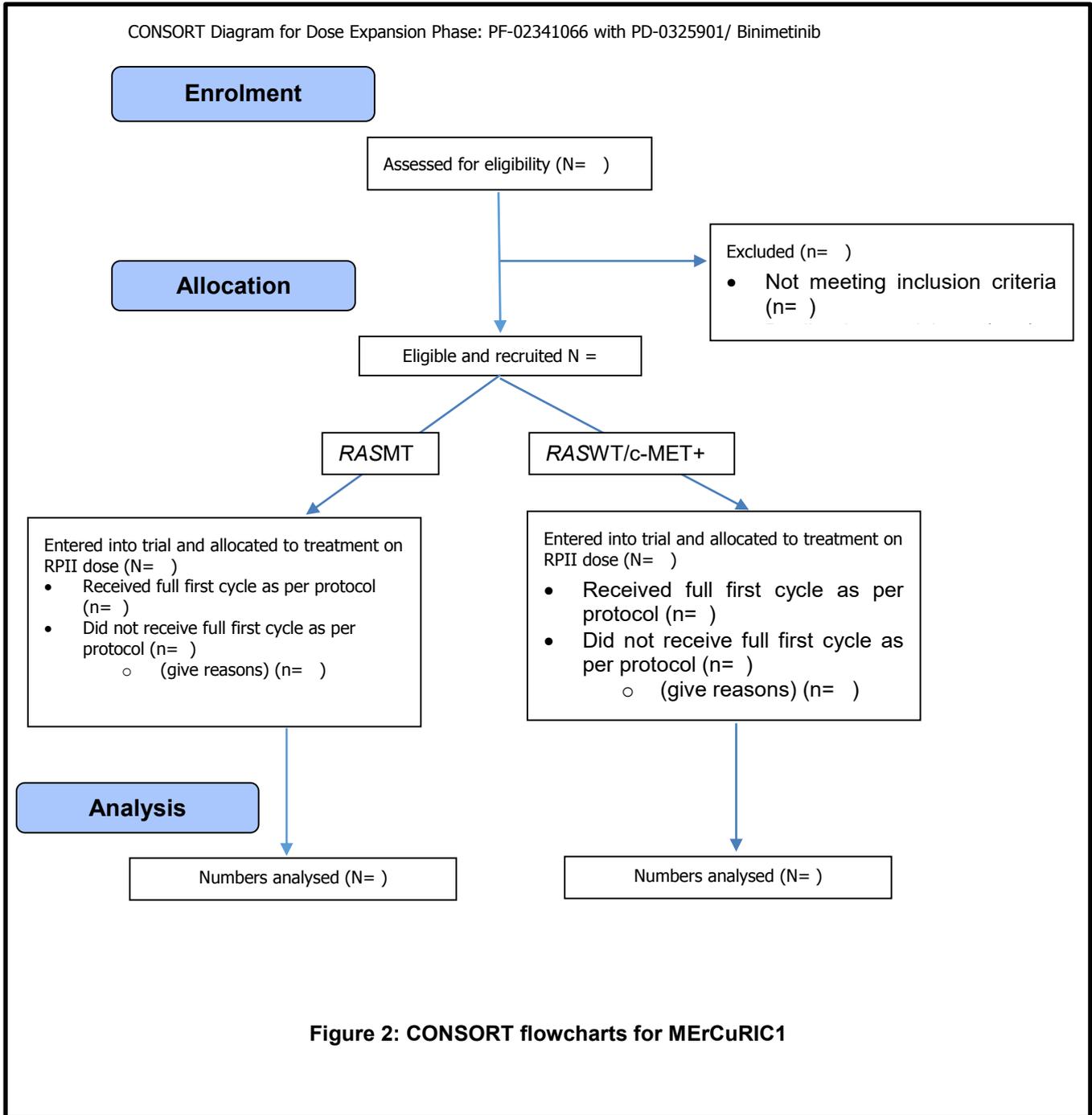
Evaluable for dose escalation N =  
DLTs experienced  
Evaluable for safety analysis N =

Evaluable for dose escalation N =  
DLTs experienced  
Evaluable for safety analysis N =

Evaluable for dose escalation N =  
DLTs experienced  
Evaluable for safety analysis N =

*Dose escalate*

*Dose escalate*



**Table 2: Reasons for patient exclusions**

Reason for exclusion	N	Subtotal
Not meeting inclusion criteria n=		
Refused to participate n=		
Other reason n=		
Total patients screened but not recruited		

The above table is required for each cohort in the dose escalation phase and for each RAS subgroup of the dose expansion phase.

### Description of Available Data

Baseline characteristics will be summarised for all evaluable patients, and all trial treatment information will be summarised. Descriptive statistics will be reported using numbers (with percentages) for binary and categorical variables, and means (+standard deviations) or medians (+lower and upper quartiles) for continuous variables.

Characteristics to be described in tabular form include:

#### Dose escalation phase:

Characteristics	Dose escalation phase	
	Cohort 1 -	Cohort 2* -
<b>Demographic</b>		
Age		
Gender n Male(%) n Female(%)		
Weight		
Height		
ECOG Performance Status n 0(%) n 1(%)		
<b>Physical exam</b>		
Tumour type		

\*This table will be repeated for each cohort for dose escalation phase: PF-02341066 with PD-0325901 and for dose escalation phase: PF-02341066 with Binimetinib

#### Dose expansion phase:

Characteristics	Dose expansion phase	
	KRAS mutant (MT)	KRAS wild type (WT) (with aberrant c-MET)
Age		

Gender n Male(%) n Female(%)		
Weight		
Height		
ECOG Performance Status n 0(%) n 1(%)		

Variables will be analysed to determine whether the criteria for the study conduct are met. This will include a description of patients who did not meet all the eligibility criteria, an assessment of protocol violations, and other data that impact on the general conduct of the study.

The number of patients who were not evaluable, who died or withdrew before treatment began will be recorded. The distribution of follow-up time will be described and the number of patients lost to follow-up will be given. Follow-up for progression events and deaths will be performed.

Completeness of data for the primary and secondary outcomes will be presented. All waivers and deviations will be summarised as reported.

### Description of Compliance with Therapy

Patients will be instructed to keep a record of compliance with treatment, by means of using a "patient diary" that will be provided to them.

A summary of the treatment received will be provided including dosage of the drug and compliance. Deviations from intended treatment will be summarised.

### Reliability

Computer calculations will be checked by hand for a minimum of 5 patients.

## 6. PATIENT GROUPS FOR ANALYSIS

The *intention-to-treat* population will include all patients who have given their informed consent. It is therefore important that every effort is made to encourage patients, including those patients who do not receive/complete their allocated treatment, to attend for follow-up clinic visits and complete tests to avoid bias in the analysis of the results.

*Evaluable* patients are those patients who completed cycle 1 or who withdraw early for experiencing a DLT.

*Toxicity analysis* will be on all patients who received at least some of at least one of the treatments in the combination. The *safety* population therefore comprises all patients who have been exposed to any dose of PD-0325901 or PF-02341066 or Binimetinib.

*Non-toxicity analyses* (i.e. response, OS, PFS) will be on an intention-to-treat basis. This means that patients will be analysed as they are consented irrespective of the amount of treatment actually received.

**The patient groups for the analysis of each aim are specified as follows:**  
(the numbering corresponds to the numbering of the aims in Section 2.1.1)

**Primary aims:**

**Dose Escalation (both)**

(1) All patients evaluable for MTD and dose escalation. Safety population for toxicity summaries.

**Dose Expansion**

(2) Intention-to-treat population (presented for each KRAS subgroup separately)

**Secondary aims:**

**Dose Escalation**

(3) All evaluable patients

(4) Not covered here; to be carried out under a separate analysis plan

(5) Not covered here; to be carried out under a separate analysis plan

(6) Intention-to-treat population

**Dose Expansion:**

(7) Intention-to-treat population (presented for each KRAS subgroup separately)

(8) Safety population

(9) Not covered here; to be carried out under a separate analysis plan

(10) Not covered here; to be carried out under a separate analysis plan

## 7. ANALYSES TO ADDRESS PRIMARY AIMS

All centres will be analysed together. It is expected that STATA or SAS will be used for the analysis.

### Evaluation/definition of Primary Endpoints

#### Dose escalation phase:

(1) Maximal tolerated dose (MTD) of PD-0325901 or Binimetinib with PF-02341066 according to toxicities graded by NCI CTCAE V4.03 in cycle 1 of treatment.

#### Dose expansion phase:

(2) Clinical and radiological response to PD-0325901 or Binimetinib with PF-02341066 as defined by stable, partially or completely responding disease using RECIST version 1.1.

## 8. STATISTICAL METHODS USED FOR ANALYSIS OF PRIMARY AIMS

The primary statistical report is due 4 months after end of recruitment. The results of the two escalation parts will be summarised separately.

#### Dose escalation:

The trial and decision process throughout the trial will be summarised. Worst severity toxicity grade per patient in cycle 1 (described using the NCI CTCAE v4.03) will be summarised in tables. The number of toxicities  $\geq$  Grade 3 per patient will also be summarised. Treatment related toxicity will be tabulated by type and grade of toxicity for cycle 1.

The variables that define the DLTs and safety variables will be summarized by descriptive statistics with patients grouped according to dose level received. Number (with percentages) of patient with and without DLT will also be presented according to dose level.

#### Dose expansion:

Best response measured by RECIST v1.1 criteria will be summarised as the proportion of patients with each response category. Each patient will be assigned one of the following categories: complete response, partial response, stable disease, progressive disease, early death from malignant disease, early death from toxicity, early death from other cause or unknown (not assessable, insufficient data).

### Missing Data

Once a patient's clinical response has been reported as progressive disease (PD) according to RECIST v1.1, or the patient is withdrawn from the trial due to progression of trial disease, the patient's clinical response will be assumed to be PD for the subsequent trial visits if no disease response is reported.

### Pre-specified Subgroup Analysis

No subgroup analyses are planned beyond those inherent in the dose expansion cohort.

### Sensitivity Analysis

None specified.

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## 9. ANALYSES TO ADDRESS SECONDARY AIMS

### Evaluation/definition of Secondary

#### Dose escalation phase using PD-0325901 in combination with PF-02341066:

- (3) To define the recommended phase II dose and schedule (RP2) of the combination, guided by safety, PK and PD data.
- (4) To investigate pharmacokinetics (PK) of the drug combination by determining plasma  $C_{max}$ ,  $C_{min}$ , AUC, oral clearance and  $t_{1/2}$  etc. for PF-02341066 and PD - 0325901 and its metabolite.
- (5) To measure pharmacodynamic (PD) biomarkers of the drug combination using ELISA for soluble c-MET and HGF in plasma; ERK phosphorylation (pERK) in PBMC; Immunohistochemistry (IHC) for pERK1/2, and c-MET<sup>Y1234/1235</sup> in (mandatory) skin and (optional) tumour biopsies.
- (6) To preliminarily assess the efficacy of RP2 dose of the drug combination, using objective response from CT scan and modified RECIST version 1.1, and progression free and overall survival.

#### Dose escalation phase using Binimetinib in combination with PF-02341066:

- (3) To define the recommended phase II dose and schedule (RP2) of the combination, guided by safety, PK and PD data.
- (4) To investigate pharmacokinetics (PK) of the drug combination by determining plasma  $C_{max}$ ,  $C_{min}$ , AUC, oral clearance and  $t_{1/2}$  etc. for PF-02341066 and Binimetinib.
- (5) To measure pharmacodynamic (PD) biomarkers of the drug combination using ELISA for soluble c-MET and HGF in plasma; ERK phosphorylation (pERK) in PBMC; Immunohistochemistry (IHC) for pERK1/2, and c-MET<sup>Y1234/1235</sup> in (mandatory) skin and (optional) tumour biopsies.
- (6) To preliminarily assess the efficacy of RP2 dose of the drug combination, using objective response from CT scan and modified RECIST version 1.1, and progression free and overall survival.

#### Dose expansion phase:

- To assess the efficacy of RP2 dose of the combination of Binimetinib and PF-02341066 in patients with RASMT and RASWT/c-MET+ CRC, using objective response from CT scan and modified RECIST version 1.1, and progression free and overall survival.
- To further investigate the safety and toxicity profile/tolerability of the drug combination using adverse events according to NCI CTCAE V4.03 across all treatment cycles.
- To investigate pharmacokinetic (PK) biomarkers of the drugs in blood by determining plasma  $C_{max}$ ,  $C_{min}$ , AUC, oral clearance and  $t_{1/2}$  etc. for PF-02341066 and Binimetinib.
- To measure pharmacodynamic (PD) effect of PF-02341066 in combination with Binimetinib using ELISA for soluble c-MET and HGF in plasma; ERK phosphorylation (pERK) in PBMC; Immunohistochemistry (IHC) for pERK1/2, and c-MET<sup>Y1234/1235</sup> in skin and tumour biopsies.

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**Statistical Methods Used for Analysis of Secondary Aims**

The results of the two escalation parts will be summarised separately.

**Dose escalation phase:**

(3) If the MTD is not defined at the highest dose level to be explored, then this dose level will be defined as the RPII dose. If the MTD is defined at the highest dose level, then this will be defined as the RPII dose unless there are frequent dose interruptions or reductions after the DLT period at this level; then the dose level below will be defined as the RPII dose. Descriptive statistics of the patients receiving the MTD dose will be presented. Toxicities for cycle 1 for patients at the MTD dose will be summarised.

(4) Not covered here; to be carried out under a separate analysis plan.

(5) Not covered here; to be carried out under a separate analysis plan.

(6) Best response measured by RECIST v1.1 criteria, will be summarised as the proportion of patients with each response at each time point. Each patient will be assigned one of the following categories: complete response, partial response, stable disease, progressive disease, early death from malignant disease, early death from toxicity, early death from other cause or unknown (not assessable, insufficient data).

Progression free survival (PFS) at 6 months will be summarised and presented alongside a Kaplan-Meier plot. Overall survival (OS) at 6 months will also be summarised and presented alongside a Kaplan-Meier plot.

**Dose expansion phase:**

(7) Progression free survival (PFS) at 6 months will be summarised and presented alongside a Kaplan-Meier plot. Overall survival (OS) at 6 months will also be summarised and presented alongside a Kaplan-Meier plot.

(8) Safety and toxicity variables will be summarized by descriptive statistics within each genetically defined subgroup to investigate the safety and feasibility of expanded cohort patients at RPII dose. Worst toxicity grade per patient across all treatment cycles (using CTCAE criteria v4.03) will be summarised in tables grouped by cycle. The number of toxicities  $\geq$  Grade 3 per patient will also be summarised. Treatment related toxicity will be tabulated by type and grade of toxicity for each cycle.

(9) Not covered here; to be carried out under a separate analysis plan.

(10) Not covered here; to be carried out under a separate analysis plan.

**Additional Exploratory Analysis Not Specified Prior to Receiving Data**

Any analyses not specified in the analysis protocol will be exploratory in nature and a significance level of 0.01 will be used to declare statistical significance. 99% confidence intervals will be presented.

**10. SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS**

All AEs reported to the trial office will be processed according to internal SOPs. The trial office may request additional information for any AE as judged necessary.

All adverse events will be listed. The number of events and the number of patients reporting events will be summarised overall all and by system body class for SAEs, AEs with CTCAE grade  $\geq$  1 and AEs with CTCAE grade  $\geq$  3.

See protocol for definitions of AE/SAE/AR/SAR/SUSARs.