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: MErCuRIC1: MEK and MET Inhibition in Colorectal Cancer

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Confidentiality Statement
This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Trials Office, the Investigator Team, host NHS Trust(s), regulatory authorities, and members of the Research Ethics Committee.

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During office hours: Clinical Queries should be directed to the MErCuRIC Trial Office and contact the Clinical Trial Coordinator. The call will be passed on to the Chief Investigator or to the Clinical Coordinator (medically qualified) or an appropriate member of the Trial Management Group.

Out of office hours: call the Churchill Hospital switchboard on Tel: +44 (0) 1865 741 841 and ask to call the MErCuRIC Clinical Coordinator.

Patient Registration: See section 4.5

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PROTOCOL SYNOPSIS

Full Title of study:	MErCuRIC1: 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:	MErCuRIC1: MEK and MET Inhibition in Colorectal Cancer
Trial Acronym:	MErCuRIC1
Objectives:	**1a. Perform a dose escalation phase with combination PD-0325901 and PF-02341066:** **PRIMARY OBJECTIVES:** • To assess the safety and toxicity profile of PD-0325901/PF-02341066 combination in patients with advanced solid tumours using the NCI CTCAE V4.03, and determine the maximum tolerated dose (MTD). **SECONDARY OBJECTIVES:** • To define the recommended phase II (RPII) dose and schedule of PD-0325901 in combination with PF-02341066. • To investigate the pharmacokinetics (PK) of PD-0325901 with PF-02341066 when administrated in combination. • To investigate pharmacodynamic (PD) biomarkers of PD-0325901 and PF-02341066 in paired skin biopsies, tumour biopsies (where possible), in serum and PBMCs. • To preliminarily assess the efficacy of RPII dose of PF-02341066 in combination with PD-0325901. **1b. Perform a further dose escalation phase with combination Binimetinib and PF-02341066:** **PRIMARY OBJECTIVES:** • To assess the safety and toxicity profile of Binimetinib/PF-02341066 combination in patients with advanced solid tumours using the NCI CTCAE V4.03, and determine the maximum tolerated dose (MTD). **SECONDARY OBJECTIVES**: • To define the recommended phase II (RPII) dose and schedule of Binimetinib in combination with PF-02341066. • To investigate the pharmacokinetics (PK) of Binimetinib with PF-02341066 when administrated in combination. • To investigate pharmacodynamic (PD) biomarkers of Binimetinib and PF-02341066 in paired skin biopsies, tumour biopsies (where possible), in serum and PBMCs. • To preliminarily assess the efficacy of RPII dose of PF-02341066 in combination with Binimetinib. **2. Perform a dose expansion cohort phase:** **PRIMARY OBJECTIVES:** • To investigate the response to treatment with RPII dose of PF-02341066 in combination with Binimetinib in patients with a) RAS mutant (MT) and b) RAS wild type (WT) c-METmut/amplified CRC and c) RAS wild type (WT) c-MET overexpressed CRC.

	SECONDARY OBJECTIVES: • To assess the efficacy of RPII dose of PF-02341066 in combination with Binimetinib in patients with a) *RAS*MT and b) *RAS*WT/c-MET mut/amplified CRC and c) RASWT/c-MET over-expressed CRC. • To further investigate the safety and toxicity profile/tolerability of Binimetinib and PF-02341066 combination. • To investigate pharmacokinetic (PK) biomarkers of PF-02341066 and Binimetinib in blood. • To measure pharmacodynamic (PD) effect of PF-02341066 in combination with Binimetinib in paired skin biopsies, tumour biopsies, plasma and PBMCs. **TERTIARY AND EXPLORATORY OBJECTIVES:** • To identify molecular signatures of response and resistance to combined PF-02341066 and PD-0325901 treatment. • To identify molecular signatures of response and resistance to combined PF-02341066 and Binimetinib treatment. • Develop a liquid biopsy platform for routine assessment of therapeutic efficacy
Scientific rationale:	To identify novel targets/pathways critical for the survival of *RAS*MT tumours, both basally and following MEK inhibitor (i) treatment, we have employed a systems biology approach, comprising gene expression profiling, metacore pathway analysis and siRNA screening. We found that JAK1/2-STAT3 and the upstream receptor tyrosine kinase c-MET are important pro-survival signals in *RAS*MT CRC (Van Schaeybroeck et al, Cancer Cell, in revision). Further studies indicated that c-MET is acutely activated following MEK1/2 inhibition in *RAS*MT CRC cells. c-MET silencing (using different siRNA sequences and/or the small molecule inhibitor crizotinib (PF-02341066) strongly decreased basal and MEK1/2-induced c-MET and JAK/STAT3 activity and resulted in potent increase in cell death when combined with the MEK1/2 inhibitor AZD6244 in *RAS*MT CRC cells. Importantly, combining PF-02341066 with the MEKi AZD6244 resulted in synergistic reduction in tumour growth in *RAS*MT xenograft models. These *in vitro* and *in vivo* data support the further clinical evaluation of combined MEKi/METi treatment to combat metastases in *RAS*MT CRC patients.
Clinical rationale:	Standard of care for treatment of mCRC in first and second line involves the use of 5-FU-containing regimens in combination with either Irinotecan (FOLFIRI) or Oxaliplatin (FOLFOX) (De Gramont, 2000; Douillard, 2000). However, development of resistance occurs in the vast majority of patients. There are activating mutations in exon 2, 3 or 4 of *KRAS* or *NRAS* in approximately 55-60% of CRC patients (*RAS*MT), while 40-45% exhibit a wild type genotype (*RAS*WT). Employing *RAS* mutational status as a selection tool for EGFR monoclonal antibody (MoAb) therapies has led to significant improvement in both PFS and OS in patients with *RAS*WT tumours, but has shown no benefit in those patients harbouring *RAS*MT metastases (Lievre, 2006). In addition, only 40-50% of wild-type *RAS* patients respond to anti-EGFR MoAbs (De Roock, 2011). Thus, clinicians now have an urgent need to better understand the biologies of both *RAS*MT and *RAS*WT disease, in order to devise effective therapies in these defined genetic settings. Thus, a significant requirement exists to identify new modalities of tumour biology targeted therapy, both for 50% of mCRC patients with *RAS*WT tumours and 100% of patients with *RAS*MT metastases.
Primary Endpoint:	**Dose escalation phase using PD-0325901 in combination with PF-02341066:** • Maximal tolerated dose (MTD) of PD-0325901 with PF-02341066 according to toxicities graded by NCI CTCAE v4.03 in cycle 1 of treatment. **Dose escalation phase using Binimetinib in combination with PF-**

	02341066: • Maximal tolerated dose (MTD) of Binimetinib with PF-02341066 according to toxicities graded by NCI CTCAE v4.03 in cycle 1 of treatment. **Dose expansion phase:** • Clinical and radiological response to Binimetinib with PF-02341066 as defined by stable, partially or completely responding disease using RECIST version 1.1.
Secondary Endpoints:	**Dose escalation phase using PD-0325901 in combination with PF-02341066:** • To define the recommended phase II dose and schedule (RPII) of the combination, guided by safety, PK and PD data. • 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. • 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$^{Y1234/1235}$ in (mandatory) skin and (optional) tumour biopsies. • To preliminarily assess the efficacy of RPII 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:** • To define the recommended phase II dose and schedule (RPII) of the combination, guided by safety, PK and PD data. • 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. • 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$^{Y1234/1235}$ in (mandatory) skin and (optional) tumour biopsies. • To preliminarily assess the efficacy of RPII 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 RPII dose of the combination of Binimetinib and PF-02341066 in patients with RASMT and RASWT/c-MET+ CRC for 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 Cmax, Cmin, AUC, oral clearance and t1/2 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 in skin (Western blotting) , and c-

	METY1234/1235 in skin and tumour biopsies.
Exploratory and Tertiary Endpoints:	• Whole exome sequencing and miRNA profiling on tumour biopsies taken prior to treatment and upon resistance to PF-02341066 and PD-0325901 treatment. • Whole exome sequencing and miRNA profiling on tumour biopsies taken prior to treatment and upon resistance to PF-02341066 and Binimetinib treatment. • Gene sequencing outputs from ctDNA in serially collected plasma samples from mCRC patients in the dose expansion phase.
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. Once the RPII dose has been identified this will be followed by a dose expansion phase recruiting patients with a) *RAS*MT metastatic CRC or b) *RAS*WT/c-METmut/amplified metastatic CRC or c) RASWT/c-MET over-expressed metastatic CRC who will receive the combined study treatment of PF-02341066 with Binimetinib. All patients in the *RAS*WT group will receive full c-MET testing prior to recruitment to detect: (a) overexpression at protein level (IHC), (b) overexpression at mRNA level (RNAscope), (c) MET amplification, and (d) MET mutation. This would allow us to assess the potential correlation between MET amplification or mutation and MET protein/mRNA overexpression, and, importantly, to assess initial benefit from this treatment in each of two different molecular groups independently: cohorts (b) *RAS*WT CRC with amplification or mutation c-MET gene or c) *RAS*WT CRC with over-expression of c-MET on protein or mRNA) **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. 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. **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. The definition of MTD is clearly outlined in the protocol and will be discussed and agreed at regular teleconferences throughout the dose escalation phase of the study. Once the MTD has been defined, dosing at a higher dose must not occur. It is now anticipated that up to 25 patients will be required for the dose escalation phase of the study. Successful first phase of dose escalation triggers preparation of participating centres for the dose expansion phase of the study. **2. Dose expansion phase of study** Once the RPII dose and schedule have been identified, up to 40 patients (22

	patients only for stage 1) with *RAS*MT CRC, up to 29 patients with *RAS*WT/c-METmut/amplified CRC (10 patients only for stage 1) and up to 29 with RASWT/c-MET over-expressed CRC (10 patients only for stage 1) will be enrolled in the RPII dose expansion phase to study the safety, PK, PD and treatment response. This phase of the study is organised over 2 phases where patients will only be recruited to Stage 2 for each cohort where evidence of responsiveness is shown at Stage 1. 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 $pMET^{Y1234/1235}$) before and after combination treatment. Other PD endpoints include sMET, sHGF in plasma and IHC for pERK1/2 in skin biopsies (for first 10 patients) 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.
Patient Numbers:	25 evaluable patients with solid tumours were recruited in order to reach the MTD for the initial dose escalation phase of the study using PF-02341066 with PD-0325901. It is anticipated that up to 25 patients will be required for the further dose escalation phase of the study using the combination of PF-02341066 with Binimetinib. The dose expansion phase will include 3 cohorts where up to 22-40 patients will be required for the *RAS*MT cohort and 10-29 each for the *RAS*WT/c-METmut/amplified CRC and RASWT/c-MET over-expressed *CRC* cohorts. The total patient number for the study will be between 92 - 148.
Target Population:	**Dose escalation phase** Adult patients with pathologically proven, advanced and incurable solid tumours for whom use of the combination of a MEK and c-MET inhibitor are considered to be a reasonable option according to clinical opinion. **Dose Expansion phase** Adult patients with a) *RAS*MT CRC or b) *RAS*WT/c-METmut/amplified CRC or c) RASWT/c-MET over-expressed *CRC*. In view of the mandatory tumour biopsies, all patients must have accessible metastatic sites suitable for biopsy and must consent to repeated biopsies.
Inclusion and exclusion criteria	**INCLUSION CRITERIA** (Inclusion criteria for the completed initial dose escalation phase using PF-02341066/PD-0325901 are listed in Appendix 7.) ***All patients*** – Age ≥ 16 years – ECOG performance status 0-1 (Appendix 1) – Adequate respiratory function on clinical assessment – Left ventricular ejection fraction (LVEF) ≥ 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) ≥ 9g/dl (transfusion to achieve this allowed), – Neutrophils ≥ 1,500/µl, – Platelet count ≥ 100,000/µl, – AST or ALT ≤ 2.5 x ULN, patient with liver metastases ≤ 5 × ULN, – Alkaline phosphatase ≤ 5 x ULN, – Serum Bilirubin ≤ 1.5 x ULN,

	– Creatinine Clearance ≥ 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:*** – 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 this phase 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 either a) *RAS*MT (KRAS codon 12, 13, 61, 117, 146; NRAS codon 12, 13, 61, 117, 146) mutations) or b) *RAS*WT/c-MET mutated or amplified CRC or c) RASWT/c-MET over-expressed with progressive disease on or within 6 months of completion of adjuvant therapy or after chemotherapy and/or targeted therapies for metastatic disease. – Prior treatment with an EGFR targeted monoclonal antibody for patients with *RAS*WT/c-MET mutated or amplified CRC or RASWT/c-MET over-expressed. – 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 echocardiogram (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 ECHO in the UK.** **EXCLUSION CRITERIA** (Exclusion criteria for the completed initial dose escalation phase using PF-02341066/PD-0325901 are listed in Appendix 7.) ***All patients*** – Unstable ischaemic 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 ≥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 ≥ 3 months. Patients must be off corticosteroid therapy for ≥ 3 weeks. – 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 e.g. 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. – Patients who have undergone major surgery ≤ 3 weeks prior to starting study drug or who have not recovered from side effects of such procedure. – Use of drugs or foods that are known potent CYP3A4 inhibitors or inhibitors 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 (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 pregnancy test before enrolment and agree to use one highly effective form of contraception (oral, injected or implanted hormonal contraception or intra-uterine device) in addition to 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 one form of highly effective contraception including oral, injected or implanted hormonal contraception or intra-uterine device) in addition to 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) to prevent exposure to the foetus or neonate. – Prior exposure to any of a HGF, cMET or a MEK inhibitor.
Trial dose and administration:	**Dose escalation phase: PF-02341066 in combination with PD-0325901** In this non-randomised study, patients with advanced solid tumours will be recruited where no potentially curative surgery is planned. 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 3. 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 capsules will be taken orally, once or twice daily on a continuous schedule. **Dose escalation phase: PF-02341066 in combination with Binimetinib** In this non-randomised study, patients with advanced solid tumours, where no potentially curative surgery is planned, will be recruited. 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 *RAS*MT, *RAS*WT/c-MET mut/amplified CRC or RASWT/c-MET over-expressed *CRC* tumours will be recruited. The RPII dose and schedule of PF-02341066 in combination with Binimetinib will be used in this part of the study. No randomisation or dose escalation will be carried out, but dose reduction or delay for toxicities will be allowed. In the dose expansion phase, patients will undergo a biopsy of a representative metastasis for c-MET testing, mutational analysis and pharmacodynamic studies. *RAS* mutational status will be determined on archival tumour tissue or a fresh biopsy if archival material is not available. CT imaging to assess disease status will be performed every 8 weeks (2 x 28 day cycles) during the study until subjects withdraw, cannot tolerate therapy or have progression of disease, as defined by RECIST v1.1 or clinically. At this time, patients who have given their consent will undergo a biopsy of a tumour metastasis for further mutational analysis. Blood samples for detection of ctDNA will be obtained every 4 weeks.

Duration on study:	Patients will continue on study (with appropriate dose delay and/or modification if necessary) until disease progression, intolerable side effects or they choose to withdraw. We estimate that the median time to progression in the expansion cohort will be 6 months.
Study Procedures and frequency:	**Dose escalation phase using PD-0325901 in combination with PF-02341066** Detailed adverse event monitoring will be conducted according to CTCAE v4.03 (or version 5.0 if this becomes available before the trial starts). The dose limiting toxicity (DLT) is defined as any adverse event or laboratory abnormality considered to be related to PF-02341066 or PD-0325901 that begins in the first treatment cycle. In the dose escalation stage patients will undergo pharmacokinetic blood testing as per the timelines outlines in section 7.3. Patients will be reviewed on day 1 of every cycle with ECG and safety bloods. An echocardiogram will be performed at screening and repeated as clinically indicated. Serum CEA and cross-sectional imaging will be performed every 2 cycles. Ophthalmologic testing will be performed at screening, in cycle 1 and repeated as clinically indicated. PBMC/plasma samples for PD assessment will be obtained on days 1, 2, 15 and 16. Fresh skin (mandatory) and tumour (optional) biopsies for PD assessment will be performed at screening. A second mandatory skin biopsy will be performed during cycle 1 on day 15. Upon disease progression, patients will undergo an optional, second biopsy of a tumour metastasis for further mutational analysis. Patients will be followed up until progression or death or study closure depending on which happens first. **Dose escalation phase using Binimetinib in combination with PF-02341066** Detailed adverse event monitoring will be conducted according to CTCAE v4.03 (or version 5.0 if this becomes available before the trial starts). The dose limiting toxicity (DLT) is defined as any adverse event or laboratory abnormality considered to be related to PF-02341066 or Binimetinib that begins in the first treatment cycle. In the dose escalation stage patients will undergo pharmacokinetic blood testing as per the timelines outlines in section 7.3. Patients will be reviewed on day 1 of every cycle with ECG and safety bloods. An echocardiogram or MUGA will be performed at screening, at 3 weeks, and then every 8 weeks until cycle 5, after which they will be performed every 12 weeks. At any time necessary, an echocardiogram or MUGA will be repeated as clinically indicated. Serum tumour marker sampling and cross-sectional imaging will be performed every 2 cycles. Ophthalmologic testing will be performed at screening, and then every 8 weeks until cycle 6, after which they will be performed every 12 weeks. At any time necessary, ophthalmic testing will be repeated as clinically indicated. PBMC/plasma samples for PD assessment will be obtained on days 1, 2, 15 and 16. Fresh skin (mandatory) and tumour (optional) biopsies for PD assessment will be performed at screening. A second mandatory skin biopsy will be performed during cycle 1 on day 15. Upon disease progression, patients will undergo an optional, second biopsy of a tumour metastasis for further mutational analysis. Patients will be followed up until progression or death or study closure depending on which happens first. **Dose expansion phase** All patients will undergo safety assessments as outlined for the PF-02341066 and Binimetinib dose escalation group. Pharmacokinetic sampling, serum tumour marker sampling and CT scans will be carried out as outlined for the dose escalation phase. Patients will undergo a biopsy of representative metastases for c-MET testing, mutational analysis and PD analysis at screening. Mandatory fresh skin biopsies for an initial cohort of 10 patients and PD assessment for all patients will be obtained at screening and on day 15 of cycle 1. For those patients who have consented, upon disease progression patients will undergo a biopsy of a metastasis for further mutational analysis. Blood samples for detection of ctDNA will be obtained every 4 weeks.
Patient care post-trial:	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.
Criteria for evaluation:	
Efficacy:	Disease status will be monitored according to RECIST version 1.1.
Safety:	Safety and toxicity will be reported using NCI CTCAE (currently version 4.03).
Pharmacokinetic assays:	**For Dose Escalation phase using PF-02341066 with PD-0325901:** Analysis of plasma samples for the determination of PF-02341066 (crizotinib) and PD-0325901 (and its carboxylic acid metabolite, PD-0315209, M15) will be carried out to ensure that the putative target level to inhibit p-cMET and pERK1/2 is met when PF-02341066 is combined with PD-0325901. Blood samples will be centrifuged to generate plasma. Plasma concentrations of PF-02341066, PD-0325901 and M15 will be determined using a validated HPLC-MS/MS assay following solid-phase extraction of the plasma sample. **For Dose Escalation phase and Dose Expansion phase using PF-02341066 with Binimetinib**: Analysis of plasma samples for determination of PF-02341066 and Binimetinib will be carried out to ensure that the putative target level to inhibit p-cMET is met when PF-02341066 is combined with Binimetinib. Plasma concentrations of PF-02341066 and Binimetinib will be determined using a validated HPLC-MS/MS assay following solid-phase extraction of the plasma sample.
Pharmacodynamic assays:	We will investigate the impact of the MEK and MET inhibitors on established histological markers. a. In both dose escalation phases, only, a PBMC/plasma sample for PD assessment will be obtained on cycle 1 on days 1, 2, 15 and 16. The inhibitory effect of PD-0325901/Binimetinib on pERK, the only known substrate for MEK, will be assessed in PBMCs. b. In both dose escalation and dose expansion phase a plasma sample for PD assessment will be obtained on cycle 1 on days 1, 2, 15 and 16. The plasma sample: plasma levels of HGF Scatter factor and soluble c-Met ectodomain will be assessed at baseline and following treatment with PF-02341066. c. Fresh skin biopsy for PD assessment is mandatory for both dose escalation phases as well as for an initial cohort of 10 patients in the dose expansion phase of the study. We will analyse pERK1/2 and $pMET^{Y1234/1235}$ by Western blotting in skin biopsy at pre-dose and on cycle 1 day 15, 3-6 hours following dosing. In addition, We will also study pAKT and other markers of proliferation and apoptosis such as KI67 and caspase3. d. Tumour biopsy for PD analysis is mandatory in the expansion phase only and optional in both of the dose escalation phases. A further metastatic tumour biopsy is an optional sample taken at disease progression in the dose expansion phase only. In the dose escalation and dose expansion phase we will analyse pERK1/2 and $pMET^{Y1234/1235}$ by IHC in tumour biopsy pre-dosing and on cycle 1 day 15, 3-6 hours following dosing. In addition, we will also study pAKT and other markers of proliferation and apoptosis such as KI67 and caspase3. **Biomarker/translational endpoints** Dose Expansion Phase: In order to identify molecular signatures of sensitivity and resistance to PF-02341066 and Binimetinib treatment in the a) *RAS*MT CRC and b) *RAS*WT/c-METmut/amplified CRC and c) RASWT/c-MET over-expressed *CRC*groups, a biopsy from a representative metastasis (minimal 2 cores: one for FFPE and one for fresh frozen (FF) material) will be obtained prior to treatment. An H&E section will be obtained from each formalin-fixed paraffin embedded

	(FFPE) core to histologically confirm CRC metastasis. Total c-MET expression levels will be determined by IHC on section of FFPE core. Computerised image analysis as well as conventional scoring will be carried out on the IHC samples. *RAS* mutational analysis will be determined on primary tumour. In addition, we will also use a commercially available platform from MTP (Multiplicom) to detect mutations in RAS, BRAF, NRAS, PTEN, EGFR, PI3KCA, ERBB2, PIK3R1, MET and MEK. Exome sequencing and miRNA profiling will be performed to identify molecular signatures of response and resistance to combined MEKi/METi treatment. A whole blood sample for germline DNA and ctDNA analyses will be obtained prior to treatment. Patients who demonstrate a response to PF-02341066 and Binimetinib (as determined by RECIST 1.1), but then develop secondary resistance, will undergo a second biopsy (2 cores for fresh frozen and 1 core for FFPE material) from a metastasis. Additional plasma samples for ctDNA analyses will be collected every 4 weeks during the course of treatment, and after patients acquire resistance to therapy. We will use next generation sequencing (NGS) to detect and monitor specific genetic markers present in ctDNA that have been identified in the mandatory baseline biopsies that are scheduled upon enrolment in the trial.
Histopathology:	**Dose Escalation Phase**: patients will have histologically or cytologically confirmed solid tumour **Dose Expansion Phase:** patients will have histologically confirmed colorectal cancer. An H&E section will be obtained from each formalin-fixed paraffin embedded (FFPE) core to histologically confirm CRC metastasis.c-MET expression levels (Ventana, 790-4430) will be measured in CRC metastases and primary tumour.
No. of Study Site(s)	5 for dose escalation cohorts, increasing to 8 -10 in total for the expansion cohorts.
End of study	Last patient last visit (LPLV)
Early closure of recruitment	Recruitment to the trial closed on 23Oct2018 with 82 patients recruited following significant difficulties encountered in recruiting to the Dose Expansion Phase RAS WT CRC patient cohorts within the constraints of the EU grant supporting the trial. The decision was made by the TMG with the support of the FP7 consortium members and trial sponsor, the University of Oxford.
Publication policy	The results of this study will be published in a peer-reviewed scientific journal and presented in academic research meetings as outlined in the grant agreement of the EU commission.

SUMMARY SCHEDULE OF EVENTS

Note: The Schedule of Events table for the Dose Escalation phase using PF-02341066 with PD-0325901 is located in Appendix 9

Dose Escalation Phase - Schedule of Events for PF-02341066 and Binimetinib

Visit Description	Screening	Cycle 1							Cycle 2				Cycle 3				Cycle 4				Cycle 5 onwards	End of Treatment [p]	Post end of treatment	Follow Up
Visit No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	17	19	20				
Day	-28 to 1	D1	D2	D8	D15	D16	D21	D22	D1	D8	D15	D21	D1	D8	D15	D21	D1	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 [a]	X	X		X	X		X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Tumour Assessment [b]	X												X									X		
Vital signs [c]	X	X		X	X		X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Height & Weight [d]	X	X		X	X		X		X				X				X					X	X	
Ophthalmic Exam [e]	X											X								X		X		
Haem & Clin Chem Bloods [f]	X	X			X				X				X				X					X	X	
Urinalysis	X	X			X				X				X				X					X	X	
Pregnancy test [g]	X	X							X				X				X					X		
12 lead ECG	X	X			X				X				X				X					X	X	
Echocardiography/MUGA [-h]	X						X									X								
Inclusion/exclusion criteria	X																							
Tumour marker [i]	X												X									X		
PK 24 hours profile [j]							X	X																
PK trough [k]												X								X				
PD PBMC/plasma [l]		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
Binimetinib administration		**Continuous administration or Days 1-21 every 28 days**																						
PF-02341066 administration		**Continuous administration**																						
Survival data (PFS and OS)																							X	X
Biomarker studies																								
Archival tumour sample	X																							
Blood sample germline DNA	X																							
PD skin biopsy [m]	X				X																			
PD tumour biopsy [n]	X				X																			
Plasma soluble biomarkers [o]		X			X				X		X		X				X							

Repeat cycle 3 and 4

[a] To include neurological examination.

[b] 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.
[c] To include pulse and systolic/diastolic blood pressure, body temperature. Blood pressure is to be measured after resting for 5 minutes in a sitting position.
[d] Height measured only at screening.
[e] Ophthalmic exam at baseline, and Day 21of 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
[f] 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, CK, Troponin, (validity period of blood samples is 3 days).
[g] Serum pregnancy test to be performed at screening and urine pregnancy test required every 3-4 weeks for women of child-bearing potential
Echo or MUGA at baseline and at Day 21 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.
[i] 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
[j] Serum PK measurements will be taken as specified in the protocol (section 7.3).
[k] PK trough sample pre-dose (morning) and 2 hours post dose Day 21 of cycles 2, 4, 6, 8, 10 and 12.
[l] PD PBMC/Plasma samples will be taken as specified in the protocol (section 7.4)
[m] At screening and Day 15 +/- 7 days.
[n] At screening and Day 15 +/- 7 days. Optional biopsy if separate consent obtained.
[o] At each sampling point 4ml of plasma is obtained.
[p] Disease progression, intolerance or withdrawal.

Dose Expansion Phase - Schedule of Events for PF-02341066 and Binimetinib

Visit Description	Pre-Screen	Screening	Cycle 1							Cycle 2				Cycle 3				Cycle 4				Cycle 5 onwards	End of Treatment [r]	Post end of treatment	Follow up
Visit No	0	1	2		3	4		5	6	7	8	9	10	11	12	13	14	15	16	17	18				
Day		-28 to -1	D1		D8	D15		D21	D22	D1	D8	D15	D21	D1	D8	D15	D21	D1	D8	D15	D21			D 28-30 post dose	
Informed Consent	X [a]	X																							
Demographics & History	X	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 [b]		X	X		X	X		X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Tumour Assessment [c]		X												X									X		
Vital signs [d]		X	X		X	X		X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Height & Weight [e]		X	X		X	X		X		X				X				X					X	X	
Ophthalmic Exam [f]		X											X								X	Repeat cycle 3 and 4	X		
Haem & Clin Chem Bloods [g]		X	X			X				X				X				X					X	X	
Urinalysis		X	X			X				X				X				X					X	X	
Pregnancy test [h]		X	X							X				X				X					X		
12 lead ECG		X	X			X				X				X				X					X	X	
Echocardiography/MUGA [i]		X						X									X								
Inclusion/exclusion criteria		X																							
Tumour marker [j]		X												X									X		
PK 24 hours profile [k]								X	X																
PK trough [l]													X								X				
AE review			X		X	X		X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Binimetinib administration			X	Continuous administration or Days 1-21 every 28 days																					
PF-02341066 administration			X	Continuous administration																					
Survival data (PFS and OS)																									X [m]
Biomarker studies																									
Archival tumour sample	X [a]	X																							
Tumour (CRC Mets)sample	X [a]																								
Blood sample germline DNA		X																							
PD skin biopsy [n]		X				X																			
PD tumour biopsy [o]		X				X																		X [s]	
Plasma soluble biomarkers [p]			X			X						X		X				X							
Plasma sample for ctDNA [q]			X							X				X				X					X		

[a] Pre-trial screening for c-MET and *RAS* status
[b] To include neurological examination.
[c] 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
[d] to include pulse and systolic/diastolic blood pressure and body temperature (Blood pressure to be measured after resting for 5 minutes in a sitting position.)
[e] Height to measured only at screening.
[f] Ophthalmic exam at baseline, and at Day 21 cycles 2, 4, 6 and 9 and every third cycle (12 weekly) after this and also as clinically indicated. This has an allowed time window of +/- 2 days
[g] 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, CK, Troponin (validity period of bloods is 3 days).
[h] Serum pregnancy test at screening and serum or urine pregnancy testing required every 3-4 weeks for women of child-bearing potential.
[i] Echo/MUGA at baseline and at Day 21of 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.
[j] Tumour markers (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
[k] Serum PK measurements will be taken as specified in the protocol (section 7.3)
[l] PK trough sample pre-dose (morning) and 2 hours post dose day 21 of cycles 2, 4, 6, 8, 10 and 12
[m] Survival status to be updated every 3 months post end of trial until death notification
[n] At screening and Day 15 +/- 7 days for initial cohort of 10 patients only
[o] At screening and Day 15 +/- 7 days. Also optional biopsy of metastases at disease progression
[p] At each sampling point 4ml of plasma obtained.
[q] Blood samples for the detection of ctDNA will be obtained every 4 weeks until disease progression.
[r] Disease progression, intolerance or withdrawal.
[s] Optional. Within 28 days following radiological confirmation of disease progression

ABBREVIATIONS

AE	Adverse Event
ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AST	Aspartate Transaminase
AUC	Area Under the Curve
BAL	Bronchoalveolar Lavage
BD	Bi Daily
BHSCT	Belfast Health and Social Care Trust
BNP	B-type Natriuretic Peptide
BRAT	Mnemonic for bananas, rice, apple and toast
CCRCB	Centre for Cancer Research and Cell Biology
CEA	Carcinoembryonic Antigen
CHF	Congestive Heart Failure
CI	Chief Investigator
CK	Creatinine Kinase
CML	Chronic Myeloid Leukaemia
CNS	Central Nervous System
CR	Complete Response
CRC	Colorectal cancer
CRF	Case Report Form
CSR	Central Serous Retinopathy
CT	Computerized Tomography
ctDNA	Circulating tumour DNA
CTA	Clinical Trials Authorisation
CTA	Clinical Trial Agreement
CTCAE	Common Toxicity Criteria Adverse Events
CTIMP	Clinical Trial of an Investigational Medicinal Product
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DSMC	Data & Safety Monitoring Committee
DSUR	Development Safety Update Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELISA	Enzyme-Linked ImmunoSorbant Assay
EMA	European Medicines Agency
EGFR	Epidermal growth factor receptor
EP	Early Progression
ERK	Extracellular-Signal-Regulated Kinases
EU	European Union
FBC	Full Blood Count
FDA	Federal Drug Administration
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FFPE	Formulin-fixed Paraffin Embedded
GAPs	GTPase Activating Proteins
GCP	Good Clinical Practice
GEPs	Guanine Nucleotide Releasing Factors
GI	Gastro-Intestinal
GMP	Good Manufacturing Practices
Hb	Haemoglobin
HCG	Human Chorionic Gonadotrophin
HDPE	High-density PolyEthylene
HGF	Hepatocyte growth factor
HGFR	Hepatocyte growth factor receptor
HIV	Human Immunodeficiency Virus
HTA	Human Tissue Act
IB	Investigator Brochure
IC_{50}	50% Inhibitory Concentration

IEPTOC	Independent Early Phase Trial Oversight Committee
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
iV	Intravenous
RAS	Rat Sarcoma
KPS	Karnofsky Performance Score
LVEF	Left-Ventricular-Ejection-Fraction
LDH	Lactate Dehydrogenase
LPLV	Last Patient Last Visit
mCRC	Metastatic Colorectal Cancer
MEK	Mitogen Activated Protein Kinase
MHRA	Medicines and Healthcare products Regulatory Agency
MoABs	Monoclonal Antibodies
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MU	Mazaryk University
MUGA	Multigated Acquisition
NCI	National Cancer Institute
NE	Not Evaluable
NGS	Next Generation Sequencing
NHS	National Health Service
NIMP	Non-Investigational Medicinal Product
NSCLC	Non-Small cell Lung Cancer
OCTO	Oncology Clinical Trials Office
OCTRU	Oxford Clinical Trials Research Unit
OD	Once Daily
ORB	Oxford Radcliffe Biobank
OS	Overall survival
PD	Pharmacodynamic **or** Progressive Disease
PDUM	Paris Descartes Universite Medecine
PFS	Progression Free Survival
PI	Principal Investigator
PK	Pharmacokinetic
PBMC	Peripheral blood mononuclear cells
PO	Per Os
PR	Partial Response
QP	Qualified Person
QT	QT interval
QTc	Corrected QT interval
QUB	Queen's University Belfast
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria In Solid Tumours
RPII	Recommended phase II dose
RR	Response Rate
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SD	Stable Disease
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
Tdp	Torsades De Pointes
TPN	Total Parenteral Nutrition
TSC	Trial Steering Committee
ULN	Upper Limit of Normal
UNITO	Italian Università degli Studi di Torino
USS	Ultrasound Scan
UZA	Universitair Ziekenhuis Antwerpen
VHIO	Vall Hebron Institute of Oncology
WBC	White Blood Count

1 INTRODUCTION

1.1 Background

Disease background

Colorectal cancer (CRC) is a significant health issue for men and women worldwide, with > 1 million cases and over 680,700 deaths each year (Malvezzi et al., 2011). In the European Union (2008), 334,092 new patients (151,478 women / 182,614 men) were diagnosed with CRC and 149,159 patients (68,999 women/80,160 men) died of the disease http://globocan.iarc.fr) (Jemal et al., 2010). Approximately 450,000 new cases of CRC will be diagnosed within Europe and 143,460 in the US in 2012 (Siegel et al., 2013). In addition, with an estimated 232,000 deaths in 2012 (Europe) and approximately 51,690 deaths (US), CRC remains the second most common cause of cancer death within the Western world (Siegel et al., 2013). The incidence increases significantly with age, with >80% of cases occurring in the 60 years or older population. Given the ageing population in Europe, CRC's already considerable health and societal burden is expected to increase significantly. Metastatic colorectal cancer (mCRC) is a malignancy with a dismal overall survival (OS) rate. Due to its asymptomatic nature, CRC is frequently diagnosed only after cancer has spread to the lymph nodes (stage III) and/or distant organs (stage IV), eg liver, lung, peritoneum.

Treatment background

Standard chemotherapy for advanced CRC include combination of 5-Fluorouracil (5-FU) with Irinotecan (FOLFIRI) or Oxaliplatin (FOLFOX). Resistance to chemotherapy, either intrinsic or acquired, ultimately results in treatment failure for the majority of CRC patients. Approximately 50% of CRC patients eventually develop metastases (stage IV disease, mCRC) and receive systemic chemotherapy, with 5-year OS rates lower than 5%. For chemotherapy-naive mCRC patients, response rates (RR) are ~40%-50% (FOLFOX, FOLFIRI) while median OS are ~16-19 months (de Gramont et al., 2000; Douillard et al., 2000). When FOLFIRI/FOLFOX is given as 2nd line treatment, RR is 10-15%, progression-free survival (PFS) is 4 months and OS is 10-11 months respectively (Guglielmi and Sobrero, 2007).
Recently, the treatment paradigm for mCRC has evolved to include targeted therapeutics. The Epidermal growth factor receptor (EGFR) signalling pathway is of key importance for the survival of CRC and other cancer cells (Laurent-Puig et al., 2012; Peeters et al., 2010; Van Schaeybroeck et al., 2005). These findings have led to the development of therapeutic monoclonal antibodies (MoAbs) (eg. chimeric MoAb cetuximab and fully human MoAb panitumumab), that inhibit ligand binding to the EGFR and subsequently EGFR activation and downstream signalling. Cetuximab and panitumumab have significantly improved PFS and OS when combined with FOLFIRI in patients with chemo-naive metastatic stage IV CRC patients (Berlin et al., 2007; Van Cutsem et al., 2011). Historically, "one-size-fits-all" approaches have been standard practice in CRC treatment, but with the increased understanding of the molecular/genetic heterogeneity of CRC, it is clear that novel treatments must be developed and tested in selected subgroups to maximize the benefit of these new developments.

RAS as a predictive biomarker in CRC

The RAS guanosine triphosphate (GTP)-ases act as critical "on-off" switches in cellular growth and survival (Ramjaun and Downward, 2007). RAS is activated by several receptor tyrosine kinases (RTKs), and is regulated by guanine nucleotide releasing factors (GEFs) and GTPase-activating proteins (GAPs). Active GTP-bound RAS interacts with a range of effectors to activate multiple downstream pathways, most notably the RAF/MEK/ERK and PI-3 kinase pathways. The RAS sub-family consists of three proto-oncogenes: *c-Harvey (H)*-ras, *c-Kirsten (K)*-ras, and *c-Neuroblastoma (N)*-ras (Reuther and Der, 2000). RAS functions downstream of EGFR and is a critical mediator of EGFR induced signalling. *RAS* genes become oncogenic by single point mutations, which alter the guanine nucleotide binding region, rendering RAS unresponsive to GAPs and resulting in constitutive RAS activation, aberrant downstream signalling, increased proliferation and survival.

The presence of activating *RAS/NRAS* mutations abolishes the ability of anti-EGFR drugs to inhibit cell survival signalling in cancer cells. *RAS* is mutated in 40%-45% of CRC (*RAS*MT*)*, and *RAS* mutations are associated with poorer survival in CRC (Richman et al., 2009). Several phase III studies, led by members of MErCuRIC, have shown that patients harbouring activating *RAS* and *NRAS* mutations (found in 4%-5% of CRC) do not benefit from anti-EGFR therapies (Maughan et al., 2011; Peeters et al., 2012; Peeters et al., 2010). These therapies represent a personalized medicine approach in CRC, as patients are stratified according to their *RAS* mutational status. The European Medicines Agency (EMA), the US Food and Drug Administration (FDA) and the American Society for Clinical Oncology (ASCO) now recommend that all mCRC patients who are candidates for anti-EGFR therapy should be tested for *RAS* mutations and, if a mutation is detected, they should not receive anti-EGFR therapies (Allegra et al., 2009).

The need for new therapeutic approaches in mCRC

Studies have also suggested that activating mutations in *BRAF*, *NRAS* and *PIK3CA,* loss of *PTEN* and expression of EGFR ligands epiregulin and amphiregulin, likewise correlated with resistance to anti-EGFR targeted therapies (Khambata-Ford et al., 2007; Perrone et al., 2009). Since its approval, cetuximab has become a €855 million p.a. drug, and > 50% of CRC patients are currently treated with anti-EGFR MoAb therapies (http://www. Firstwordpharma.com/node/1017862). Nevertheless, between 50%-60% of *RAS* Wild Type (*RAS*WT) or indeed quadruple WT patients (i.e. *KRAS*, *NRAS*, *BRAF*, *PI3KCA* WT with high levels of epiregulin and amphiregulin and no loss of *PTEN*) will not benefit from the addition of an EGFR MoAb to standard chemotherapy (De Roock et al., 2010). Hence, novel treatment strategies are urgently needed for *RAS*MT patients and >50% of *RAS*WT CRC patients, especially in second line where responses to standard chemotherapy are relatively low.

*RAS*MT mCRC patients have few therapeutic options post-chemotherapy failure. Inhibitors of farnesyl protein transferase (resulting in impaired RAS membrane localization and activity) as single agents failed to show significant activity in unselected patient groups in CRC and NSCLC (Adjei et al., 2003; Rao et al., 2004). Chemical library screens using isogenic *RAS*WT and MT cell lines have identified compounds exhibiting greater lethality in tumour cells harbouring mutations in *RAS (Guo et al., 2008; Ji et al., 2009).* Translation of these studies into the clinical setting has been impeded by the difficulty in identifying the protein target for these compounds, a prerequisite for further drug development. More recently, genome wide shRNA screens have unravelled novel biology associated with oncogenic *RAS,* but these studies have yet to be translated into the clinic (Barbie et al., 2009; Luo et al., 2009).

MErCuRIC is a pan-European collaboration to use a personalised medicine clinical trial strategy to target two key proteins, MEK and MET, which are deregulated in both *RAS* WT and *RAS* MT mCRC. The trial hypothesis is that inhibition of both MEK and MET in combination (MEKi)/METi), will improve PFS and ultimately OS in the stratified mCRC cohort. The comprehensive scientific dissection of disease biology will not only provide new insights on efficacy, but will also underpin development of new diagnostic and predictive tools to combat mCRC. The clinical trial has unique characteristics of (i) employing a novel treatment strategy targeting the biology of the disease; (ii) using next generation sequencing (NGS), miRNA and companion diagnostics strategies to identify/stage CRC patient subgroups who will maximally benefit from this novel treatment strategy and (iii) deploying (a) non-invasive detection tools (b) relevant preclinical models to underpin novel stratified solutions for patients with acquired drug-resistance.

1.2 Investigational Medicinal Products used in the study

The Investigational Medicinal Products (IMPs) in this trial are PF-02341066, PD-0325901 and Binimetinib. PF-02341066 (Crizotinib); Pfizer) has a Marketing Authorisation in the EU for the indication of previously treated ALK+ NSCLC (http://www.medicines.org.uk/EMC/medicine/27168/SPC/Xalkori+200mg+and+250mg+hard+capsule/) but is not authorised for use in colorectal cancer. PD-0325901 is a new chemical agent developed by Pfizer and is provided in capsule form. Binimetinib is a new chemical agent developed by Array Biopharma and is provided in tablet form.

PF-02341066 (Crizotinib)

PF-02341066 (Crizotinib) is a selective ATP-competitive small-molecule oral inhibitor of the anaplastic lymphoma kinase (ALK), c-Met/hepatocyte growth factor receptor (HGFR), Recepteur d'Origine Nantais (RON), and ROS receptor tyrosine kinases (RTKs) and their oncogenic variants (e.g., c-Met/HGFR mutations and ALK or ROS fusion proteins). PF-02341066 demonstrated a mean Ki value of 0.5 nM for inhibition of recombinant human ALK and a mean Ki value of 0.62 nM for inhibition of recombinant human c-Met/HGFR. PF-02341066 also demonstrated a mean Ki value of 9.1 nM for inhibition of the RON RTK which was approximately 20-fold higher than the Ki for inhibition of ALK.

PF-02341066 inhibited cell proliferation (EC50 = 54 nM) and induced apoptosis (EC50 = 110 nM) at concentrations comparable to those required to inhibit EML4- ALK phosphorylation (EC50 = 63 nM) in NCIH3122 lung adenocarcinoma cells expressing EML4-ALK variant 1. PF-02341066 also inhibited proliferation of Karpas 299 or SU-DHL-1 ALCL cells that express an NPM-ALK fusion protein due to a t(2;5) chromosomal translocation. Growth inhibition by PF-02341066 in these NPM-ALK positive lymphoma cells was associated with G0/G1 cell cycle arrest and induction of apoptosis. PF-02341066 has also been found to inhibit potently HGF (ligand for cMET)-stimulated human NCI-H441 lung carcinoma cell migration and invasion through a matrigel matrix (IC50 values of 11 nM and 6.1 nM, respectively), and HGF-stimulated MDCK cell motility/scattering (IC50 = 16 nM). PF-02341066 inhibited cell proliferation (EC50 = 59 nM) at concentrations comparable to those required to inhibit ROS phosphorylation (EC50 = 44 nM) in HCC78 lung

adenocarcinoma cells expressing the SLC34A-ROS fusion variant. *In vivo* PF-02341066 inhibited xenograft growth in a variety of models while inhibiting ALK or cMET activity.

PF-02341066 has a long $t_{1/2}$ (42 hrs), takes 15 days to reach steady-state and has stable exposure unaffected by body weight, gender, age, and race. PF-02341066 is excreted by the faecal route and is both a CYP3A substrate and inhibitor. The extent and duration of inhibition of c-MET is directly linked to its antitumor efficacy - near complete inhibition (>90%) of c-MET activity during the entire treatment period is necessary to achieve robust antitumor effects. PK/PD analyses established the target efficacious free plasma concentration range of 8.1 to 12.8 nM (40 – 62 ng/mL in human plasma) for c-MET (and approximately 2-fold greater for ALK inhibition). Vision disorders are seen in >50% (98% mild) of patients, so there is a need for baseline ophthalmic assessment which is repeated if patients become symptomatic. Expected toxicities (usually mild) include nausea, vomiting, diarrhoea, constipation, peripheral oedema, fatigue and rashes and oesophageal-related disorders, and significant myelosuppression is rare. Responses have been seen in c-MET aberrant tumours.

In a phase I study in patients with ALK-positive non-small-cell lung cancer, dose-limiting fatigue in the cohort receiving 300mg BD led to the establishment of a regimen of 250mg BD as the MTD (Camidge et al., 2012; Kwak et al., 2010). As a single agent for ALK+ve NSCLC, PF-02341066 is licensed for use at 250mg BD. If this is not tolerated, the suggested dose reductions are 200mg BD, then 250mg once daily (OD), then to permanently discontinue. Available capsule sizes are 200mg and 250mg, with no current availability for the previous 150mg formulation. Doses of 200 mg or more once daily resulted in a mean plasma trough concentration of more than 60 ng per milliliter, the pre-clinically predicted effective concentration to inhibit c-MET (J Clin Oncol 27:15s, 2009 (suppl; abstr 3509). Hence, 250mg OD will be the lowest concentration tested in combination with PD-0325901. Inhibition of c-MET activity is critical, so the dose of PF-02341066 will be increased initially in cohort 2. Doses that will be explored for PF-02341066 to be used in combination with PD-0325901 are 250mg OD and 200mg BD. The highest dose to be evaluated is 200mg BD in combination with PD-0325901 8mg BD. If this is the Maximum Tolerated Dose we have put the provision to check the lower PF-02341066 dose (250mg OD) with the higher dose of PD-0325901 (8mg BD see below). We will not explore a higher dose of PF-02341066 (eg. 250mg BD) in combination with MEK inhibitor PD-0325901 for the following reasons (1) the PF-02341066 target trough dose needed to inhibit our target (c-MET) is approximately 50% of that needed to inhibit ALK, (2) a consistent increase in toxicity is seen, albeit at acceptable frequency and severity, with escalation of the monotherapy PF-02341066 dose level from 200mg BD to 250mg BD, and (3) our experience and that of others over the last few years has been that combining oral targeted agents in oncology clinical trials has been rarely achievable with both compounds at full monotherapy doses, with lower dosing needed of one or both and/or a change to alternative schedules with less frequent dosing. Within the restrictions of available capsule size and known single dose tolerability, our current design explores the full range of possible doses. PF-02341066 in combination with PD-0325901 will be administrated in this phase I dose escalation and dose expansion until disease progression, intolerance or withdrawal.

PF-02341066 is approved in the United States for the treatment of patients with locally advanced or metastatic NSCLC that is ALK-positive as detected by an FDA-approved test. PF-02341066 is also approved in the Republic of Korea for the treatment of patients with ALK-positive locally advanced or metastatic NSCLC. PF-02341066 has been authorised in the European Union under an EMA 'conditional approval' scheme, which means that further evidence on this medicinal product is awaited, and is indicated for the treatment of adults with previously treated ALK-positive NSCLC.

Randomized phase 3 studies of single-agent PF-02341066 vs. standard chemotherapy are ongoing in the first- and second-line ALK-positive advanced NSCLC treatment settings. Other indications under study with single-agent PF-02341066 treatment include but are not limited to MET-amplified NSCLC, ROS-positive NSCLC, ALK-positive anaplastic large cell lymphoma, ALK-positive inflammatory myofibroblastic tumor, and ALK-positive neuroblastoma. Clinical trials of PF-02341066 in combination with EGFR TKI in advanced NSCLC patients are ongoing. PF-02341066 is also under investigation in advanced cancer patients with various degrees of hepatic impairment, subjects with severe renal impairment, and pediatric cancer patients.

PD-0325901

PD-0325901 is a highly specific non-ATP-competitive inhibitor of MEK1 and MEK2. The Ki^{app} of PD-0325901 for an activated form of MEK1, MEK1-S218D/S222D, was 1.1±0.2 nM, while the Ki^{app} of PD-0325901 for an activated form of MEK2, MEK2-S222D/S226D was 0.79±0.2 nM. Specificity of PD-0325901 was also

evaluated against a panel of 27 kinases. This panel, which was comprised of tyrosine kinases as well as a multitude of serine/threonine kinases, was completely refractory to inhibition by PD-0325901 at a concentration of 10 µM. Therefore, PD-0325901 appears to be exquisitely specific for MEK1/2.

In vitro studies have shown that PD-0325901 inhibits phosphorylation of ERK of colon 26 (murine), HCT-116 colon (human), and MDCK (dog) cells with IC_{50} values of 0.34, 0.28, and 0.31 nM, respectively. In vivo, PD-0325901 has been found to inhibit potently phosphorylation of ERK in 2 human tumour xenograft models (HT-29 colon, and MiaPaCa2 pancreatic). Oral administration of 25 mg/kg PD-0325901 resulted in 79% and 93% inhibition of pERK expression 24 hours after dosing, as measured in excised HT-29 and MiaPaCa2 tumours, respectively.

Four studies evaluating the safety, efficacy, and/or PK of PD-0325901 have been undertaken. Study A4581001 was a phase 1/2 study in cancer patients, with 79 patients dosed (66 in Phase 1 (LoRusso et al., 2010) and 13 in Phase 2). The phase I component evaluated the toleration of alternate treatment regimens [eg, intermittent (3 wk on treatment/1 wk off), continuous (daily (OD), and continuous with breaks (5 d on/2 d off treatment). 5 days on/2 days off dosing). Doses ≥2 mg BD, the dose level at which the plasma concentration of PD-0325901 exceeded the target inhibition based on xenograft mouse models (16.5-53.5 ng/mL), consistently caused >60% suppression of pERK in melanoma samples from patients. The most frequently reported treatment-related AEs on all treatment schedules were rash, diarrhoea, fatigue, nausea, and visual disturbances/eye disorders, a toxicity profile consistent with those observed for other MEK inhibitors. The maximum tolerated dose (MTD), based on first cycle dose-limiting toxicities, was 15 mg BD continuously. However, 10 and 15 mg BD continuous dosing and 10 mg BD 5 days on/2 days off schedules were associated with delayed development of RVO; thus, further enrolment to this trial was stopped. Intermittent dose scheduling between 2 and 10 mg BD should be explored to identify a recommended dose with long-term PD-0325901 use.

Study A4581002 was a phase 2 study in patients having advanced non small cell lung cancer (NSCLC) (N = 34) (Haura et al., 2010). PD-0325901 was initially administrated orally 15mg BD on an intermittent schedule (3 wk on/1 wk off; schedule A). This schedule was not well tolerated. Consequently the same dose 15mg BD was administrated with additional weekends “off treatment” (i.e. 5 d on/2d off for 3 wk, followed by 1 wk off, schedule B). The introduction of treatment breaks was thought more likely to improve patient safety. Treatment related toxicities included diarrhoea, fatigue, rash, vomiting and nausea. There was a substantial decrease in the incidence of visual disturbances with schedule B, neurologic events were similar between the 2 schedules. Visual disturbances include blurred vision, halo vision, photopsia and diplopia. There were no objective responses. Conclusion was that further studies should focus on PD-0325901, rational combination strategies and enrichment of patient selection based on the mode of action.

Study B1271002, is an ongoing phase 1, open label, triple-arm, multi-centre, dose escalation study of two dual PI3K/mTOR inhibitors, PF-04691502 and PF-05212384, each in combination with irinotecan or PD-0325901 in patients with advanced cancer. In this study PD-0325901 has been explored in combination with PF-04691502 in RAS or RAF mutated tumours (N = 7). In addition, a formal food effect study (A4581004) in healthy subjects (N = 23) evaluated the effect of food on plasma pharmacokinetics of PD-0325901. Doses have been administered on an intermittent (i.e., 3 weeks on/1 week off) or continuous daily dosing schedule.
Study B1271002 is a Phase 1b study that explores two PI3K/mTOR inhibitors (PF-04691502 and PF-05212384) in combination with either PD-0325901 or irinotecan in patients with advanced cancer. This is the first clinical trial exploring PD-0325901 in combination, in this case with the oral PI3K/mTOR inhibitor, PF-04691502. However because PF-05212384 when combined with irinotecan showed a better safety profile and higher antitumor activity than the combination of PF-04691502 and irinotecan, the arm assessing the combination of PD-0325901 with PF-04691502 will be closed and a new arm combining PD-0325901 with PF-05212384 will be explored. Once identified the recommended phase 2 dose (RP2D) of the combination an expansion cohort will be conducted in up to 20 patients with advanced, *RAS* mutated, colorectal cancer.

As of 20 June 2012, six patients were diagnosed with significant findings on eye examinations. These included 3 cases of retinal vein occlusion, 2 cases of optic neuropathy, 1 case of optic atrophy and 1 case of iridocyclitis and retinal detachment. The case of retinal detachment was reported in study B1271002.
In humans, the plasma pharmacokinetics of PD-0325901 was characterized by rapid absorption, with peak concentrations occurring within 1 to 2 hours of dosing, generally dose proportional changes in exposures, and an average elimination half-life of 8.6 hours (range 5 to 18 hours across dosing cohorts). Food appeared to reduce PD-0325901 peak plasma concentrations, but the effect on AUC was variable. The plasma half-life of the carboxylic acid metabolite PD-0315209 was longer than that for the parent.

Dose of PD-0325901 at 4mg inhibits pERK1/2 for >12 hours in xenograft mouse models. We will start with the suggested dose from the xenograft model of 4mg BD and then define a cohort taking 8mg BD. Dose levels of 8mg BD or lower (continuous and intermittent) are safe and did not result in any CNS toxicity or retinal vein occlusion/thrombosis. We therefore have no desire to exceed 8mg BD on safety grounds and as this is a dose that will inhibit the target of MEK1 and MEK2.

Based on in vitro studies, PD-0325901 and its circulating metabolite, PD-0315209, have a low potential to inhibit CYP2D6, CYP3A4, CYP1A2, and CYP2C19. However, the metabolite (PD-0315209) has the potential to inhibit CYP2C8 and CYP2C9. Caution should be exercised when co-administering PD-0325901 with drugs that are substrates for CYP2C8 or CYP2C9. Patients taking concomitant phenytoin and/or warfarin should be monitored on a regular basis.

During the dose escalation phase of this trial studying the combination of PF-02341066 and PD-0325901, a decision was made by Pfizer that they would not pursue clinical development of PD-0325901 whilst continuing to be fully supportive of the underlying rationale for this trial. Pfizer retained their commitment to use of PF-02341066 as a cMET inhibitor in all components of the clinical trial. It was agreed that we would proceed to completion of the dose escalation phase of the trial using the combination of PF-02341066 and PD-0325901, but that the investigators should explore the use of an alternate MEK inhibitor in combination with PF-02341066.An abbreviated dose escalation combination trial was considered suitable for the PF-02341066 and Binimetinib combination as Binimetinib is further on its research development than the MEKi PD-0325901, thus providing good evidence for the choice of dosage level to be studied in this trial. The new combination of PF-02341066 and Binimetinib will then be used for the dose expansion phase of this trial. The MEK inhibitor Binimetinib has proceeded through phase I-III clinical trials as both monotherapy (in phase III trials in low-grade serous ovarian cancer, BRAF-mutant melanoma and NRAS-mutant melanoma, with the latter indication likely to proceed to registration filing in 2016) and in combination with various cytotoxics and other novel agents in phase I and II trials and was agreed as the preferred combinatorial partner with PF-02341066for this trial. Array BioPharma have agreed to provide Binimetinib for use in the MErCuRIC trial in combination with PF-02341066.

Binimetinib

Binimetinib (also known as MEK162 or ARRY-438162) is an orally bioavailable, selective and potent mitogen-activated protein (MAP) kinase kinase (MEK) 1 and MEK 2 inhibitor. Binimetinib is currently being investigated as a single agent and in combination with a variety of additional compounds including paclitaxel, and inhibitors of PI3K, RAF, EGFR, PKC, CDK4/6 and IGF-1R in patients with selected advanced or metastatic solid tumors, including, among other tumors, melanoma, biliary, colorectal, and ovarian cancers. The clinical development program of binimetinib encompasses patients with selected advanced or metastatic solid tumors, including NRAS- and BRAF-mutant melanoma, BRAF- and KRAS- mutant NSCLC, high-grade platinum-resistant ovarian cancer, low-grade serous ovarian cancer, biliary, colorectal, and pancreatic cancers.

Binimetinib is an ATP-uncompetitive inhibitor of MEK1/2. In cell-free systems, binimetinib inhibits MEK1/2 with an IC50 of 12 nM. *In vitro*, binimetinib potently inhibits MEK- dependent phosphorylation of ERK in human BRAF-mutant melanoma cell lines as well as NRAS-mutant melanoma lines. *In vivo*, Binimetinib treatment results in dose- and time-dependent inhibition of phosphorylation of ERK in the HT-29 human colorectal carcinoma xenograft. Similarly, levels of both pERK and DUSP6 mRNA (a target gene of phosphorylated ERK) are reduced in the A375 melanoma xenograft. Lastly, in ex vivo experiments, Binimetinib reduces pERK levels in human whole blood cells. *In vitro*, Binimetinib potently inhibits the proliferation of human cancer cell lines. Binimetinib is particularly active in cells harboring activating mutations in the BRAF, NRAS and KRAS genes, although activity is also observed in cell lines that lack such mutations. Synergistic interactions with the RAF inhibitor encorafenib and PI3K inhibitors BEZ235 (pan-PI3K/mTOR), buparlisib and BYL719 (PI3Kα) have been observed in subsets of melanoma, colorectal, pancreatic and lung-derived cancer cell lines. *In vivo*, single-agent Binimetinib inhibits the growth of tumours in numerous xenograft models, including those derived from colorectal, non-small cell lung, pancreatic and melanoma cancers. Binimetinib is also active in primary human explant models derived from several cancer types including colorectal. Combining Binimetinib with a variety of standard chemotherapy agents such as cisplatin, gemcitabine, taxanes or 5-FU/oxaliplatin resulted in enhanced anti-tumour activity in numerous *in vivo* tumour models. Similarly, combinations of Binimetinib with a variety of targeted agents have shown activity in vivo in multiple tumour models. In subsets of xenograft models of CRC, NSCLC and pancreatic cancer, anti-tumour effects have been observed when Binimetinib was combined with a variety of PI3K inhibitors.

As of 07-January-2015, a total of 2430 healthy subjects and patients have been enrolled in Binimetinib studies and 1945 of whom received at least one dose of Binimetinib, and have been evaluated for safety, including 204 healthy subjects, 6 liver dysfunction patients, 164 patients with rheumatoid arthritis and 1571 patients with advanced cancer. As of the data-cut off Binimetinib experience as a single agent in 705 cancer patients includes 6 studies:

- [ARRAY-162-111]: phase I, dose-escalation study in patients with advanced solid tumours followed by expansion cohorts in patients with advanced or metastatic biliary cancer or KRAS- or BRAF-mutant metastatic colorectal cancer (CCR).
- [CMEK162X2201]: phase II study in patients with locally advanced and unresectable or metastatic malignant cutaneous melanoma, harbouring BRAFV600 or NRAS mutations.
- [CMEK162X1101]: phase I, dose escalation study in Japanese patients with advanced solid tumours with the expansion part in patients whose tumours harbour RAS or BRAF mutations.
- [CMEK162A2301]: phase III, two-arm, randomized study in patients with advanced unresectable or metastatic NRAS Q61 mutation-positive melanoma.
- [ARRAY-162-311]: phase III, two-arm, randomized study in patients with recurrent or persistent low-grade serous carcinomas of the ovary, fallopian tube or primary peritoneum.
- [CMEK162AUS11]: phase II study in patients with RAS/RAF/MEK activated tumours.

The study [ARRAY-162-111] was a phase I, open-label, dose-escalation of oral Binimetinib in patients with advanced solid tumours followed by expansion cohorts in patients with advanced or metastatic biliary cancer or KRAS- or BRAF-mutant metastatic CRC. A total of 93 patients received at least 1 dose of Binimetinib. Four dose levels were evaluated: 30 mg BID, 45 mg BID, 60 mg BID and 80 mg BID. Two of 4 patients receiving 80 mg BID experienced dose- limiting toxicities (DLTs), thus the 80 mg BID dose was declared non-tolerable. Seven patients were enrolled at 60 mg BID and no DLTs were observed, therefore, 60 mg BID was declared the MTD. Following completion of the Dose-Escalation Phase, a total of 74 patients were enrolled in the Expansion Phase. The dose of 45 mg BID was determined as the recommended phase II dose (RP2D) mainly due to the frequency of ocular AEs in patients at the 60 mg dose level.

The study [CMEK162X1101] is an ongoing, phase I, open label, dose escalation study of Binimetinib in Japanese patients with advanced solid tumors with an expansion part in patients whose tumours harbour RAS or BRAF mutations. A total of 21 patients received at least 1 dose of Bnimetinib: 6 patients received 30 mg BID and 15 patients received 45 mg BID. Eighteen patients (as of 10-February-2014) were discontinued from the study and 3 patients were still ongoing. Two patients in the 45 mg BID dose level cohort (dose escalation part) reported 2
DLTs, both were recurrent Grade 2 detachment of retinal pigment epithelium. Therefore, 45 mg BID was declared the MTD in Japanese patients. No DLT was reported in patients enrolled in the expansion part.

The most frequently reported AEs suspected to be related to Binimetinib, regardless of grade and Binimetinib dose were dermatological events (rash, dermatitis acneiform), gastrointestinal (GI) events (nausea, vomiting, diarrhea), edema peripheral, fatigue and CPK increased. The majority of these AEs were Grade 1 or 2 with less than 5% of cases Grade 3 or 4, with the exception of elevation of blood CPK, reported as 24% (44/183 patients) Grade 3 or 4 in [CMEK162X2201] and 17.2% (10/58 patients) in dose escalation and 16.6% (11/66 patients) in dose expansion [CMEK162X1101] studies.

Binimetinib experience in combination with others agents include 866 patients in 13 studies:

Five studies with RAF inhibitors Encorafenib or RAF265:

- [CMEK162X2102]: phase II study of sequential, single-agent Encorafenib followed by a rational combination with targeted agents (including Binimetinib) after progression, to overcome resistance in adult patients with locally advanced or metastatic BRAFV600 melanoma.
- [CMEK162X2110]: phase Ib dose finding, dose escalation study of Binimetinib in combination with encorafenib, in selected advanced solid tumors.
- [CLGX818X2102]: phase II study of Binimetinib in combination with Encorafenib in patients with locally advanced or metastatic BRAFV600 mutant melanoma.
- [CMEK162B2301]: phase III, randomized, 2-part study in patients with BRAFV600- mutant locally advanced unresectable or metastatic melanoma.
- [CLGX818X2109]: phase II, open-label study of Encorafenib and Binimetinib, followed by a rational combination with targeted agents after progression on Encorafenib and Binimetinib, to overcome resistance in adult patients with locally advanced or metastatic BRAF V600 melanoma.

Three studies with PI3KC/AKT pathway inhibitors BEZ235 (pan-PI3K/mTOR) Buparlisib (pan-PI3K) or BYL719 (PI3Kα):

- [CMEK162X2103], [CMEK162X2101] and [CMEK162X2109]: all three are phase Ib, dose escalation and expansion studies in selected advanced solid tumours.

One study with PKC-selective inhibitor sotrastaurin

- [CMEK162X2203]: phase Ib/II study in patients with metastatic uveal melanoma.

One study with CDK4/6 inhibitor LEE011

- [CMEK162X2114]: phase Ib/II study, in patients with NRAS mutant melanoma.

One study with IGF-1R monoclonal inhibitor Ganitumab

- [CMEK162X2111]: phase Ib/II dose-escalation and expansion study in patients with selected advanced solid tumours.

One study with EGFR inhibitor Panitumumab

- [CMEK162X2116]: phase Ib/II, dose-escalation study in patients with mutant RAS or wild-type RAS metastatic CRC.

One study with standard chemotherapy agent paclitaxel

- [ARRAY-162-112] phase Ib, dose-escalation and expansion study in women with platinum-resistant or refractory epithelial ovarian, fallopian tube or primary peritoneal cancer.

The target RP2D of Binimetinib for combination studies with targeted agents is 45 mg BID. Overall, the frequently reported AEs suspected to be related to Binimetinib in combination studies were found to be similar to those found in single-agent studies, which include GI events (diarrhea, nausea, vomiting), dermatological events (dermatitis acneiform, rash) CPK elevation and retinal events. The percentage of patients that discontinued study drug due to AEs regardless of relationship to Binimetinib ranged from 2.6% [CMEK162X2203] to 36% [CMEK162X2101]. A total of 52 DLTs were observed in the dose-escalation part of combination studies, as following: 10 DLTs in [CMEK162X2102], 6 DLTs in [CMEK162X2110], 7 DLTs in [CMEK162X2111], 6 DLTs in [CMEK162X2103], 13DLTs in [CMEK162X2101] and 10 DLTs in [CMEK162X2201] study. Of these 52 DLTs, 13 were reported in the [CMEK162X2101] study combining Binimetinib with the PI3K inhibitor Buparlisib. The most frequents DLTs reported were gastrointestinal events, followed by ocular and dermatological events. A total of 128 deaths were reported during the study or within 30 days of last dose of study drug in cancer patients, either in single-agent or combination studies (45 and 46 respectively). The most frequent cause of treatment discontinuation was disease progression and other events not related to study drug. Based on the experience from the 13 completed phase I studies (9 in healthy subjects , 3 in cancer patients, 1 in rheumatoid arthritis patients) and 1 completed phase II study (in rheumatoid arthritis patients), Binimetinib has demonstrated an acceptable and manageable safety profile with the majority of AEs Grades 1 or 2 of intensity and reversible.

Currently one phase III study of Binimetinib at 45mg BID is being conducted in patients with unresectable or metastatic BRAFV600-mutant melanoma in combination with encorafenib [CMEK162B2301]. The exposure of Binimetinib when combined with Bncorafenib described by Cmax and AUC has the same ranges of values founded in the single agent studies.

Binimetinib has demonstrated an acceptable safety profile in non-clinical toxicology and clinical studies. As with any new investigational drug, unexpected AEs may occur. Regarding reproductive toxicity (teratogenicity), there are no clinical data. However, Binimetinib must not be used in pregnant women or nursing women and the use of highly-effective contraception is recommended for male and female subjects participating in clinical trials. Patients with a history or current evidence of retinal vein occlusion (RVO) or risk factors for RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndrome) should be excluded from studies with binimetinib. Patients with a medical history of deficient liver glucuronidation (Gilbert syndrome) should be excluded from the clinical studies.
Strict attention should be given to cardiovascular comorbidities, specifically, coronary artery disease and hypertension. Before Binimetinib administration patients should have a baseline left ventricular ejection fraction (LVEF) evaluation. Investigators should follow specific recommendations for dose adjustments due to specific toxicities like dermatologic events, diarrhoea, hepatic abnormalities, decrease of LVEF, increase in blood pressure (systolic and diastolic), retinal events and CPK elevation in blood. Supportive

therapy for the management of binimetinib associated toxicities should be based on Investigator experience; guidance is provided in the protocols. Patients reporting de-novo or worsening of visual symptoms should be referred to an ophthalmologist. Ocular coherence tomography should be used for diagnosis and monitoring of retinal events. Early intervention is recommended for skin toxicities (including prophylactic measures, topical and/or systemic treatment and referral to a specialist as necessary), and management of diarrhoea.

1.3 Other research interventions

Fundamental to our approach is the evaluation of the effects of drug administration on tumour biology. This requires access to tumour and surrogate tissues for detailed molecular analyses. **T**o identify molecular signatures of sensitivity to MEKi/METi treatment in the *RAS*MT and *RAS*WT/cMET+ subgroups, 2 core biopsies from representative metastases (one for fixation and one for fresh frozen material) will be obtained prior to treatment. In addition, a whole blood sample for germline DNA and ctDNA analyses will be obtained prior to treatment. Patients who demonstrate a response to MEKi/METi (as determined by RECIST 1.1), but then develop secondary resistance, will undergo a second biopsy (2 cores fresh frozen and 1 for fixation) from a metastasis. At the time of trial enrolment, 20 mL of whole blood will be collected from each patient for extraction of cell free circulating DNA.

1.4 Rationale for the study

Scientific Rationale:

We have employed a systems biology approach, comprising gene expression profiling, metacore pathway analysis and siRNA screening, to identify novel targets/pathways critical for the survival of *KRAS*MT tumours, both basally and following MEK inhibitor treatment. We found that JAK1/2-STAT3 and the upstream receptor tyrosine kinase c-MET are important pro-survival signals in *KRAS*MT CRC (Van Schaeybroeck et al, Cancer Cell, in revision). Further studies indicated that c-MET is acutely activated following MEK1/2 inhibition in *KRAS*MT CRC cells. c-MET silencing (using different siRNA sequences and/or the small molecule inhibitor crizotinib (PF-02341066) strongly decreased basal and MEK1/2-induced c-MET and JAK/STAT3 activity and resulted in potent increase in cell death when combined with the MEK1/2 inhibitor AZD6244 in *KRAS*MT CRC cells. Importantly, combining PF-02341066 with the MEKi AZD6244 resulted in synergistic reduction in tumour growth in *KRAS*MT xenograft models. These preclinical *in vitro* and *in vivo* data support the further clinical evaluation of combined MEKi/METi treatment to combat metastases in *RAS*MT CRC patients (Figure 1).

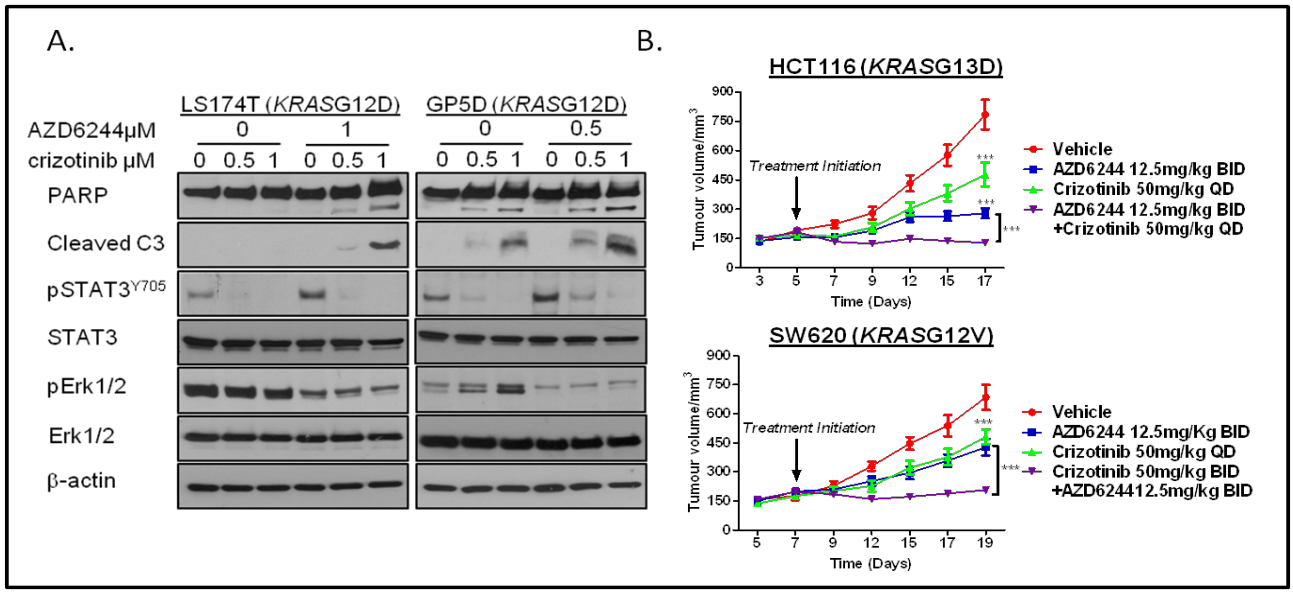


Figure 1(as above). Preclinical *in vitro* and *in vivo* data of combined treatment with MEK inhibitor AZD6244 and c-MET inhibitor crizotinib in *KRAS*MT CRC models. (A) *KRAS*MT CRC cell lines, LS174T and GP5D (mutations in codon 12), were co-treatment with AZD6244 and crizotinib for 24 hours and apoptosis (cell death) was determined by Western blotting for PARP and caspase 3 cleavage. These data show a synergistic increase in cell death with combined AZD6244/crizotinib treatment in both models. **(B)** Growth rate of *RAS*MT HCT116 (upper panel) and SW620 (lower panel) xenografts in BALB/c SCID mice.

Mice were treated with vehicle, AZD6244, crizotinib or combined AZD6244/crizotinib treatment. Differences in growth were determined using Student's t test and by calculating subsequent P values. ***, P < 0.001. These data show a synergistic reduction in tumour growth in mice treated with combination of AZD6244 and crizotinib.

Clinical rationale: Evidence underpinning the scientific rationale:

Functional dysregulation of c-MET in cancer

Under normal conditions, c-MET activation is tightly regulated by ligand activation on the cell surface, ligand-activated receptor internalization/degradation and paracrine ligand delivery. Despite these controls, pathway deregulation occurs in multiple cancers. Binding of the physiological ligand HGF induces c-MET autophosphorylation on the tyrosine residues Y1234 and Y1235 at the tyrosine kinase domain c-MET, which leads to autophosphorylation of the carboxy-terminal bidentate substrate-binding site (Tyr 1349 and Tyr 1356) of MET (Ponzetto et al., 1994; Weidner et al., 1996). Various cytoplasmic effector proteins, including GAB1, GRB2, phospholipase C and SRC are directly recruited to this site and become phosphorylated on tyrosine residues, resulting in a diversity of cellular responses such as cell survival, cell proliferation, migration, invasion and epithelial-to-mesenchymal transition (Birchmeier et al., 2003; Zeng et al., 2008). A number of reports have shown the role of c-MET in metastatic progression (Moshitch-Moshkovitz et al., 2006).

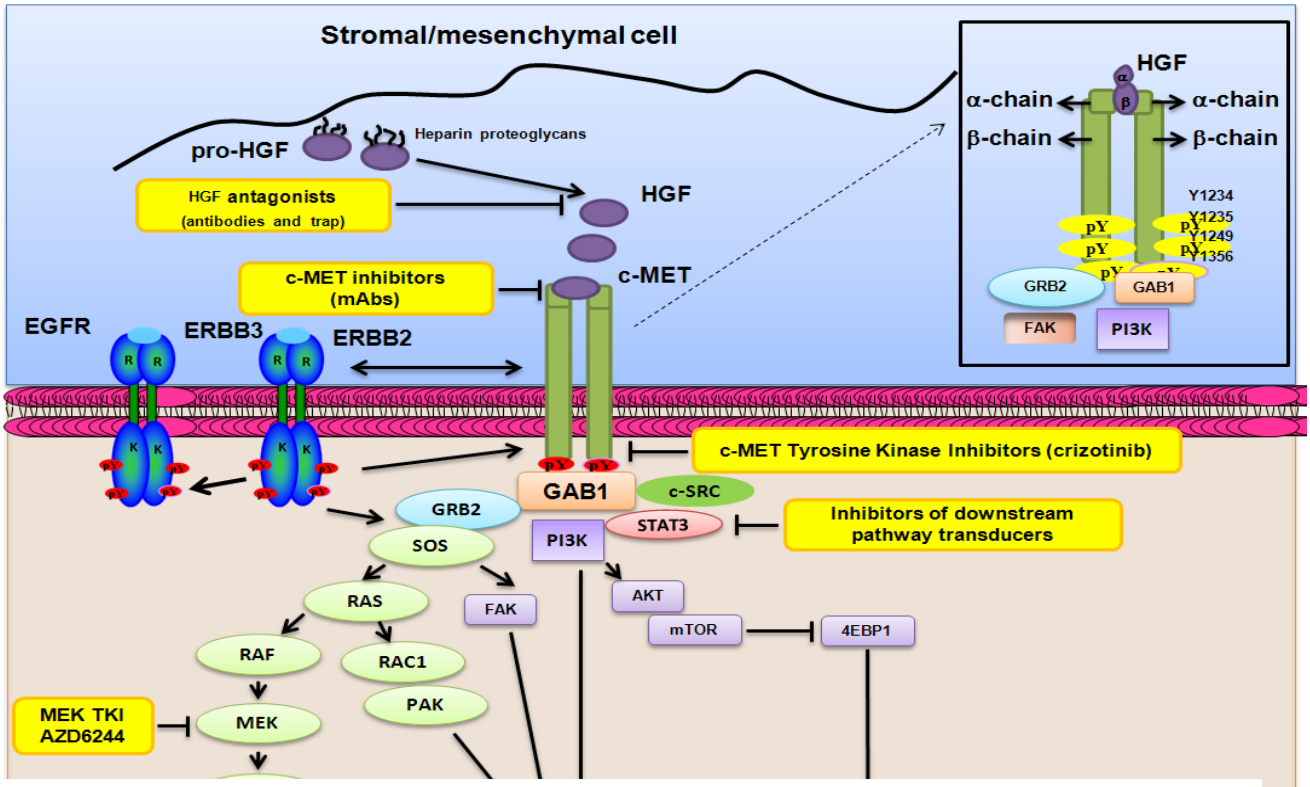
MEK as a potential therapeutic target in mCRC

Inhibition of MEK1/2, a downstream effectors of RAS, is an attractive treatment strategy for *RAS*MT CRC (Van Schaeybroeck et al., 2011). A number of preclinical *in vivo* models have shown that the MEKi (AS703026 and AZD6244) could inhibit *RAS*MT CRC tumour growth (Little et al., 2011; Yoon et al., 2011). [37] A phase II study of the MEKi AZD6244 in highly pre-treated unselected mCRC patients showed similar efficacy compared to oral 5-FU (capecitabine). However, acute activation of pro-survival pathways and other resistance mechanisms such as driver oncogene amplification can cause resistance, limiting its success as a single agent in the clinic (Little et al., 2011).

c-MET mediates resistance to anti EGFR therapies in mCRC

c-MET is overexpressed in ~50%-60%, amplified in ~10% and mutated in ~5% of CRC (Di Renzo et al., 1995; Fumagalli et al., 2010). A number of studies have shown that activation of c-MET is an important resistance mechanism following treatment with EGFR inhibitors in NSCLC and head and neck cancers (Wheeler et al., 2008; Yano et al., 2008). Ectopic overexpression of the MET receptor or paracrine activation of *c-MET* using its ligand HGF in quadruple WT CRC cells, conferred resistance to cetuximab or panitumumab to a degree equivalent to that triggered by mutant *RAS*. Notably, the ability of WT *c-MET* to drive resistance to EGFR was abolished by concomitant treatment with the anti-cMET inhibitor, JNJ-38877605 (Bardelli et al, Cancer Discovery, submitted). These studies highlight the role of c-MET in mediating primary and secondary resistance to anti-EGFR targeted therapies in CRC. A recent retrospective study in 73 mCRC patients, suggested that c-MET overexpression may have a role in resistance to anti-EGFR targeted therapies in *RAS*WT CRC (Inno et al., 2011). All these studies indicate that patients with *RAS*WT tumours with aberrant c-MET (*RAS*WT/c-MET+) expression do not respond to EGFR targeted therapies and may benefit from anti-c-MET targeted therapies.

Figure 2. The HGF-c-MET axis signalling network and targeted therapies strategies.
The pathway which transduces invasive growth signals from mesenchymal to epithelial cells is activated by HGFA. C-MET kinase activation results in auto-phosphorylation and binding of adaptor proteins, forming scaffolds for recruitment and activation of signalling proteins. Activation of downstream signalling results in increased proliferation, survival, migration and metastasis.



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Targeting c-MET in colorectal cancer, rationale and progress.
The tight regulation of HGF and MET signalling that is observed in development and regeneration is lost in cancer at multiple levels. Functional crosstalk of c-MET with the receptor tyrosine kinases EGFR, ERBB2, ERBB3 or insulin-like growth factor 1 receptor has been reported in several systems and has emerged as a major mechanism for cancer progression and resistance to therapy (Engelman et al., 2007). Recent data, including studies from this consortium, indicate that c-MET overexpression correlates with poor overall survival and resistance to cetuximab in *RAS*WT CRC (Inno et al., 2011). These data further suggest that c-MET is an attractive target in a significant subpopulation of CRC patients. Currently, multiple agents targeting HGF or c-MET are in phase I-III clinical trials. These targeted therapies can be HGF-competitive analogs (competing for ligand for receptor binding), decoy c-MET compounds, antibodies against HGF (eg. Rilotumumab, Ficlatuzumab, TAK-701), antibodies against cMET (eg. MetMab or Onartuzumab, LY-2875358) and small molecule tyrosine kinase inhibitors (eg. Crizotinib, tivantinib, foretinib) (Figure 2). With respect to CRC, a phase Ib/II trial in patients with *RAS*WT CRC, found that the combination of panitumumab plus rilotumumab was superior in term of response rate to panitumumab alone (31% versus 21%) (Eng et al. J Clin.Oncol. 29 (Suppl.), abstract 3500).

Patient selection for treatment with HGF-cMET axis inhibitors.
"One-size-fits-all" approaches have been standard practice in CRC treatment, but with our increased understanding of the molecular/genetic heterogeneity of CRC, it is clear that novel treatments must be developed and tested in selected subgroups to maximize the benefit of this new knowledge. In Chronic Myeloid Leukaemia (CML), the anti-apoptotic BCR-ABL fusion protein provides a disease specific target for the tyrosine kinase inhibitor imatinib mesylate. Since its introduction in 2001, Imatinib Mesylate and second and third generation TKIs directed against BCR-ABL have become the gold standard therapy in CML, replacing allogeneic stem cell transplantation (Kantarjian et al., 2002). In Non-Small Cell Lung Cancer

(NSCLC), tumours harbouring an EGFR mutation are selected for gefitinib treatment, (Lynch et al., 2004) while recent exciting data has demonstrated that patients carrying an EML4-ALK fusion gene respond to small molecule TKIs such as crizotinib, again demonstrating how molecular stratification informs state-of-the-art treatment in patients with poor prognosis disease (Camidge et al., 2012). In this regard, the c-MET-HGF axis represents a viable target for molecular stratification, with a number of retrospective studies indicating benefit from molecularly targeted agents, particularly in patients whose tumour has high expression (amd/or amplification) of c-MET (Okamoto et al., 2012). Investigators of the randomized phase Ib/II study of rilotumumab with panitumumab versus panitumumab alone found that CRC tumours that overexpressed MET were more likely to respond to the combination of rilotumumab and panitumumab. Other studies in NSCLC and gastric cancer with Moab directed against MET and rilotumumab respectively have also indicated that the best responses are observed in patients expressing high levels of c-MET in the tumour (Spigel et al. J Clin Oncol: suppl; abstract 7505).

Recent pilot data from the consortium (QUB, BHSCT)[1] has led to an increased understanding of aberrant MET in *RAS*WT CRC patients, which can be used to better define cohorts in the MErCuRIC clinical trials. This data indicates: (1) there is discordance between MET expression status as defined by immunohistochemistry (IHC) and RNA scope, (2) the prevalence of high MET (3+) defined with combination of IHC and RNA scope is ~ 1%, (3) MET amplification is not always associated with high MET measured by IHC or RNA scope, and (4) there is clear evidence that MET amplified patients might benefit from crizotinib treatment, however the data for high MET IHC or RNA scope as predictive markers for anti-cMET therapies is less clear. In addition, new data[2] has arisen over the last year showing the role of c-MET mutations (exon 14 skipping) as a determinant of response to anti c-MET targeted therapies in Non-Small Cell Lung Carcinoma (NSCLC). Thus, there remains uncertainty as to which precise molecular alterations in cMET will drive sensitivity: is a structural alteration in the gene by mutation or copy number amplification required, or is over-expression as measured at RNA or protein level an acceptable biomarker? In this study, we will therefore enter patients into two parallel cMET altered cohorts defined as below.

1.5 Primary hypothesis of the trial

Combined MEK/MET inhibitor treatment is well tolerated and results in superior response and progression free survival of patients with either
a) *RAS*MT CRC or
b) *RAS*WT CRC with amplification or mutation c-MET gene or
c) *RAS*WT CRC with over-expression of c-MET on protein or mRNA
compared to standard chemotherapy treatment.

This study, which is the first component of the overall MErCuRIC programme, will evaluate 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.

Expansion phases will be undertaken in the three molecular cohorts to determine clinical activity measured by response to combined Binimetinib with PF-02341066:
a) *RAS*MT CRC or
b) *RAS*WT CRC with amplification or mutation c-MET gene or
c) *RAS*WT CRC with over-expression of c-MET on protein or mRNA

The outputs from this trial will inform a further study to compare the effect of combined MEKi/METi treatment (experimental arm) with standard therapy in any of these molecular cohorts where sufficient activity to warrant further investigation as defined in the statistical plan is observed.

As part of this clinical trial we will develop, validate and apply a comprehensive diagnostic assay for assessing *c-MET* dysregulation. This will enable us to apply "smart recruiting" protocols for selection of future trial participants. Based on NGS data obtained during the trial, the MErCuRIC Consortium will also develop a customised NGS-CRC gene assay to predict response/resistance to combination MEKi/METi.

[1] Bradley et al. Transcriptional upregulation of c-MET is associated with invasion and tumor budding in colorectal cancer Oncotarget DOI: 10.18632/oncotarget.12933

[2] Frampton et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov. 2015 Aug;5(8):850-9

2 TRIAL DESIGN

2.1 Outline

This is a phase I combination study of the MET inhibitor PF-02341066 with the MEK inhibitors 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. Following the discontinuation of PD-0325901, the study design has been updated to include a further short dose escalation phase using patients with advance solid tumours receiving the combined study treatment of PF-02341066 with Binimetinib. This will be followed by a dose expansion phase recruiting patients with *RAS*MT and *RAS*WT/cMET over-expressing metastatic CRC.

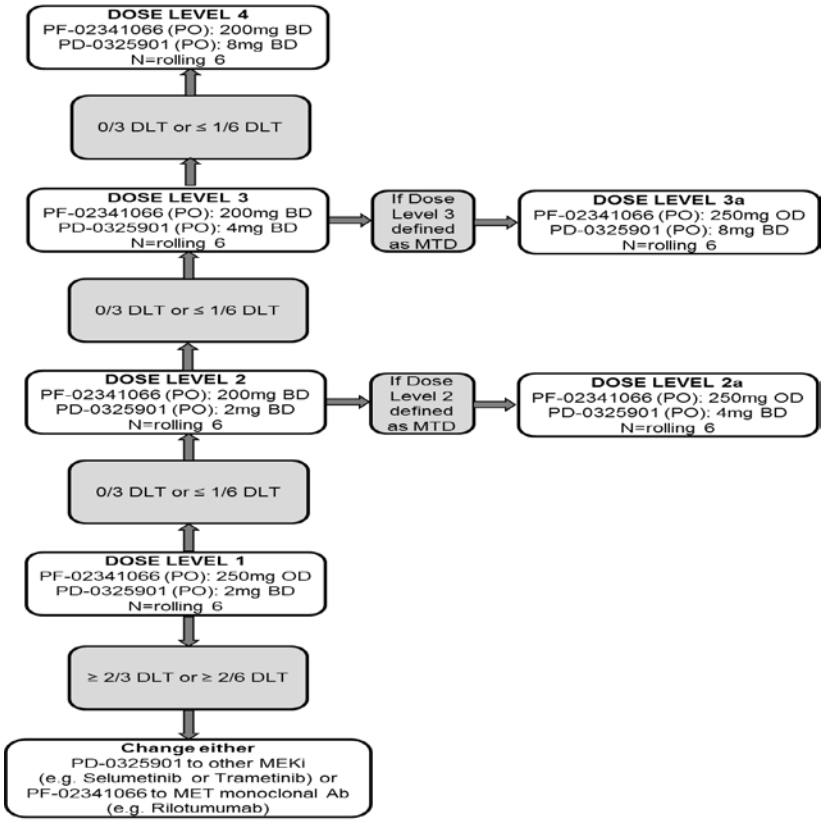
In the initial dose escalation study using PF-02341066 with PD-0325901, 25 patients were recruited. In the further dose escalation study using PF-02340166 in combination with Binimetinib, 20 patients were recruited. In the dose expansion phase an additional 42-98 patients with biopsiable metastatic disease will be treated at the RPII dose to further evaluate safety, PK, PD and treatment response. In the dose expansion phase additional biopsy and blood samples will be obtained to define mechanisms of response/resistance to PF-02341066/Binimetinib therapy.
Early closure of recruitment: Recruitment to the trial closed on 23Oct2018 with a total of 82 patients recruited, 45 patients to the dose escalation phases and 37 patients to the dose expansion phase. Significant difficulties were encountered in recruiting to the RAS WT CRC patient cohorts and it was decided that the dose expansion phase patient recruitment target of 42-98 patients was non-feasible within the constraints of the EU grant supporting the trial. The decision was made with the support of the TMG, FP7 consortium members and trial sponsor, the University of Oxford.

2.2 Treatment Schedule and duration

2.2.1 Dose escalation phase of study using PF-02340166 in combination with PD-0325901.

In this first dose escalation phase of the study, patients with advanced solid tumours will be recruited. It is anticipated that 12-24 patients will be required for the dose escalation phase of the study, which uses a rolling six design. This method minimises delays in the dose escalation phase and up to six patients can be enrolled concurrently onto the study. Accrual to the study will only be suspended when awaiting data from six patients and/or a decision from the Trial Management Group. Decisions as to whether to enrol a new patient onto the current, next highest, or next lowest dose level will be made based on available data at the time of new patient enrolment.

Figure 3. Schema for dose levels in the escalation phase using PF-02341066 in combination with PD-0325901



Dose levels

Dose levels 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.

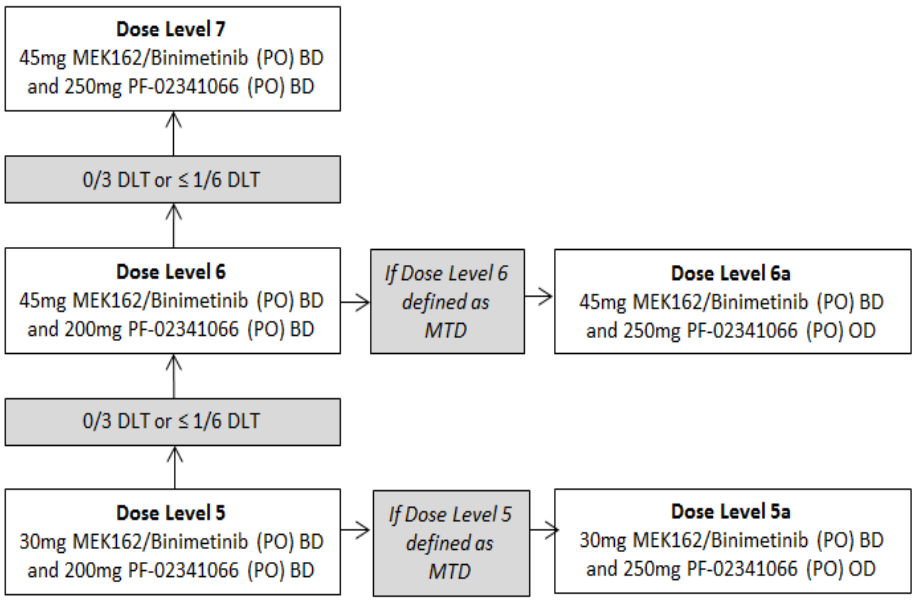
Dose Level	PD-0325901	PF-02341066
1	2mg BD	250mg OD
2	2mg BD	200mg BD
2a	4mg BD	250mg OD
3	4mg BD	200mg BD
3a	8mg BD	250mg OD
4	8mg BD	200mg BD

Dose 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 enrols 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 (Dose Level 4, Figure 3), then this dose level will be defined as the RPII dose. The definition of MTD is outlined in the protocol section 8.4.2 and will be discussed and agreed at regular teleconferences throughout the dose escalation phase of the study. Once the MTD has been defined, dosing at a higher level must not occur.

2.2.2 Dose escalation phase of study using PF-02341066 in combination with Binimetinib.

In this second dose escalation phase of the study, patients with advanced solid tumours will be recruited. It is now anticipated that up to 25 patients will be required for this dose escalation phase of the study to provide for exploring the tolerability of the combination at intermediate dose levels from those previously envisaged, based upon the emerging tolerability and safety profile. The rolling six design is the method that minimises delays in the dose escalation phase and up to six patients can be enrolled concurrently onto the study. Accrual to the study will only be suspended when awaiting data from six patients and/or a decision from the Trial Management Group. Decisions as to whether to enrol a new patient onto the current, next highest, or next lowest dose level will be made based on available data at the time of new patient enrolment.

Figure 4. Schema for dose levels in the escalation phase using PF-02341066 in combination with Binimetinib



Dose levels

Dose levels 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

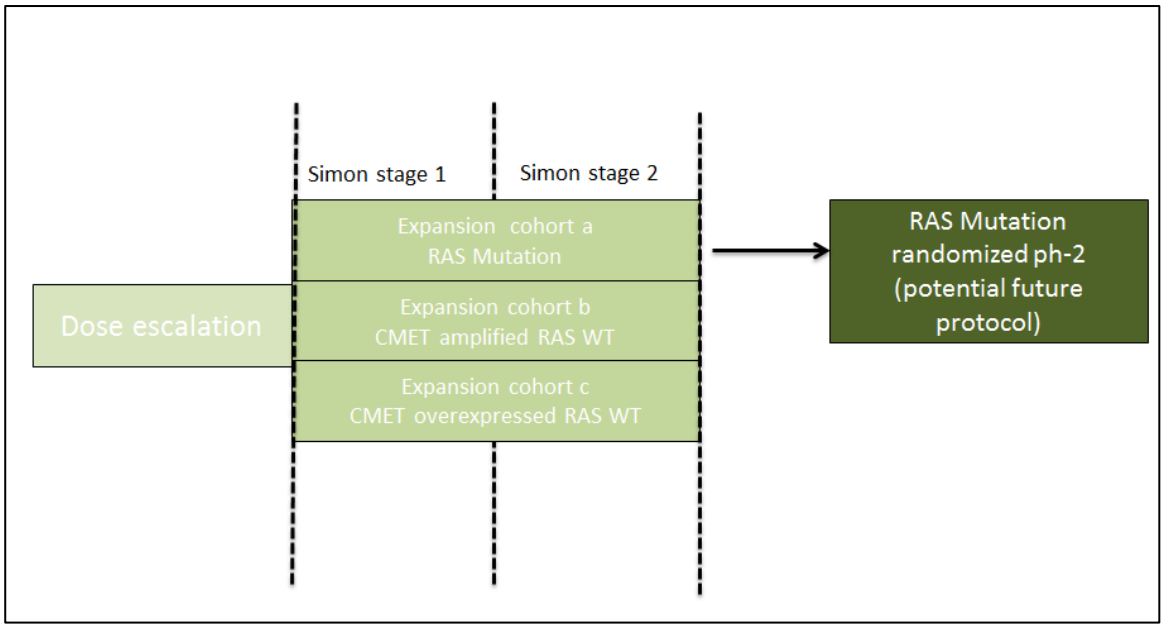
Dose level assignment will be based on the number of patients currently enrolled in the cohort, the number of dose limiting toxicities (DLTs) observed, and the number of patients at risk for developing a DLT (i.e. patients enrolled but who are not yet evaluable for toxicity) . For example, when three 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 enrols 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 (Dose Level 7,), then this dose level will be defined as the RPII dose. The definition of MTD is outlined in the protocol section 8.4.2 and will be discussed and agreed at regular teleconferences throughout the dose escalation phase of the study. Once the MTD has been defined, dosing at a higher level must not occur.

2.2.3 Dose expansion phase of study

Once the RPII dose has been identified, up to 40 patients with biopsiable *RAS*MT CRC or up to 29 with biopsiable *RAS*WT CRC with amplification or mutation in the *MET* gene or 29 patients with biopsiable *RAS*WT CRC with over-expression of c-MET protein or mRNA
will be enrolled in the dose expansion phase to further evaluate the safety, PK, PD and treatment response.

Figure 5: Schema for dose expansion phase



Note: Simon staging is further explained in the protocol
sample size sec 15.1

All patients in the *RAS*WT group will receive full c-MET testing prior to recruitment to detect: (a) overexpression at protein level (IHC), (b) overexpression at mRNA level (RNAscope), (c) MET amplification, and (d) MET mutation. This would allow us to assess the potential correlation between MET amplification or mutation and MET protein/mRNA overexpression, and, importantly, to assess initial benefit from this treatment in each of *two different molecular groups independently: C*ohort (b) *RAS*WT CRC with amplification or mutation in the-*MET* gene or Cohort c) *RAS*WT CRC with over-expression of c-MET on protein or mRNA)

2.3 Projected Number of Subjects

The study will be conducted in 4-5 EU centres for the dose escalation phase, increasing to 8-10 for the dose expansion phase. It was anticipated that 12-24 patients would be required for the initial dose escalation phase of the study. 25 patients were actually recruited for this initial dose escalation phase using PF-02341066 in combination with PD-0325901. In the further dose escalation study using PF-02341066 in combination with Binimetinib it was anticipated that up to 25 patients would be required. 20 patients were actually recruited as required for the the exploration of the tolerability of the combination at intermediate dose levels from those previously envisaged, based upon the emerging tolerability/safety profile. For the dose expansion phase of the study it was anticipated that 42 - 98 patients would be required, bringing the expected total patient number for the trial to between 92 and 148, not counting any replacements. This target patient number will now not be realised for lack of feasibility of recruiting to the specific RAS WT CRC patient cohorts.

2.4 Replacement of Subjects

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.

2.5 Post-trial care and follow-up

Following the end of study visit, patients will receive subsequent standard active, clinical trial, supportive and palliative care as appropriate. All patients will be followed up for post-progression survival (PFS and OS), with details of further lines of treatment.

3 OBJECTIVES AND ENDPOINTS

Primary Objective (Dose Escalation)	Endpoints or Outcome Measures
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.
Primary Objective (Dose Expansion)	
To investigate the response to treatment with RPII dose of PF-02341066 in combination with Binimetinib in patients with a) *RAS*MT CRC or b) *RAS*WT/c-METmut/amplified CRC or c) RASWT/c-MET over-expressed CRC.	Clinical and radiological response to Binimetinib with PF-02341066 as defined by stable, partially or completely responding disease using RECIST version 1.1.
Secondary Objectives (Dose Escalation)	
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.
Secondary Objectives (Dose Expansion)	
To assess the efficacy of RPII dose of PF-02341066 in combination with Binimetinib in patients with a) *RAS*MT CRC or b) *RAS*WT/c-METmut/amplified CRC or c) RASWT/c-MET over-expressed CRC.	Progression free survival using RECIST version 1.1. and overall survival.
To further investigate the safety and toxicity profile/tolerability of Binimetinib/ PF-02341066 combinations.	Adverse events according to NCI CTCAE v4.03 across all treatment cycles.
To investigate pharmacokinetic (PK) biomarkers of PF-02341066 and Binimetinib in blood.	Determine plasma Cmax, Cmin, AUC, oral clearance and t1/2 etc. for PF-02341066 and Binimetinib.
To measure pharmacodynamic (PD) effect of PF-02341066 in combination with Binimetinib in paired skin biopsies, tumour biopsies (where possible), plasma and PBMCs.	ELISA for soluble c-MET and HGF in plasma; Western blotting for pERK1/2 in skin (10 patients).
Tertiary and Exploratory Objectives	
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.
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

4 PATIENT SELECTION

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 a) *RAS*MT CRC or b) *RAS*WT/c-METmut/amplified CRC or c) RASWT/c-MET over-expressed CRC 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.

4.1 Inclusion Criteria

(Inclusion criteria for the completed initial dose escalation phase using PF-02341066/PD-0325901 is listed in Appendix 7.)

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

4.1.1 All patients

- Age ≥ 16 years
- ECOG performance status 0-1 (Appendix 1)
- Adequate respiratory function on clinical assessment.
- Left ventricular ejection fraction (LVEF) ≥ 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) ≥ 9g/dl (transfusion to achieve this allowed),
    - Neutrophils≥ 1,500/µl,
    - Platelet count ≥ 100,000/µl,
    - AST or ALT ≤ 2.5 x ULN, patient with liver metastases ≤ 5 ULN, Alkaline phosphatase ≤ 5 x ULN,
    - Serum Bilirubin ≤ 1.5 x ULN,
    - Creatinine Clearance ≥ 50ml/min (Calculated by Cockcroft Gault equation, or by EDTA) (Appendix 2)
- Able to swallow oral medication
- Life expectancy of at least 3 months.

4.1.2 Dose escalation phase

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

4.1.3 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 either a) *RAS*MT (KRAS codon 12, 13, 61,117, 146; NRAS codon 12, 13, 61, 117, 146 mutations) or b) *RAS*WT/c-MET mutated or amplified or c) RASWT/c-MET over-expressed with progressive disease on or within 6 months of completion of adjuvant therapy or after chemotherapy/targeted therapies for metastatic disease.
- Prior treatment with an EGFR targeted monoclonal antibody for patients with *RAS*WT/c-METmutated or amplified CRC or RASWT/c-MET over-expressed CRC.
- 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.**

4.2 Exclusion criteria

(Exclusion criteria for the completed initial dose escalation phase using PF-02341066/PD-0325901 is listed in Appendix 7.)

4.2.1 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 ≥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 ≥ 3 months. Patients must be off corticosteroid therapy for ≥ 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 e.g. 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.

- Patients who have undergone major surgery ≤ 3 weeks prior to starting study drug or who have not recovered from side effects of such procedure
- Use of drugs or foods that are known potent CYP3A4 inhibitors or inhibitors 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 pregnancy test before enrolment and agree to use one highly effective form of contraception (oral, injected or implanted hormonal contraception or intra-uterine device) in addition to 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 one form of highly effective contraception including: oral, injected or implanted hormonal contraception or intra-uterine device in addition to 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.

4.3 Protocol deviations and waivers to entry criteria

Protocol adherence is a fundamental part of the conduct of a clinical study. Changes to the approved protocol need prior approval unless for urgent safety reasons.

Systems for prospectively approving protocol deviations, in order to effectively widen the scope of a protocol should not be used. Doing so might erode the scientific and ethical value of the protocol and its authorisation and might have an impact on the processes put in place for the care and safety of the study subjects.

Investigators must contact the MErCuRIC Office to obtain guidance and/or clarification as necessary if unsure whether the patient satisfies all the entry criteria and to clarify matters of clinical discretion. OCTO will contact the chief investigator or clinical coordinators as necessary. Investigators should not request a protocol waiver to enter a patient who does not satisfy the selection 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. Examples might include the addition or deletion of tests, dosing, duration of treatment etc. 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.

4.4 Re-screening if patient does not meet inclusion/exclusion 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.

4.5 Patient registration procedure

Patients will be recruited from those referred to oncology services at participating sites for management of their advanced solid cancers (escalation phase) or colorectal cancer (expansion phase). A screening log must be kept of all patients considered for the study including any that are subsequently excluded; the reason for exclusion must be recorded on this form. A copy of the screening log should be sent to the trial office on request, but without patient identifiers. The original must be retained on site.

Before entering a patient onto the study the Principal Investigator or designee will confirm eligibility. If in any doubt the Chief Investigator must be consulted before entering the patient. Details of the query and outcome of the decision must be documented on the registration/ eligibility checklist.

After completing suitability checks, Informed Consent Form for trial participation and Informed Consent Form for blood and tissue sample collection, the site staff will scan and email the Registration Form, where applicable, to confirm the patient's eligibility.

Registration of patients

OCTO Registration by email to octo-MErCuRIC.ox.ac.uk

The patient will then be registered. Once the Investigator / research nurse has a study number for the patient, they will be asked to provide the original Registration Form along with c-MET and RAS mutation status report and a copy of the histology report (expansion phase) to the Trials office

5 TRIAL ASSESSMENTS AND PROCEDURES

5.1 Pre-trial screening consent and procedure (dose-expansion phase only)

Written informed consent will be obtained to perform *RAS* mutational status on archival tumour tissue (if not already known) and to perform a biopsy of representative CRC metastasis for c-MET status assessment (using mutation, amplification and immunohistochemistry) before seeking consent for the main study. The Investigator will explain the principles and rationale for evaluating c-MET and RAS mutational status using patient information and consent form A. Patients may give consent to c-MET and RAS screening testing without the usual 24 hour period for consideration if they wish. This is to reduce the time required to obtain c-MET and RAS mutational status, and to minimise delays in evaluating patients' suitability for the protocol.

Once the patient has consented to tRAS and cMET screening demographic information and medical history will be recorded. No further study specific investigations will be made until the RAS and cMET status is known. Patients whose RAS mutational status on primary tumour is already known do not require re-testing of primary tumour; however, these patients still require biopsy of CRC metastasis for c-MET status. The Investigator must ensure that a copy of the relevant test report is obtained and held in the medical record.

Patients consenting to RAS and cMET trial screening tests must be logged with the trials office in order to obtain a screening number before the sample is dispatched (see 7.5). The responsible analytical laboratory will provide the Investigator with a written report within 5 working days of receipt of a suitable sample. The study site will maintain a log of all patients screened for RAS and c-MET status along with details of the outcome and date of the test result. A copy of this log must be provided to the trial office on request.

Patients will only be eligible for the main study if the *RAS* mutational status and cMET report confirms a RAS mutant or RASWT/c-MET+ status. If the result is inconclusive the patient is not eligible for the dose expansion phase. Note that the responsible laboratory will assess the sample quality and perform the assay and any re-test in accordance with their internal standard operating procedures. Hence any inconclusive result is final and no further re-testing will be done for the trial.

Once the patient *RAS* and c-MET status is confirmed to be a) RAS mutant, b) *RAS*WT/c-MET mutated or amplified or c) RASWT/c-MET over-expressed status the trial entry procedures detailed below (for the dose expansion phase) may start.

5.2 Informed consent for main study

Potential participants will be given a current, approved version of the patient information sheet. They will also receive clear verbal information about the study detailing no less than: the nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be explained that they will be free to withdraw from the study at any time, for any reason, without prejudice to future care, and with no obligation to give a reason for withdrawal. They will have at least 24 hours to consider the information provided and the opportunity to question the Investigator, their GP or other independent parties before deciding whether to participate.

The Investigator (or delegate) who obtains consent must be suitably qualified and experienced. All delegates working on behalf of the investigator must be authorised by the PI. The Investigator is responsible for ensuring that the trial consent procedures comply with current applicable GCP Regulatory and ethical requirements. Informed consent discussions and outcomes must be well documented in the medical record. The Investigator (or delegate) must be satisfied that the patient has made an informed decision before taking consent. The patient and the Investigator (or delegate) must personally sign and date the current approved version of the informed consent form in each other's presence. A copy of the information and signed consent form will be given to the participant. The original signed form will be retained in the Site File, whilst a copy is to be filed in the medical record. A copy of the signed and dated consent form is to be sent to the MErCuRIC Office, for the purpose of central monitoring. If patients agree to donate samples to the licenced tissue bank a copy of the signed consent form is to be sent to the tissue bank. If local policies differ from the above, the site should discuss this at the stage of site activation before the trial is opened.

Contraceptive/ Pregnancy counselling

All participants must be advised on the need to use reliable methods of contraception during the study. The advice should include:

(1) The acceptable methods, including: male or female sterilization, implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), and abstinence.

(2) Male patients with partners of child-bearing potential unless they agree to take measures not to father children by using one form of highly effective contraception (oral, injected or implanted hormonal contraception or intra-uterine device) in addition to 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. A barrier method (condom with spermicide) should be used in addition to a highly effective form of contraception.

(3) Males should continue to take these precautions for a minimum 6 months after the last dose of study drug.

(4) Females should continue to take these precautions a minimum of 6 months after the last dose of study drug.

(5) That any pregnancy (also applies to females partners of male trial subjects) occurring within six months of the last administration of study drug / other trial intervention will be followed up and the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) will be reported and followed up even if participant is discontinued from the study.

5.3 Informed consent for translational sub-studies

Patients, who agree to participate in the dose escalation part of the trial, will also be informed of the MErCuRIC translational studies. Subjects who agree to donate samples for the sub-study will have these taken during the screening period, and a biopsy of a representative metastasis taken upon developing resistance to either the PF-02341066/PD-0325901 or PF-02341066/Binimetinib treatment. The translational component is fundamental to the dose expansion part of the trial and participation is therefore mandatory.

Note: Study procedures 5.4 – 5.8 below refer to participants treated with the combination of PF-02341066 with Binimetinib. For participants treated with PF-02341066 with PD-0325901, these study procedures are detailed separately in Appendix 8.

5.4 Main screening: pre-dosing evaluations

The following must be performed/obtained within the 28 days before the patient receives the first administration of study drug.

All patients

- Written informed consent
- Demographic details
- Medical history (including prior diagnosis, prior treatment, concomitant diseases, concomitant medications, therapies received by patient within 28 days prior to cycle 1, day1, known ophthalmologic medical history).
- ECOG Performance Status (PS)
- Full physical examination
- Clinical and radiological (CT chest/abdomen/pelvis or CT chest with MRI abdomen/pelvis) disease assessment
- Vital signs (systolic/diastolic blood pressure, pulse, body temperature), height and weight.
- Ophthalmic assessment, including visual acuity, pressure, perimetry, slit lamp examination, fundoscopy with digital photography, optical coherence tomography (OCT).
- Safety blood laboratory examination Haematology: haemoglobin, white blood cells (WBC) with differential count and platelets; Clinical chemistry: sodium, potassium, calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (alk phos), AST and/or ALT and LDH; Coagulation screen: APTT, PT)
- Blood for assessment of tumour markers (if appropriate)
- Cardiac muscle/enzymes levels - CK and troponin
- Urinalysis
- Serum pregnancy test for women of childbearing potential.
- 12-lead electrocardiogram
- Echocardiography or MUGA
- Review of inclusion and exclusion criteria

Dose escalation phase

- Obtain archived tumour tissue for biomarker analysis
- Draw blood sample for germline DNA
- Obtain fresh skin biopsy for PD assessment
- Obtain fresh tumour biopsy for PD assessment, where additional consent has been given.

Dose expansion phase

- Obtain archived tumour tissue for biomarker analysis
- Draw blood sample for germline DNA
- Obtain fresh skin biopsy for PD assessment (first 10 patients only)
- Obtain fresh biopsy of metastases for biomarker assessment

5.5 Evaluations during dosing

Cycle 1 day 1

All patients

- ECOG PS
- Record of concomitant medications
- Full physical examination
- Vital signs (systolic/diastolic blood pressure, pulse, body temperature) and weight.
- ECG (12-lead)

- Blood for assessment of haematology, clinical chemistry, cardiac/muscle enzymes - CK and troponin status and coagulation status,
- Urinalysis
- Serum or urine Human Chorionic Gonadotropin (HCG) pregnancy test for women of childbearing potential.
- Plasma samples for biomarkers; blood draws as per section 7.4.
- Assessment of adverse events
- Start dosing with PF-02341066 and Binimetinib.

Dose expansion phase only

- Obtain blood sample for ctDNA as per section 7.5.

Cycle 1 day 8

- ECOG PS
- Record of concomitant medications
- Full physical examination
- Vital signs (systolic/diastolic blood pressure, pulse, body temperature) and weight.
- Assessment of adverse events
- Dosing with PF-02341066 and Binimetinib.

Cycle 1 day 15

- ECOG PS
- Record of concomitant medications
- Full physical examination
- Vital signs (systolic/diastolic blood pressure, pulse, body temperature) and weight.
- ECG (12-lead)
- Blood for assessment of haematology, clinical chemistry, cardiac/muscle enzymes – CK and troponin status and coagulation status
- Urinalysis
- Plasma samples for biomarkers; blood draws as per section 7.4.
- Assessment of adverse events
- Dosing with PF-02341066 and Binimetinib
- 3-6 hours post-dose fresh skin biopsy for PD assessment (for dose escalation phase and initial cohort of 10 patients in dose expansion phase)
- 3-6 hours post-dose fresh tumour biopsy for PD assessment (for patients in the dose expansion phase and those patients who have consented to the biopsy in the escalation phase).

Cycle 1 day 21

- ECOG PS
- Record of concomitant medications
- Full physical examination
- Vital signs (systolic/diastolic blood pressure, pulse, body temperature) and weight.
- Echocardiography or MUGA
- PK sampling: blood draws as per section 7.3.
- Assessment of adverse events
- Dosing with PF-02341066 and Binimetinib.

Cycle 1 day 22

- PK sampling (24 hour sample)
- Dosing with PF-02341066 only and Binimetinib (if continuous dosing)

Cycle 2 day 1

All patients

- ECOG PS
- Record of concomitant medications
- Full physical examination
- Vital signs (systolic/diastolic blood pressure, pulse, body temperature) and weight.
- ECG (12-lead)
- Blood for assessment of haematology, clinical chemistry, cardiac/muscle enzymes – CK and troponin status and coagulation status
- Plasma samples for biomarkers; blood draws as per section 7.4.
- Serum or urine Human Chorionic Gonadotropin (HCG) pregnancy test for women of childbearing potential.
- Urinalysis
- Assessment of adverse events
- Dosing with PF-02341066 and Binimetinib

Dose expansion phase only

- Blood sample for ctDNA

Cycle 2 onwards, Day 8 assessments

- ECOG PS
- Record of concomitant medications
- Full physical examination
- Vital signs (systolic/diastolic blood pressure, pulse, body temperature).
- Assessment of adverse events
- Dosing with PF-02341066 and Binimetinib

Cycle 2 onwards, Day 15 assessments

- ECOG PS
- Record of concomitant medications
- Full physical examination
- Vital signs (systolic/diastolic blood pressure, pulse, body temperature).
- Assessment of adverse events
- Plasma samples for biomarkers; blood draws as per section 7.4 (cycle 2 only).
- Dosing with PF-02341066 and Binimetinib

Cycle 2 onwards, Day 21 assessments

- ECOG PS
- Record of concomitant medications
- Full physical examination
- Vital signs (systolic/diastolic blood pressure, pulse, body temperature).
- PK sampling: blood draws as per section 7.3 (trough level and 2h after morning dosing, cycles 2, 4, 6, 8, 10 and 12).
- Assessment of adverse events

- Ophthalmic assessment, including visual acuity, pressure, perimetry, slit lamp examination, and fundoscopy with digital photography
- Dosing with PF-02341066 and Binimetinib

Cycle 3 onwards Day 1 asessments

All patients

- ECOG PS
- Record of concomitant medications
- Full physical examination
- Clinical and radiological (CT chest/abdomen/pelvis or CT chest with MRI abdomen/pelvis) disease assessment
- Vital signs (systolic/diastolic blood pressure, pulse, body temperature) and weight.
- ECG (12-lead)
- Blood for assessment of haematology, clinical chemistry, cardiac/muscle enzymes - CK and troponin status and coagulation status
- Serum or urine Human Chorionic Gonadotropin (HCG) pregnancy test for women of childbearing potential.
- Blood for assessment of tumour markers (if appropriate)
- Plasma samples for biomarkers; blood draws as per section 7.4.
- Urinalysis
- Assessment of adverse events
- Dosing with PF-02341066 and Binimetinib

Dose expansion phase

- Blood sample for ctDNA

Cycle 3 onwards: Day 21 assessments

- Echocardiography or MUGA

5.6 End of treatment evaluations

All patients

- ECOG PS
- Record of concomitant medications
- Full physical examination
- Assessment of adverse events
- Vital signs (systolic/diastolic blood pressure, pulse, body temperature) and weight.
- ECG (12-lead)
- Urinalysis
- Serum or urine Human Chorionic Gonadotropin (HCG) pregnancy test for women of childbearing potential.
- Blood for cardiac/muscle enzymes - CK and troponin status
- Blood for assessment of haematology, clinical chemistry, and coagulation status
- Blood for assessment of tumour markers (if appropriate)
- Ophthalmic assessment, including visual acuity, pressure, perimetry, slit lamp examination, fundoscopy with digital photography, optical coherence tomography and fluorescin angiography (OCT and flourescin angiography only if required).
- Tumour assessment: CT scan chest/abdomen/pelvis (or CT chest with MRI abdomen/pelvis) using RECIST v1.1.

Dose expansion phase

- Blood for ctDNA
- Biopsy of representative metastases for molecular profiling (optional)

5.7 Post treatment follow-up - evaluations

All patients

- Assessment of adverse events
- Record of post-trial therapy
- Patients will be followed up every 3 months for survival status until death or study closure, whichever happens first.

Dose expansion phase

- Tumour biopsy (optional)

5.8 Evaluations on early withdrawal

If the patient is withdrawn from treatment, for any of the reasons indicated in section 6, a final off-study visit assessment should be performed 28 - 30 days after the last administration of PF-02341066 and Binimetinib. The following assessments will be done:

- ECOG PS
- Record of concomitant medications
- Full physical examination
- Assessment of adverse events
- Vital signs (systolic/diastolic blood pressure, pulse, body temperature) and weight.
- ECG (12-lead)
- Urinalysis
- Blood for cardiac/muscle enzymes - CK and troponin status
- Blood for assessment of haematology, clinical chemistry, and coagulation status

If the patient is withdrawn from the trial and declines attendance for a final off-study visit, then a withdrawal assessment should be performed, if possible on the day the decision is made to take the patient off-study or as soon as possible. Telephone review is permitted in these circumstances. These patients will be followed up for progression and overall survival.

6. EARLY PATIENT WITHDRAWAL

6.1 Treatment Withdrawal

During the course of the trial, a patient may withdraw early from treatment. This may happen for a number of reasons, including:

- Unacceptable toxicity, including but not limited to:
  - Life threatening grade 4 toxicity.
  - Repetition of non-life threatening grade 4 toxicity despite per protocol dose reduction.
  - Delay of a treatment cycle for more than 3 consecutive weeks beyond the due date
- Objective evidence of progressive disease as determined by CT scan and/or X-ray and/or ultrasound and/or clinical examination
- Clinical decision by the investigator that continued participation in the trial is contrary to the patient's best interests
- Patient decision to discontinue treatment (as opposed to participation in all aspects of the study)

When a patient stops treatment early, an 'End of Treatment' Form should be completed, and any other relevant form (for example a SAE Form). The reason for withdrawing from treatment early should be clearly documented in the medical records. An off-study visit assessment should be performed and the results of the evaluations and observations reported in the CRF.

6.2 Withdrawal of Consent

Withdrawal of consent means that a patient has expressed a wish to withdraw from the study altogether. Under these circumstances, the site needs to document all relevant discussions in the patient notes and notify the Trials Office. Under these conditions, ongoing SAEs require follow up until resolution.

6.3 Patient evaluability and replacement

In the dose escalation phase, if a patient comes off treatment due to a DLT, they will not be replaced. If however, a patient withdraws, for reasons other than safety/toxicity, prior to the end of cycle 1, they will need to be replaced and will not receive any further PF-02341066/PD-0325901 or PF-02341066/Binimetinib. All withdrawn patients will no longer receive the study drugs and will be followed up for progression free and overall survival unless they withdraw their consent.

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.

• SAMPLES FOR LABORATORY ANALYSIS

7.1 Samples to be analysed in local laboratories

Diagnostic Laboratories

Samples for haematology, biochemistry and coagulation analysis will be labelled with standard patient identifiers and sent to the local hospital diagnostic laboratory. Results will be processed in the standard way and entered into the routine hospital reporting system. Samples will be stored, held, reported and subsequently destroyed in accordance with standard local laboratory practice.

Pathology

The routine diagnostic pathology samples taken at participating centres will also be labelled, processed and reported according to local hospital protocols. With regard to the dose expansion study, an H&E section will be obtained from each FFPE core of each of the 2-3 tumour biopsies prior to and during treatment and also upon resistance (where consent provided) to confirm the presence of tumour.

RAS mutational analysis –dose expansion phase

RAS mutational analysis will be determined on primary tumour using the applicable local technique according to local policies.

7.2 Samples to be sent to and analysed in a Central Laboratory

Details of sample preparation, labelling and despatch are provided in the sample handling manual for the MErCuRIC1 protocol.

The following samples will be sent to the CCRCB Molecular pathology lab (Prof Manuel Salto-Tellez):

- Block of FFPE core from the pre-screening biopsy, during treatment and end of treatment biopsy (optional) to evaluate cMET expression, amplification and mutation (only in dose expansion study)
- Pharmacodynamic FF tumour and skin samples for pERK1/2 by Western blotting
- Pharmacodynamic blood samples to measure soluble HGF and MET
- Fresh frozen cores for DNA extraction and molecular profiling. DNA extraction will be performed by QUB NI-MPL and DNA send to PDUM lab for analysis of *MET* amplification and mutational status.
- Blood samples for germ-line DNA

The following blood samples will be sent according to the procedures described in the sample handling manual:

- Pharmacokinetic studies for PF-02341066, PD-0325901 and M15, Binimetinib
- Pharmacodynamics blood samples to measure soluble c-MET

Blood samples for ctDNA analysis will be sent to Professor A. Bardelli's lab (UNITO).

7.3 Pharmacokinetic assays

PF-02341066 in combination with PD-0325901

Analysis of plasma samples for the determination of PF-02341066, PD-0325901, M15 will be carried out to ensure that the putative target levels to inhibit cMET and ERK1/2 signalling pathways respectively are met when PF-02341066 is combined with PD-0325901.
Blood samples for the determination of PF-02341066 and PD-0325901, and M15 levels will be collected pre-dose, 1, 2, 4, 6, 8, 10 and 24 hours post morning dose of PF-02341066 and PD-0325901 on cycle 1 days -1/1, cycle 1 days 21/22 and cycle 1 days 28/29 (cycle 2 day 1). The levels being determined at the various time points are summarised in the table below:

	Pre-dose and, 1, 2 , 4, 6, 8, 10 (hours post-morning dose) Cycle 1 Day -1	24 hours (pre-morning dose) Cycle 1 Day 1	Pre-dose, 1, 2 , 4, 6, 8, 10 (hours post-morning dose) Cycle 1 Day 21	24 hours (pre-morning dose) Cycle 1 Day 22	Pre-dose, 1, 2 , 4, 6, 8, 10 (hours post-morning dose) Cycle 1 Day 28	24 hours (pre-morning dose) Cycle 1 Day 29/Cycle 2 Day 1
PF-02341066			X	X	X	X
PD-0325901 + M15	X	X	X	X		

PK trough samples will also be collected pre-dose and 2 hours post morning dose of PF-02341066 and PD-0325901 on cycle 2 day 21, cycle 4 day 21, cycle 6 day 21, cycle 8 day 21, cycle 10 day 21 and cycle 12 day 21.

Blood samples will be centrifuged to generate plasma. Plasma concentrations of PF-02341066, PD-0325901 and M15 will be determined using validated HPLC-MS/MS assays following solid-phase extraction of the plasma sample.

Pharmacokinetic assays for PF-02341066 in combination with Binimetinib

Analysis of plasma samples for the determination of PF-02341066 and Binimetinib will be carried out to ensure that the putative target levels to inhibit cMET and ERK1/2 signalling pathways respectively are met when PF-02341066 is combined with Binimetinib.
Blood samples for the determination of PF-02341066 and Binimetinib levels will be collected pre-dose, 1, 2, 4, 6, 8, 10 hours post morning dose of PF-02341066 and Binimetinib on cycle 1 day 21 and immediately prior to dosing on the morning of day 22. Further PK profiling on Cycle 1 Day 28/29 is not required for the dose escalation and dose expansion phases using PF-02341066 with Binimetinib as the study drugs are being taken together. The levels being determined at the specified time points are summarised in the table below:

	Pre morning dose Cycle 1 day 21, And at 1, 2 , 4, 6, 8, 10 hours post morning dose on Cycle 1 Day 21	24 hours (pre morning dose) On Cycle 1 Day 22
PF-02341066	X	X
Binimetinib	X	X

PK trough samples will also be collected pre-dose and 2 hours post morning dose of PF-02341066 and Binimetinib on cycle 2 day 21, cycle 4 day 21, cycle 6 day 21, cycle 8 day 21, cycle 10 day 21 and cycle 12 day 21.

Blood samples will be centrifuged to generate plasma. Plasma concentrations of PF-02341066 and Binimetinib will be determined using validated HPLC-MS/MS assays following solid-phase extraction of the plasma sample.

7.4 Pharmacodynamic assays

Pre-dose and post-dose fresh skin biopsy. Samples will be collected at site and the sections will be forwarded to the central laboratory where the Western Blotting technique will be used for for analysis of pERK1/2. These samples will be collected at screening and Cycle 1, day 15 (+/- 7 days) during the Dose Escalation phase and from the first 10 patients during the Dose Expansion phase.

Pre-dose and post-dose fresh tumour biopsy.

Samples will be fixed in formalin and paraffin embedded at site. Sections will be forwarded to QUB, where immunohistochemistry for pERK1/2 and pcMET$^{Y1234/1235}$ will be performed. These will be collected at screening and Cycle 1, day 15 (+/- 7 days) as mandatory for the Dose Expansion phase, but optional for the Dose Escalation phase. A further optional metastatic tumour biopsy will be collected at disease progression during the Dose Expansion phase only.

Plasma sample for soluble biomarkers. c-MET ectodomain and HGF scatter factor will be analysed using commercially available Invitrogen ELISAs. Blood samples will be collected to assess biomarkers pre-dose and 6 hours post-dose (morning dose) on days 1 and 15 of Cycle 1; pre-dose and 6 hours post-dose (morning dose) on day 1 and 15 of Cycle 2; pre-dose and 6 hours post-dose (morning dose) on day 1 of cycles 3 through to 6.

7.5 Samples for molecular analysis and patient derived xenografts

Fresh frozen cores from pre-dose and post-dose fresh tumour biopsies will be processed for DNA extraction and molecular profiling. Where sufficient material exists fresh frozen cores may also be used to develop xenografts. Blood samples will be processed for **germ-line DNA** and **ctDNA.**

7.6 Summary of samples/assays to be taken during the study

Assay/sample handling and storage will be managed according to separate written instructions. The following summarises the arrangements for collection, close to patient handling, timings, and analytical laboratories responsible. Research assays will be performed according to separate laboratory SOPs.

7.7 Samples for Biobanking

Participants in this trial will be invited to permit the long term retention of samples left over after protocol-specified analyses for use in possible other future research linked to trial data. Consent to participate in this aspect of the trial is optional and not a requirement of participation in the main study.

7.8 Labelling and confidentiality of samples sent

All samples sent to analytical laboratories will be labelled with the trial code, trial patient number, dosing cohort and date/time taken. Should a laboratory receive any samples carrying unique patient identifiers the recipient must immediately obliterate this information and re-label the samples. The study site will be informed of their error.

7.9 Clinical reporting of exploratory research assay results

The results of the MErCuRIC trial research assays are exploratory and are not intended to influence the individual patient's medical care. Findings for exploratory research assays will not be reported routinely in real time to the responsible clinician.

7.10 Trial sample retention at end of study

The Chief Investigators have overall responsibility for custodianship of the trial samples. Laboratories are instructed to retain any surplus samples pending instruction from the Chief Investigators on use, storage or destruction. It is possible that new or alternative assays may be of future scientific interest. At the end of the research study any surplus samples may be retained for use in other projects that have received ethical approval. Hence, any surplus study samples may be transferred to a licensed tissue bank where they will be managed in accordance with applicable host institution policies and the Human Tissue Act (HTA) requirements.

7.11 Withdrawal of consent for sample collection and/or retention

A patient may withdraw consent to provide samples for research at any time without giving a reason. The Investigator must ensure that their wishes are recorded in the medical record and will inform the trials office accordingly. The investigator should discuss with patients the valuable use of samples that have already been provided and under circumstances where these samples have already been processed and anonymised, it would not be possible to destroy such samples.

• INVESTIGATIONAL MEDICINAL PRODUCTS (IMPS)

8.1 Name of IMPs

PF-02341066 (Crizotinib)
PD-0325901
Binimetinib (MEK162)

8.2 Treatment dose

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.

Dose escalation phase: PF-02341066 in combination with Binimetinib

PF-02341066 (Crizotinib): 250mg orally once or twice 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.

Dose expansion phase:

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..

8.3 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)

8.4 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-02341066and 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-02340166 and Binimetinib dosing will be evaluated by capsule/tablet count during scheduled visits to the trial site by pharmacy staff.

8.4.1 Dose limiting Toxicity (DLT)

PF-02341066 in combination with PD-0325901 or Binimetinib

The dose limiting toxicity (DLT) and maximum tolerated dose (MTD) are defined using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. DLTs identified during the first cycle will inform the decision to dose escalate through the increasing dose levels.

A DLT is defined as an almost certainly or probably drug-related adverse event to PF-02341066 and/or PD-0325901 or Binimetinib.

- neutropenia Grade 4 for ≥5 days duration *(See note)
- febrile neutropenia (without clinically or microbiologically documented infection) with an absolute neutrophil count <1000/mm^3 and a single temperature of >38.3˚C or a sustained temperature of ≥38˚C for more than one hour.
- infection (documented clinically or microbiologically) with Grade 3 or 4 neutropenia (ANC <1.0 x 10^9/L)
- thrombocytopenia Grade 4:
    a) for ≥5 days duration * (See note), or
    b) associated with active bleeding, or
    c) requiring platelet transfusion.
- CK elevation ≥ Grade 3 associated with an increase in creatinine ≥ 1.5 × the patient's Baseline screening creatinine.
- Grade 2 pneumonitis
- Total bilirubin Grade ≥ 3
- AST or ALT Grade ≥ 3 in conjunction with total bilirubin Grade ≥ 2 of any duration
- AST or ALT Grade 3 for > 7 consecutive days
- AST or ALT Grade 4
- Serum creatinine Grade ≥ 3
- Grade 3 or 4 toxicity to organs other than the bone marrow but including Grade 3 and Grade 4 biochemical AEs EXCLUDING:
    a) Grade 3 nausea in patients who have not received optimal treatment with anti-emetics
    b) Grade 3 or 4 vomiting in patients who have not received optimal treatment with anti-emetics
    c) Grade 3 or 4 diarrhoea in patients who have not received optimal treatment with anti-diarrhoeals and Grade 2 diarrhoea for more than 7 days in patients who have received optimal treatment with anti-diarrhoeals.
    d) Grade 3 fatigue, unless there is an increase by at least two grades from baseline
- AE with a fatal outcome

*** Note: In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia, a full blood count must be performed at least on Day 5 after the onset of the event to determine if a DLT has occurred. The Investigator must continue to monitor the patient closely until resolution to Grade 3 or less.**

Should any change be made to the grade or causality of an AE during the trial that may alter its DLT status, OCTO must be informed immediately as this may affect dose escalation decisions.

8.4.2 Maximum Tolerated Dose (MTD)

PF-02341066 in combination with PD-0325901
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.

PF-02341066 in combination with Binimetinib
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.

8.5 Dose modification

a. PF-02341066 in combination with PD-0325901

Every effort should be made to administer trial treatment on the planned schedule. The toxicity of each cycle of PF-02341066 and PD-0325901 must be recorded before the administration of the next one and graded according to the current version of the Common Terminology Criteria for Adverse Events (CTCAE Version 4.03). If individual patients experience treatment related toxicity, subsequent trial treatment may be delayed, omitted and/or dose modified according to the worst toxicity observed during the previous cycle as described below. Dose reductions are permanent (no intra-patient dose re-escalation is permitted). The following outlines provide guidance for the management of toxicities for patients treated with PF-02341066 and/or PD-0325901.

If $\geq$ 2/3 or $\geq$ 2/6 DLTs occur during cycle 1 in the first patient cohort (ie defined as exceeding the MTD), then the planned schedule of PF-02341066 on continuous dosing and/or PD-0325901 on day 1 – 21 every 28 day dosing will be discontinued. In that case, we need to explore:

- alternate intermittent schedules of both oral agents in combination, whereby a substantial amendment will be submitted to the MHRA prior to administering the proposed new dosing schedule.
- use of a monoclonal antibody directed against HGF (e.g. from AVEO or AMGEN), the ligand of cMET or the ectodomain of c-MET (eg MetMAb from Roche/Genentech) instead of PF-02341066

For grade 3, grade 4 or intolerable grade 2 toxicities, the treatment will be interrupted until recovery to <grade 2 or to base line (in the judgement of the investigator). If the patient fails to recover to this extent within 3 weeks, then trial treatment will be discontinued. If a patient cannot tolerate treatment after two successive dose reductions, trial treatment will be discontinued. This trial investigates the use of combined cMET and MEK inhibition, and so complete cessation of either drug will result in the patient discontinuing all trial treatment. In any of these circumstances, patients then will undergo end of treatment evaluation as per section 5.6 and will be followed up at the end of study visit at day 28-30 following the last treatment. Patients will then be monitored for progression and survival as per section 5.7.

b. PF-02341066 in combination with Binimetinib

Every effort should be made to administer trial treatment on the planned schedule. The toxicity of each cycle of PF-02341066 and Binimetinib must be recorded before the administration of the next one and graded according to the current version of the Common Terminology Criteria for Adverse Events (CTCAE Version 4.03). If individual patients experience treatment related toxicity, subsequent trial treatment may be delayed,

omitted and/or dose modified according to the worst toxicity observed during the previous cycle as described below. Dose reductions are permanent (no intra-patient dose re-escalation is permitted). The following outlines provide guidance for the management of toxicities for patients treated with PF-02341066 and/or Binimetinib.

If ≥ 2/3 or ≥ 2/6 DLTs occur during cycle 1 in the first patient cohort (i.e. defined as exceeding the MTD), then the planned schedule of PF-02341066 on continuous dosing and/or Binimetinib on either continuous dosing or day 1 – 21 every 28 day dosing, will be discontinued. In that case, we need to explore alternate intermittent schedules of either or both oral agents in combination, whereby a substantial amendment will be submitted to the MHRA prior to administering the proposed new dosing schedule.

For grade 3, grade 3 CPK rise associated with creatinine increase of 50% over baseline, grade 4 or intolerable grade 2 toxicities, the treatment will be interrupted until recovery to <grade 2 or to base line (in the judgement of the investigator). If the patient fails to recover to this extent within 3 weeks, then trial treatment will be discontinued. If a patient cannot tolerate treatment after two successive dose reductions, trial treatment will be discontinued. This trial investigates the use of combined cMET and MEK inhibition, and so complete cessation of either drug will result in the patient discontinuing all trial treatment. In any of these circumstances, patients then will undergo end of treatment evaluation as per section 5.6 and will be followed up at the end of study visit at day 28-30 following the last treatment. Patients will then be monitored for progression and survival as per section 5.7.

Comprehensive information on recommended guidelines for dose modification for Binimetinib is included in Appendix 6 and updated in Appendix 6A.

8.5.1 Non Haematological Toxicities:

Skin toxicities:

Maculopapular erythematous (acneiform) rash, similar to that described in patients with EGFR inhibitors, has been noted with MEK inhibitors (LoRusso et al., 2010). While most often of mild or moderate severity, grade 3 rash (associated with pain, ulceration, disfiguration or desquamation) has been noted. Patients should be informed about the frequent related cutaneous adverse reactions associated with PD-0325901 or Binimetinib and the need to avoid the exposure to extreme temperatures, the use of lotions (since lotions can contain alcohol) and direct sunlight (or tanning beds). The employment of preventive topical treatments, such as bathing techniques using bath oils or mild moisturizing soaps and bathing in tepid water may help to prevent the appearance of cutaneous toxicity or reduce its intensity. The use of regular moisturizing creams is also recommended to keep an appropriate skin hydration and humidity, which is useful to reduce the symptoms in case of rash appearance.
Rash, including erythematous, macular, papular, and pruritic rash, has been reported in 47 (7%) patients treated with single-agent PF-02341066. All of these cases were Grade 1 or 2 in severity.

Grade of AE Maculo-Papular rash	**Rash severity**	**Management of rash**	**Alterations to IMP doses**
Grade 1	Localised Minimally symptomatic No impact on activities of daily living (ADL) No sign of superinfection	Initiate prophylactic regimen if not already started. Consider using moderate strength topical steroids[a]	PD-0325901: no change Binimetinib: no change PF-02341066: no change Reassess after 2 weeks; if rash worsens or does not improve, proceed as for Grade 2.
Grade 2	Generalized Mild symptoms (e.g. pruritis, tenderness) Minimal impact on ADL No sign of superinfection	Initiate prophylactic regimen if not already started, using moderate strength topical steroids[a]	PD-0325901 or Binimetinib: Hold until ≤ grade 1, then restart at the same dose level. PF-02341066: no change Reassess after 2 weeks, if rash worsens or does not improve, proceed as for Grade 3.
Grade 3	Generalized Severe symptoms (e.g., pruritis, tenderness) Significant impact on ADL	Initiate prophylactic regimen if not already started, using moderate strength topical steroids[a] plus methylprednisone	PD-0325901 or Binimetinib: Hold until ≤ grade 1, then resume with -1 dose level. PF-02341066: Hold until ≤ grade 1, then resume with

	Sign of, or potential for, superinfection	dose pack. Consider obtaining dermatology consultation. Manage rash per dermatologist's recommendation.	same dose level. If rash worsens or does not improve in 2 weeks, permanently discontinue PD-0325901/Binimetinib and PF-02341066.

[a] **Hydrocortisone 2.5% cream or fluticasone proprionate 0.5% cream.**

The need for oral or topical antibiotics (e.g., clindamycin cream, oral minocycline or doxycycline etc) and higher strength topical steroids is a clinical decision of the investigator. Oral or topical retinoids are not recommended.
It is strongly recommended that subjects who develop rash or other skin toxicities have a consultation with a dermatologist to determine appropriate management.

- For **pruritic lesions**, the use of cool compresses and oral antihistamine agents may be helpful.
- For **fissuring**, the use of Monsel's solution, silver nitrate, or zinc oxide cream is advised.
- For **desquamation**, thick emollients and mild soap are recommended.
- For **paronychia**, antiseptic bath and local potent corticosteroids, in addition to oral antibiotics, are recommended. If no improvement is seen, a dermatology or surgery consultation is recommended.

For **infected lesions**, bacterial and fungal culturing followed by the appropriate culture-driving systemic or topical antibiotics is indicated.

Fatigue:

Fatigue has been reported as a common side effect for PD-0325901, Binimetinib and PF-02341066, with the majority of these cases of grade 1 or 2 in severity.

Grade of event	**Clinical presentation**	**Alterations to IMP doses**
Grade 1	Fatigue relieved by rest	PD-0325901: no change Binimetinib: no change PF-02341066: no change
Grade 2	Fatigue not relieved by rest; limiting instrumental ADL	PD-0325901: no change Binimetinib: no change PF-02341066: no change
Grade 3	Fatigue not relieved by rest, limiting self care ADL	Hold until grade 1 – resume -1 dose level PD-0325901/Binimetinb
Grade 4	-	Off protocol; STOP all study drug agents

Diarrhoea:

Diarrhoea has been reported as a common side effect for all 3 IMPs. The majority of these cases were grade 1 or 2 in severity and can be symptomatically managed with loperamide 2mg PRN.

Grade of event	**Diarrhoea Severity**	**Adverse Event Management guidelines**	**Alterations to IMP doses**
Grade 1 Uncomplicated diarrhoea	Increase of <4 stools per day over baseline; mild increase in colostomy output compared to baseline.	***Diet*****:** Stop all lactose-containing products; eat small meals, BRAT diet (bananas, apples, rice, toast) is recommended. ***Hydration****:* 8 to 10 large glasses of clear liquids per day (e.g., Gatorade or broth) ***Loperamide****:* initially 4mg, followed by 2mg every 4 hours or after every unformed stool, to a maximum of 16mg/ day.	PD-0325901: no change Binimetinib: no change PF-02341066: no change
Grade 2 Uncomplicated diarrhoea	Increase of 4-6 stools per day over baseline; moderate increase in colostomy output compared to baseline.		PD-0325901: no change Binimetinib: no change PF-02341066: no change If diarrhoea is Grade 2 for >48 hours, interrupt study treatment

		Continue until diarrhoea-free for 12 hours. ***Diarrhoea > 24 hours****:* Loperamide 2mg every two hours to a maximum of 16mg/ day. Consider adding oral antibiotics. ***Diarrhoea >48 hours*****:** Loperamide 2mg every two hours to a maximum of 16mg/ day. Add budesonide or other 2nd line therapies (otreotide, or tincture of opium) and oral antibiotics.	until resolution to ≤ Grade 1. Restart study treatment at the current dose level.
Grade 3 Any complicated diarrhoea.	Increase of ≥7 stools per day over baseline; incontinency; hospitalization indicated; severe increase in colostomy output compared to baseline; Limiting self-care ADL.	Clinical evaluation is mandatory. *Loperamide*[c]: initially 4mg, followed by 2mg every 4 hours or after every unformed stool, to a maximum of 16mg/ day. Continue until diarrhoea-free for 12 hours. *Oral antibiotics and 2nd line therapies* should be implemented if clinically indicated. *Hydration:* intravenous fluids should be administered if clinically indicated. *Antibiotics (oral or iV)* should be administered if clinically indicated. Interventions should be continued until the patient is diarrhoea-free for ≥ 24 hours. Intervention may require hospitalisation for patients at risk of life-threatening complications.	Interrupt study treatment until diarrhoea recovers to ≤ Grade 1. Restart study treatment with a one dose level reduction. If 3 dose reductions of study treatment are clinically indicated, **permanently discontinue study treatment.**
Grade 4	Life threatening consequences; urgent intervention indicated.		Off protocol; STOP all study drug agents

Other, frequent causes for diarrhoea including concomitant medications (e.g., stool softeners, laxatives, antacids, etc.), infections by *C. difficile* or other pathogens, partial bowel obstruction, etc., should be clinically excluded. Guidelines regarding management and dose reduction for diarrhoea considered to be related to study treatment by the investigator are provided in this Table.

- Uncomplicated diarrhoea is defined by the absence of symptoms such as cramping, nausea/vomiting ≥Grade 2, decreased performance status, pyrexia, sepsis, neutropenia ≥Grade 3, frank bleeding, and/or dehydration requiring iV fluid substitution.

- Complicated diarrhoea is defined by the presence of symptoms such as cramping, nausea/vomiting ≥Grade 2, decreased performance status, pyrexia, sepsis, neutropenia ≥Grade 3, frank bleeding, and/or dehydration requiring iV fluid substitution.

- Loperamide should be made available to the patient prior to the start of study treatment so that loperamide administration can begin at the first signs of diarrhoea.

- Escalation of study treatment to the previous dose level is allowed after consultation with the trial coordination team in the absence of another episode of complicated or severe diarrhoea in the 4 weeks subsequent to dose reduction.

Nausea/vomiting:

Nausea has been reported as a common side effect for all 3 IMPs. The majority of these cases were grade 1 or 2 in severity and can be symptomatically managed. Standard anti-emetics such as cyclizine may be used for the treatment of vomiting. Taking PF-02341066 with food may reduce nausea. Prophylactic anti-emetics may be used.

Grade of event	Clinical presentation	Alterations to IMP doses
Grade 1	**Nausea:** Loss of appetite without alteration in eating habits **Vomiting**: 1-2 episodes (separated by 5 minutes) in 24h	PD-0325901: no change Binimetinib: no change PF-02341066: no change
Grade 2	**Nausea**: Oral intake decreased without significant weight loss, dehydration or malnutrition **Vomiting**: 3-5 episodes (separated by 5 minutes) in 24 h	PD-0325901: no change Binimetinib: no change PF-02341066: no change
Grade 3	**Nausea**: Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated **Vomiting**: ≥6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Hold until < grade 1 – resume -1 dose level
Grade 4	Life-threatening consequences; urgent intervention indicated	Off protocol; STOP all study drug agents

Visual disturbances/retinal vein occlusion (RVO):

Grade 1-2 visual symptoms, such as blurred vision, photopsia, and halos, generally with preservation of acuity, have been reported for PD-0325901 and also for Binimetinib. All episodes of RVO with PD-0325901 presented quite late, after 13, 15 and 36 weeks of therapy. A retrospective analysis of relevant visual episodes found predisposing factors for retinopathy (hypertension, diabetes, hypercholesterolemia, and glaucoma).
Diplopia; photopsia; vision blurred; visual brightness; visual field defect; vitreous floaters; visual impairment, mostly grade 1 or 2 have been seen with PF-02341066 (Camidge et al., 2012).
Baseline ophthalmologic examination including visual acuity, pressure, perimetry and slit lamp examination with fundoscopy and digital photography should be performed for all patients. Optical coherence tomography and fluorescin angiography should also be performed with PD-0325901, or if clinically indicated. If the patient develops new visual disturbances/symptoms suggestive of RVO, ophthalmologic investigation will be urgently repeated.

Grade of event	Eye disorder severity	Alterations to IMP doses
Grade 1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	a. If the changes are clearly not due to retinal or retinal vein abnormalities or are clearly unrelated to study drug(s), (e.g., conjunctivitis), PD-0325901/Binimetinib and PF-02341066 may continue with close observation. b. If drug attribution or aetiology is unclear, immediately refer the patient for an ophthalmic exam. If an ophthalmic exam cannot be performed within 7 days of onset of the event, then interrupt PD-0325901/Binimetinib and PF-02341066 until the exam can be performed. c. If a retinal abnormality is noted, interrupt PD-0325901/Binimetinib immediately and consider referral to a retinal specialist if available for further evaluation. d. If RVO is diagnosed, then report as SAE and permanently discontinue PD-

		0325901/Binimetinib. e. If CSR is diagnosed, then interrupt PD-0325901/Binimetinib until signs and symptoms have resolved. Resume PD-0325901/Binimetinib with a 1 dose level reduction. f. If there is no evidence of RVO or CSR, then resume PD-0325901/Binimetinib at the same dose level.
Grade 2	Moderate, minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL.	a. Immediately interrupt PD-0325901/Binimetinib and PF-02341066 and refer the patient to an ophthalmologist for evaluation. For all patients with findings consistent with RVO or CSR based on the ophthalmic exam, consider referral to a retinal specialist if available for further evaluation. b. If RVO is diagnosed, then report as SAE and permanently discontinue PD-0325901/Binimetinib and PF-02341066 c. If CSR is diagnosed, then interrupt PD-0325901/Binimetinib and until signs and symptoms have resolved. Resume PD-0325901/Binimetinib with a 1 dose level reduction. d. If there is no evidence of RVO or CSR, interrupt PD-0325901/Binimetinib and PF-02341066 until signs and symptoms have returned to Grade 1 or resolved. Resume PD-0325901 or Binimetinib with a 1 dose level reduction, resume PF-02341066. MEK inhibition at the initial dose level may be considered if visual changes are clearly unrelated to PD-0325901/Binimetinib.
Grade 3	Severe or medically significant but not immediately sight-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	
Grade 4	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye.	Off protocol; STOP all study drug agents; Repeat ophthalmic consultation

For all visual changes, regardless of grade, a blood sample for pharmacokinetic analysis must be drawn as close as possible to the time of onset of the event.

Neurologic toxicity:

PD-0325901 has been associated with acute neurotoxicity (balance, gait disorders) in patients receiving ≥15mg BD, regardless of the schedule. Nervous system disorders (burning sensation; dizziness; dysgeusia; hypoesthesia; hypoaesthesia facial; neuralgia; neuropathy peripheral; paraesthesia; peripheral sensory neuropathy; peripheral motor neuropathy; sensory disturbance), usually grade 1 or 2 have also been seen with PF-02341066 (Appendix 3).

Grade of event Neuro-sensory Neuro-motor Neuro-mood Neuro-cortical or cerebellar	**Clinical presentation** **(see also Appendix 3)**	**Alterations to IMP doses**
Grade 1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	PD-0325901: no change Binimetinib: no change PF-02341066: no change
Grade 2	Moderate; minimal, local or Non-invasive intervention indicated; limiting age-appropriate instrumental ADL	PD-0325901: no change Binimetinib: no change PF-02341066: no change

Grade 3	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Hold until < grade 1 – resume -1 dose level
Grade 4	Life-threatening consequences; urgent intervention indicated	Off protocol; STOP all study drug agents

Transaminitis:

Transient and mild (grade 1 or 2) elevation of ALT has been reported for PD-0325901, Binimetinib and PF-02341066 (Kwak et al., 2010; LoRusso et al., 2010). The following guidelines are recommended:

Grade of event	Alterations to IMP doses
Grade 1 ALT, AST≤ 2.5 x N Bilirubin normal	PD-0325901: no change Binimetinib: no change PF-02341066: no change
Grade 2 ALT, AST 2.6 - 5.0 xN Bilirubin <1.5 x N	PD-0325901: no change Binimetinib: no change PF-02341066: no change
Grade 3 ALT, AST 5.1 - 20.0 xN Bilirubin 1.5 - 3.0 x N	Withhold until toxicity is grade 1 or better, or has returned to baseline, then resume treatment -1 dose level
Grade 4 ALT, AST > 20.0 x N Bilirubin > 3.0 x N	Off protocol; STOP all study drug agents

Pneumonitis:

Pneumonitis and Interstitial Lung Disease (ILD) at <1% frequency has been associated with PF-02341066 and Binimetinib. The following guidelines (in absence of disease progression, pulmonary embolism, positive cultures or radiation effect) are recommended:

Grade of event	Clinical presentation	Alterations to IMP doses
Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated.	PD-0325901: no change Binimetinib: no change PF-02341066: withhold dose until toxicity is grade 0, i.e. has returned to baseline, then resume treatment at the same dose. Discontinue permanently if pneumonitis recurs.
Grade 2	Symptomatic; medical intervention indicated; limiting instrumental ADL	PD-0325901: no change Binimetinib: withhold dose until improves to grade 0 or 1; then resume at lower dose; if not resolved within 3 weeks, permanently discontinue PF-02341066: withhold dose until toxicity is grade 0, then resume treatment at the same dose. Discontinue permanently if pneumonitis recurs.
Grade 3	Severe symptoms; limiting self-care ADL; oxygen indicated.	PD-0325901: no change PF-02341066 or Binimetinib: discontinue treatment and do not re-treat
Grade 4	Life-threatening respiratory compromise; urgent intervention indicated (e.g. tracheotomy or intubation).	Off protocol; STOP all study drug agents

Investigators must evaluate thoroughly patients who demonstrate potential signs/symptoms of pneumonitis/pneumonia. If a patient has a potential diagnosis of pneumonitis or drug related lung injury the following evaluations/procedures should be considered to assist or exclude the diagnosis of pneumonitis during this period:

- A sputum gram stain and culture (induced sputum if needed) bacterial, viral, fungal, protozoal, and mycobacteria
- Blood culture should be performed in febrile patients
- Thoracenthesis if pleural fluid is present (examined for same pathogens as sputum)
- Bronchoscopy with bronchoalveolar lavage (BAL) if appropriate. The BAL fluid should be sent for culture and cytology (same pathogens as above).
- Lung biopsy (e.g.open or thorascopic preferable, bronchoscopy with transbronchial biopsy) if appropriate.
- A plasma sample for BNP (B-type Natriuretic peptide) to evaluate for evidence of CHF,
- For Asian patients or any other in whom it is suspected, a blood sample for β-D-glucan to evaluate for the presence of protozoal pneumonia (e.g. Pneumocystis jerovicii)

If clinically appropriate, high dose corticosteroid treatment should be initiated. Should the event be fatal an autopsy is highly recommended to confirm/exclude the diagnosis. For any case of suspected pneumonitis please contact the Sponsor.

Left ventricular systolic dysfunctions:

Decreases of the left-ventricular-ejection-fraction (LVEF) have been observed in subjects receiving PD-0325901 and Binimetinib. LVEF changes are common and the severe, sometimes fatal, events can occur in patients treated with crizotinib. A review by European medicines regulators of data from clinical trials and reports of clinical practice has concluded that this side effect is common (i.e, occurs in between 1 in 10 and 1 in 100 patients who take crizotinib).
Up to 25 February 2015, about 14,700 patients worldwide have received crizotinib since licensing. Forty cases of cardiac failure have been reported in the post-marketing setting. In most cases cardiac failure occurred within 1 month of starting treatment with crizotinib, and affected patients with or without pre-existing heart disorders. The reports included some cases with evidence of symptoms of cardiac failure resolving on stopping crizotinib, and cases with evidence of symptoms reoccurring when it was reintroduced.

Grade of event	Clinical presentation	Alterations to IMP doses
Grade 1	Asymptomatic absolute decrease of > 10% in LVEF compared to baseline and the LVEF is below the institutions' LLN	-Hold Binimetinib and PF-02341066 and repeat LVEF within 2 weeks If LVEF recovers (defined as LVEF ≥ 50% or ≥ LLN and absolute decrease ≤ 10% compared to B/L) in ≤ 21 days, reduce 1 dose level . Repeat ECHO/MUGA at 2 weeks after resuming Binimetinib and PF-02341066, then every 4 weeks for 12 weeks until resolution If the LVEF does not recover in ≤ 21 days, permanently discontinue Binimetinib and PF-02341066. Closely monitor LVEF until resolution or for up to 16 weeks
Grade 2		
Grade 3 resting LVEF 39-20% or >20% absolute reduction from baseline	Symptomatic	Permanently discontinue study treatment Consult with cardiologist Repeat ECHO/MUGA after 2, 4, 8, 12 and 16 weeks or until resolution.
Grade 4 resting LVEF <20%		

Symptoms may include: dyspnoea, orthopnoea, and other signs and symptoms of pulmonary congestion and oedema.

Prolonged QTc interval:

Prolonged QTc interval has been reported as a common side effect in all 3 IMPs.

Grade of event	Alterations to IMP doses
Grade 1 QTc 450-470ms	PD-0325901: no change Binimetinib: no change PF-02341066: no change
Grade 2 QTc 470-500ms	Assess electrolytes and concomitant medications. Correct any electrolyte or magnesium abnormalities. Continue study treatment at the same dose level.
Grade 3 QTc >500ms on at least 2 separate ECG's	Interrupt both PF-02341066 and PD-0325901/Binimetinib until recovery to baseline. Assess electrolytes and concomitant medications. Correct any electrolyte or magnesium abnormalities. Resume treatment by reducing one dose level of either PF-02341066/PD-0325901 or PF-02341066/Binimetinib if no other cause for QTc prolongation is found otherwise resume with the same dose level.
Grade 4 QTc >= 501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Off protocol; STOP all study drug treatment

Based on an average QTc (Bazett's) value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period e.g. at least 2 minutes apart each, and then use the averaged QTc values of the 3 ECGs to determine if study treatments should be interrupted or discontinued.

Bradycardia:

For a heart rate <40 beats per minute, evaluate patient fully including an assessment of concomitant medications. Adjust the dosage of any medication known to be associated with bradycardia e.g. beta blockers. If the bradycardia is symptomatic at any time or does not improve within 7 days of adjusting the concomitant medications, hold PF-02341066 and Binimetinib dosing until recovery. Patient may continue treatment only with the agreement of both the sponsor and investigator

CK Elevations:

Serum CPK elevation has been observed in some patients receiving Binimetinib both as a single agent and also as part of a combined therapy.

Grade of event	Alterations to IMP doses
Grade 1 - 2 total CK ≥ 3 × ULN	Maintain dose level of Binimetinib and PF-02341066 Measure CK, CK isoenzymes and myoglobin in blood or urine weekly for 3 weeks and if total CK remains ≥ Grade 2, continue to assess CK, CK isoenzymes and myoglobin along with regularly scheduled clinical chemistry assessments
Grade 3 total CK ≥ 5 to 10 × ULN	• If asymptomatic, maintain dose of Binimetinib and PF-02341066 but monitor closely Measure CK, CK isoenzymes and myoglobin in blood or urine weekly for 3 weeks and if total CK remains ≥ Grade 3, continue to assess CK, CK isoenzymes and myoglobin along with regularly scheduled clinical chemistry assessments • If symptomatic (muscle pain/spasms), or asymptomatic with serum creatinine ≥ 1.5 x baseline creatinine, interrupt Binimetinib only until

	resolved to Grade ≤ 1 and monitor closely, then: If resolved in ≤ 21 days, reduce 1 dose level of Binimetinib If not resolved in ≤ 21 days, permanently discontinue Binimetinib and PF-02341066
Grade 4 total CK >10 x ULN	• If asymptomatic , hold Binimetinib only until resolved to Grade ≤ 1 and monitor closely, then: o If resolved in ≤ 21 days, reduce 1 dose level of Binimetinib. PF-02341066 no change. • If symptomatic , or asymptomatic withserum creatinine ≥ 1.5 x baseline creatinine, permanently discontinue Binimetinib and PF-02341066 If not resolved in ≤ 21 days, permanently discontinue Binimetinib - Off protocol; STOP Binimetinib and PF-02341066

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8.5.2 Haematological Toxicities:

Haematological abnormalities have been observed with all 3 IMPs, are usually of grade 1 and 2 severity and occur in less than 5% of patients.

Asymptomatic neutropaenia (ANC)

Grade of event	Alterations to IMP doses
≤1.5-≥1.0	Continue both drugs, repeat ANC in 1 week
<1.0 ≥0.5	Withhold PF-02341066 and PD-0325901/Binimetinib until toxicity is ≤2, or has returned to baseline, then resume treatment at the same dose level.
<0.5	Withhold PF-02341066 and PD-0325901/Binimetinib until toxicity is ≤2, or has returned to baseline, then reduce dose level -1.

Febrile neutropaenia/neutropenic sepsis:

If ANC is ≤ 1.0 with a declining trend and is associated with temperature above 38.0° C on two separate occasions and or associated with signs or symptoms of sepsis, treatment with both drugs should be held. Patients should be assessed immediately and treated as in patients with intravenous antibiotics (in accordance with the local hospital neutropenic sepsis guidelines) and supportive treatment as deemed necessary. G-CSF support may be given as deemed appropriate by the physician and in keeping with institutional guidelines (and recorded as concomitant medication).

Further treatment is issued after the patient has completely recovered from infection and ANC has resolved to ≥1.5, then reduce dose level -1.

On subsequent events of neutropaenic sepsis, the same protocol as above is followed and the combination therapy is discontinued.

Lymphopaenia:

No dose modification of the combination therapy is necessary if other laboratory parameters are normal and the lymphocyte counts are ≥ 0.5 x 10^9/l (normal reference range 2.0-3.5 x 10^9/l). Consider dose reduction of PD-0325901/Binimetinib or PF-02341066 at physician's discretion if lymphocyte count ≤0.5 x 10^9/l (grade 4).

Anaemia (Hb < 8g/dl or 80 g/l).

Grade of event	Alterations to IMP doses
≤10 g/dl > 8 g/dl, not symptomatic	No change in dose. .
≤ 8 g/dl > 6 g/dl	Blood transfusion according to local guidelines. No change in dose.
≤ 6g/dl > 5g/dl	Blood transfusion according to local guidelines. Withhold till Hb > 8 g/dl. Dose reduction of PD-0325901 or Binimetinib. Continue PF-02341066 at same dose
≤ 5g/dl	Blood transfusion according to local guidelines. Withhold till Hb > 8 g/dl. Off protocol; STOP both agents.

8.6 Compliance

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.

8.7 Management of overdose

In the event of a PF-02341066 or PD-0325901/Binimetinib overdose (defined as any dose above that specified in the protocol), the investigator should contact the OCTO and the Chief Investigator immediately and closely monitor the patient for AEs/SAEs and laboratory abnormalities. The investigator will use clinical judgment to treat any overdose.

Information regarding the quantity of the excess dose as well as the duration of the overdosing should be documented in the eCRF for treatment.

9 OTHER TREATMENTS (NON-IMPS)

9.1 Supportive medication

Local anti-emetic and anti-diarrhoeal drug policy may be followed.

9.2 Concomitant medication and non-drug therapies

Concomitant medication may be given as medically indicated. All patients will be asked to provide a complete list of prescription, over-the-counter and complementary and alternative medications that have been taken within the previous 4 weeks prior to the first treatment visit. They must also inform the Investigator about any new medication started while in the trial.
Details (including indication, doses, frequency and start / stop dates) of concomitant medication taken during the trial until the completion of the off-study visit must be recorded in the medical record and the appropriate CRF.

9.3 Prohibited therapies

Patients should not be prescribed any other anti-cancer or investigational therapies while participating in this study.

9.4 (Potential) Drug Interactions

PF-02341066 (Appendix 5)

Agents That May Increase Crizotinib Plasma Concentrations
Coadministration of PF-02341066 with strong CYP3A inhibitors may increase PF-02341066 plasma concentrations. The concomitant use of strong CYP3A inhibitors, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, and voriconazole, should be avoided. Grapefruit or grapefruit juice and Seville oranges, their juice and marmalade containing them may also increase plasma concentrations of crizotinib and should be avoided. Caution should be exercised with concomitant use of moderate CYP3A inhibitors.

Agents That May Decrease Crizotinib Plasma Concentrations

Coadministration of crizotinib with strong CYP3A inducers may decrease crizotinib plasma concentrations. The concurrent use of strong CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's Wort, should be avoided.

Agents Whose Plasma Concentrations May Be Altered By Crizotinib
PF-02341066 has been identified as an inhibitor of CYP3A both *in vitro* and *in vivo.* Coadministration of PF-02341066 with CYP3A4 substrates with narrow therapeutic indices associated with life-threatening arrhythmias including, but not limited to dihydroergotamine, ergotamine, pimozide, astemizole, cisapride, and terfenadine must be avoided during PF-02341066 treatment. In addition, caution must be exercised in patients receiving PF-02341066 in combination with other CYP3A4 substrates, particularly those with narrow therapeutic indices, including but not limited to alfentanil, cyclosporine, fentanyl, quinidine, sirolimus, and tacrolimus.

In addition to drug interactions due to enzyme inhibition and induction, the possibility of an additive pharmacodynamic interaction of PF-02341066 and other negatively chronotropic medications (e.g., beta-blockers and non-dihydropyridine calcium-channel blockers) should be considered. Co-administration of PF-02341066 with these medications may lead to significant decreases in heart rate.

PD-0325901

Drug interaction studies have not been conducted for PD-0325901 in humans. Based on *in vitro* studies, PD-0325901 and its circulating metabolite, PD-0315209, have a low potential to inhibit CYP2D6, CYP3A4, CYP1A2, and CYP2C19. However, the metabolite (PD-0315209) has the potential to inhibit CYP2C8 and CYP2C9. Caution should be exercised when co-administering PD-0325901 with drugs that are substrates for CYP2C8 or CYP2C9. Patients taking warfarin should be switched to low molecular weight heparin for the duration of the study. Other interactions may exist that are as yet unknown.

Binimetinib

A human ADME study identified direct glucuronidation as a main metabolic pathway of Binimetinib, and in vitro studies identified UGT1A1 as the main enzyme mediating direct glucuronidation. The impact of UGT1A1 inhibitors or inducers has not been assessed to date; therefore, inhibitors or inducers of UGT1A1 should be co-administered with caution. *In vitro* solubility data indicates that Binimetinib's solubility is pH dependent. Currently, the impact of pH modifying agents (such as proton pump inhibitors) on the PK of Binimetinib is unknown. If a patient is prescribed a pH modifying agent, it is recommended that patients take the pH modifying agent at least two hours after Binimetinib administration. Binimetinib has been shown to be a substrate for P-gp and BCRP *in vitro*. The impact of P- gp/BCRP inhibitors on the PK of Binimetinib in vivo is unknown; therefore, it is recommended that P-gp and BCRP inhibitors are dosed with caution. Patients taking warfarin should be switched to low molecular weight heparin for the duration of the study. Other interactions may exist that are as yet unknown.

10 DRUG MANAGEMENT

10.1 Drug supplies

PF-02341066 will be provided as clinical stock by Pfizer. PF-02341066 is formulated as capsules containing 200 or 250 mg of study medication and packaged in HDPE bottles.

PD-0325901 will be supplied as clinical stock by Pfizer. PD-0325901 is provided in 1 and 5 mg strength hard gelatin capsules (42 capsules per bottle). Both IMPs will be manufactured and QP released to the specifications of an existing IMPD (Investigational Medicinal Product Dossier) under strict GMP conditions.
For both their IMPs, Pfizer provides these as bulk stock and repackaging, labelling, QP release and distribution to the local hospital pharmacies will be performed free of charge by Almac Clinical Services.

Binimetinib will be provided as clinical stock by Array. Binimetinib is provided in 15mg strength tablets and packaged in HDPE bottles (70 tablets per bottle). Array provides this stock as bottled, labelled and QP released to Almac Clinical Services who will then store and distribute the stock, free of charge, to the participating site local pharmacies.

All supportive medication is to be sourced and funded locally.
Drugs will be prescribed, tracked, and dispensed according to the local policy for investigator initiated studies.

10.2 Drug ordering

Initial supplies of PF-02341066 and PD-0325901 or Binimetinib are distributed by Almac Clinical Services after they have been informed by the Trials office that all approvals are in place. Re-supply of PF-02341066, PD-0325901 and Binimetinib will be managed by the Trials office. If any supplies of PF-02341066, PD-0325901 or Binimetinib are damaged the pharmacist should contact the Trials office for replacement patient supplies.

10.3 IMP Receipt

Upon receipt of each drug delivery, the site must complete and return the scanned enclosed acknowledgement of receipt by email within 24 hours.

If supplies are damaged on arrival, please contact OCTO promptly.

10.4 Handling and storage

The investigator or an approved representative (e.g. pharmacist) will ensure that all study drugs are stored in a secured area, under recommended storage conditions in accordance with applicable regulatory requirements

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PF-02341066 should be stored at room temperature (15°C - 30°C) and there are no specific restrictions.
PD-0325901 capsules are stored at 15°C - 25°C and there are no specific restrictions.
Binimetinib tablets are stored at 15°C - 25°C and there are no specific restrictions

10.5 Labelling

PF-02341066, PD-0325901 and Binimetinib will be supplied to participating sites appropriately labelled in accordance with all applicable regulatory requirements.

10.6 Dosing dispensing

PF-02341066 is formulated as capsules containing 200 or 250 mg of study medication and packaged in HDPE bottles and will be provided as 60 capsules per bottle for the 200mg strength and 60 capsules per bottle for the 250mg strength.

PD-0325901 is formulated as 1 and 5 mg strength hard gelatin capsules and will be supplied as 42 capsules per bottle. The number of bottles to be dispensed must be sufficient for the cycle of treatment. Patient specific details and the number of capsules to be taken per day must be added to the label prior to dispensing.

Binimetinib drug product is supplied as film-coated tablets in a-dosage strength of 15 mg. The film coated-tablets consist of Binimetinib drug substance; colloidal silicon dioxide/silica colloidal anhydrous; croscarmellose sodium; lactose monohydrate; magnesium stearate; microcrystalline cellulose/cellulose, microcrystalline; and a commercial film coating. The tablets are yellow to dark yellow and capsule shaped. The number of bottles to be dispensed must be sufficient for the cycle of treatment. Patient specific details and the number of tablets to be taken per day must be added to the label prior to dispensing.

10.7 Drug accountability

Full drug accountability records must be maintained for PF-02341066, PD-0325901 and Binimetinib using the Drug Accountability Logs provided. Sites can use their own logs provided their use is approved in advance by the Trials office.

The Drug Accountability Logs should be kept up to date and have to contain the following information; patient identifier, date and quantity received at site, date and quantity dispensed, date and quantity returned/destroyed at site.

The Drug Accountability Logs must be available for inspection by the Sponsor or its representative at every monitoring visit.

At the conclusion of the study the overall numbers of drug shipped to the centre, the number dispensed and the number destroyed or returned will be provided by the pharmacy. An account must be given of any discrepancy.

10.8 Drug returns from patients

Patients will be asked to return all bottles, whether empty or not, to the hospital. Unused PF-02341066, Binimetinib and PD-0325901 must be returned to pharmacy for counting and recording in the patient's Drug Accountability Log. Returns must be retained until permission to destroy is given by the trial office at the end of the study.

10.9 Drug destruction

Returned, unused and expired drugs should be destroyed only once permission has been granted by the Sponsor, as per the following table:

Expired drug	At the end of the study, once authorised to do so by the Sponsor, any unused drug should be destroyed by the site. A signed & dated Drug Destruction form must be completed scanned and emailed to OCTO.
Drug left unused/not dispensed	At the end of the study, once authorised to do so by the Sponsor, any unused drug should be destroyed by the site. A signed & dated Drug Destruction form must be completed scanned and emailed to OCTO.
Patient returns	Upon receipt, number of capsules returned to be recorded on patient's Drug Accountability Log. At the end of the study, once authorised to do so by the Sponsor, any unused drug should be destroyed by the site. A signed & dated Drug Destruction form must be completed and scanned and emailed OCTO.

10.10 Occupational safety

The product is not expected to pose an occupational safety risk to site staff under normal conditions of use and administration.

11 EVALUATION OF RESPONSE

11.1 Measurement of disease for solid tumour

Objective disease response must be measured according to the RECIST version 1.1 criteria given in Appendix 4.
In the dose escalation and expansion phase, radiological tumour response with CT scan chest/abdomen/pelvis will be evaluated prior to study entry and then after 2nd, 4th, 6th cycle, and every 2 cycles thereafter, until intolerable toxicity or progressive disease.

11.2 Tumour assessment

A clinical and CT-graphic evaluation of malignancy, as judged appropriate by the Investigator, and in line with the protocol, must be performed before starting the study treatment. The same methods that detect lesions at baseline will be used to follow these lesions throughout the study. To ensure compatibility, the radiological assessments used to assess response must be performed using identical techniques.

11.2.1 Baseline evaluations

These will include radiological measurements of the extent of disease by CT chest/abdomen/pelvis or CT chest with MRI abdomen/pelvis). All areas of disease present must be mentioned (even if specific lesions are not going to be followed for response) and the measurements of all measurable lesions must be recorded on the scan reports. Any non-measurable lesions must be stated as being present. For clinical measurements, documentation by colour photography including a ruler to estimate the size of the lesion is recommended to aid external independent review of responses.
All patients with at least one measurable lesion are included in the trial.

11.2.2 Evaluations during treatment and at off-study

Tumour assessment will be repeated as per the schedule of events given or more frequently if clinically indicated. All lesions measured at baseline must be measured at subsequent disease assessments, and recorded on the scan reports. All non-measurable lesions noted at baseline must be reported as present or absent.

Investigators must ensure that their radiologists are aware of the requirement to follow up and measure every target lesion mentioned at baseline and comment on the non-target lesions in accordance with RECIST 1.1 criteria.

11.3 Tumour response

All patients included in the study must be assessed for response to treatment, even if there is a major protocol treatment deviation or if they are ineligible, or not followed/re-evaluated. 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).

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented.

Date of progression is defined as the first day when RECIST (version 1.1) PD is observed.

Early death is defined as any death occurring before the first per protocol time point of tumour re-evaluation. The responsible investigator will decide if the cause of death is malignant disease, toxicity or other cause.

Patients for whom response is not confirmed will be classified as "unknown", unless they meet the criteria for stable disease (or the criteria for partial response in case of an unconfirmed complete response). Patients' response will also be classified as "unknown" if insufficient data were collected to allow evaluation per these criteria.

Should rapid tumour progression occur before the completion of 8 weeks treatment the patient will be classified as having early progression (EP).

Tumour response should be classified as "not evaluable" (NE), only when it is not possible to classify it under another response category, e.g., when baseline and/or follow-up assessment is not performed or not performed appropriately.

The applicable overall response category for each visit that includes disease assessment must be recorded in the medical record for inclusion in the appropriate CRF in OpenClinica.

11.4 Other definitions of outcome:

Toxic death: Any death to which drug toxicity is thought to have a major contribution.
Early death: Death during the first three weeks of treatment that is not a toxic death.

12 ASSESSMENT OF SAFETY

The Investigator will monitor each patient for clinical and laboratory evidence of adverse events on a routine basis throughout the study. Should an Investigator become aware of any study drug related SAEs following this period these must also be reported as stated below. Adverse event monitoring starts from the time the patient consents to the study until they complete the trial. All reportable AEs will be followed to a satisfactory conclusion. Any reportable AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF.

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.

12.1 Adverse Event Definitions

An Adverse Event or experience (AE) is any untoward medical occurrence in a study subject temporally associated with the administration of an investigational medicinal product (IMP) or a comparator product,

whether or not considered related to the IMP or a comparator product. An AE can therefore be any unfavourable and unintended sign, symptom, disease (new or exacerbated) and /or significant abnormal laboratory or physiological observation temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be reported as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

A Serious Adverse Event (SAE) is any AE, regardless of dose, causality or expectedness, that:

• **Results in death**	
• **Is life-threatening**	This refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
• **Requires in-patient hospitalisation or prolongs existing inpatient hospitalisation**	In general, hospitalisation signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether hospitalisation occurred or was necessary, the AE should be considered serious.
• **Results in persistent or significant incapacity or disability**	This means a substantial disruption of a person's ability to conduct normal life functions. It does not include experiences of relatively minor medical significance or accidental trauma (e.g. sprained ankle), which does not constitute a substantial disruption.
• **Is a congenital anomaly or birth defect**	
• **Is any other medically important event**	Defined as an event that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above. Any new primary cancer must be reported as an SAE.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above, and are usually associated with events that pose a threat to a patient's life or ability to function. The seriousness criteria in the table above should be used to determine if the event is serious.

An Adverse Drug Reaction (ADR) is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

An Unexpected Drug Reaction is an adverse drug reaction, the nature or severity of which, is not consistent with applicable reference safety information section (referring to SPC or IB).

A Suspected Unexpected Serious Adverse Drug Reaction (SUSAR) is a serious adverse drug reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or SPC for an approved product).

12.2 Clinical laboratory abnormalities and other abnormal assessments as AEs and SAEs

Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g., ECGs, X-rays and scans) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definitions given above.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

12.3 Determining adverse event causality

The Investigator will assess and classify the relationship of an AE to the trial IMP ((PF-02341066 (Crizotinib) and PD-0325901 or PF-02341066 (Crizotinib) and Binimetinib)) as follows:

Classification	Relationship	Definition
drug-related	**Definitely related**	• Starts within a time related to the study drug administration *and* • No obvious alternative medical explanation.
	Probably related	• Starts within a time related to the study drug administration *and* • Cannot be reasonably explained by known characteristics of the patient's clinical state.
	Possibly related	• Starts within a time related to the study drug administration *and* • A causal relationship between the study drug and the adverse event is at least a reasonable possibility.
not drug related	**Probably not related**	• The time association or the patient's clinical state is such that the study drug is not likely to have had an association with the observed effect.
	Definitely not related	• The AE is definitely not associated with the study drug administered.

The Investigator must endeavour to obtain sufficient information to confirm the causality of the adverse event (i.e. relation to surgery, study drug, background treatment, other illness, progressive malignancy etc) and give their opinion of the causal relationship between each AE and study drug. This may require instituting supplementary investigations of significant AEs based on their clinical judgement of the likely causative factors and/or include seeking a further specialist opinion.

12.4 Expected adverse events

Section 6.2 of the IB for PD-0325901 lists all the expected side effects associated with the use of PD-0325901. Section 6.0 of the IB for MEK 162 (Binimetinib) lists all the expected side effects associated with the use of Binimetinib. Section 4.8 of the SmPC for PF-02341066 lists all the expected side effects associated with the use of PF-02341066. A copy of the current, approved version of RSI documents for each IMP must be held in the Site File for reference. Please note that the list of expected side effects for PF-02341066 (Crizotinib) in the SmPC are those listed for advanced non-small cell lung carcinoma (NSCLC) patients. It should also be noted that the side effects for Binimetinib in the SmPC are those listed for

advanced unresectable or metastatic NRAS mutation-positive melanoma. It is therefore possible that in this study population other side effects may occur, or the patient might suffer a more severe reaction.

12.5 Suspected Unexpected Serious Adverse Drug Reactions (SUSARs)

All SUSARs must be reported to the responsible Authority and main REC within very tight deadlines depending on the outcome, so it is imperative that sites report potential SUSARs to the trials office without delay. OCTO will report SUSARs according to their SOPs. In addition, other safety issues qualify for expedited reporting where they might materially alter the current risk assessment of an IMP or be sufficient to change IMP administration or the overall conduct of the trial. Responsibility for expedited safety reporting will be assigned by the Sponsor.

OCTO must ensure that all SUSARs are reported to the competent authorities of the EU countries in which the trial is taking place

12.6 Expedited reporting of SAEs

The following SAE reporting requirements apply regardless of the Investigator's assessment of the causality of the SAE (See section 12.9 for exceptions). All SAEs should be reported on the trial SAE report form (see SAE report form and instructions for completion). Please note that the SAE report form is a paper form and these data cannot be entered into the eCRF system (OpenClinica).

The SAE form must be completed, scanned and emailed to the Oxford MErCuRIC Pharmacovigilance Team at OCTO: octo-safety@oncology.ox.ac.uk :

SAE forms must be completed with all critical information as soon as possible and submitted within 24hrs of becoming aware of the event by scanning the report and sending as an attachment in email to:
octo-safety@oncology.ox.ac.uk.

If the SAE has not been reported within the specified timeframe, a reason for lateness must be provided when sending the SAE Report Form.

Investigators should also adhere to their local policy for incident and SAE reporting in research.

Safety issues that qualify for expedited reporting where they might materially alter the current risk-benefit assessment of an IMP or be sufficient to change the IMP administration or the overall conduct of the trial. For instance:

- Single case reports of an expected serious adverse reaction with an unexpected outcome.
- An increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important.
- Post study SUSARS that occur after the patient has completed a clinical trial and are reported by the investigator to OCTO.
- New event relating to the conduct of the trial or the development of the IMP likely to affect the safety of the subjects.

OCTO will send all SAE reports to Pfizer (or designee) and Array Biopharma (or designee) within 24 hours of receipt as per any agreement.

12.7 Follow-up of Serious Adverse Events

If new or amended information on a reported SAE becomes available, the Investigator should report this on a new SAE form or update the existing form, without obscuring any initial information. All new data must be initialled and dated so that all changes are clearly identified. . .

Follow up will continue until all the necessary safety data for the event has been gathered. Any SAE that is ongoing when a subject completes his/her participation in the trial must be followed until any of the following occurs:

- The event resolves or stabilizes;
- The event returns to baseline condition or value (if a baseline value is available);
- The event is attributed to other agent(s) or to factors unrelated to study conduct.

AEs which are serious must be reported to OCTO from the first dose of PF-02341066 (Crizotinib) and PD-0325901 and up to and including 30 days after administration of the last dose of PF-02341066 (Crizotinib) and PD-0325901 or PF-02341066 (Crizotinib) and Binimetinib . Any SAE that occurs at any time after completion of PF-02341066 (Crizotinib) and PD-0325901 or PF-02341066 (Crizotinib) and Binimetinib treatment, or after the designated follow-up period that the investigator considers to be related to any study drug, must be reported.

12.8 Reporting Adverse Events on the CRF

All AEs, including Serious AEs, occurring during treatment and within 30 days after the last protocol treatment must be recorded on the case report forms (CRF) for that patient. The information provided will include date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome and relationship of the AE to study drug. Any concomitant medications or other any therapy used to treat the event must be listed. The Investigator will provide an "other" cause for serious AEs considered to be unrelated to the study drug. Sites should ensure data entered into the CRF is consistent with the SAE report information where applicable.

Each separate AE episode must be recorded. For example, if an AE resolves completely or resolves to baseline and then recurs or worsens again, this must be recorded as a separate AE. For AEs to be considered intermittent, the events must be of similar nature and severity.

Adverse Events reporting requirements

Subjects having adverse events will be monitored with relevant clinical assessments and laboratory tests as determined by the Investigator. All adverse events must be followed to satisfactory resolution or stabilization of the event(s) including the investigation for the likely causative factor. Any actions taken and follow-up results must be recorded in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation. For all adverse events which require the subject to be discontinued from the study, relevant clinical assessments and laboratory tests will be repeated, on at least a weekly basis, until final resolution or stabilisation of the event(s).

12.9 Events exempt from being reported as AE/ SAEs

Abnormal findings associated with the disease being studied:

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the patient's condition, or that are present or detected at the start of the study and do not worsen, should not be reported as AEs or SAEs

Progression of underlying disease

Disease progression and resultant death will be captured on the CRF. An event that is part of the natural course of the disease under study (i.e., disease progression or admission for standard treatment) should not be reported as an AE/SAE. However, if the progression of the underlying disease is greater than that which would normally be expected, or if the investigator considers that there may be a causal relationship between the IMP or protocol design/procedures and the disease progression, then it must be reported.

Every effort should be made to document the objective progression of underlying malignancy. In some cases, the determination of clinical progression may be based on symptomatic deterioration. For example, progression may be evident from clinical symptoms, but is not supported by tumour measurements. Or, the disease progression is so evident that the investigator may elect not to perform further disease assessments.

Death on study

Death due to disease under study is to be recorded on the Death CRF form providing the death is not unexpected or if a causal relationship suspected. The investigator must clearly state whether the death was expected or unexpected and whether a causal relationship to the study IMP or other protocol treatment intervention is suspected.

Elective admissions and supportive care
Elective admissions to hospital for patient convenience or for planned procedures or investigations or treatment as specified in this protocol and standard supportive care are not SAEs, and do not require SAE reporting. Hospital admission for the following supportive care procedures are considered standard for this patient group and should not be reported as SAEs:

- insertion of stent
- insertion of Port-A-Cath, PICC line etc.
- admission for hydration
- admission for transfusion

12.10 Development Safety Update Reports

DSURs will be co-ordinated by OCTO and prepared in collaboration with the CI and submitted in parallel to the regulatory authority and responsible Research Ethics Committee within 60 days of the anniversary of the date of regulatory approval. A copy of each report will be provided to Pfizer, Array Biopharma and the sponsor.

12.11 Informing Investigators of new safety information

OCTO or the Chief Investigator will ensure that all investigators are kept informed in a timely manner, as new safety profile information becomes available. Investigators are responsible for briefing their study team and onward transmission to R&D office as appropriate.

13 PREGNANCY AND BREAST FEEDING

Pregnancies (in a participant or partner) occurring within 6 months of treatment dosing with PF-02341066, PD-0325901 or Binimetinib must be reported using the Pregnancy Notification Form which should be scanned and emailed to OCTO within 24 hours of receipt of information at octo-safety@oncology.ox.ac.uk. In the event that the pregnancy results in an abnormal outcome and meets the criteria for immediate classification as a serious adverse event, (i.e. spontaneous abortion, still birth, neonatal death or congenital anomaly), the investigator should follow the procedures for reporting serious adverse events. **Note:** Pregnancy itself is only considered an AE/SAE if there is reason to believe it may be the result of an interaction between the study IMP and the contraceptive used.

Women who become pregnant should be withdrawn from treatment at the earliest opportunity. All reported pregnancies should be followed up until the outcome. Pregnancy outcome must be recorded in the medical record and in the follow-up section of the Pregnancy Notification Form. Any abnormal outcome (other than elective abortion) for the mother or child should also be reported as a SAE.

Pfizer should also be informed by OCTO of any pregnancy arising in a study participant or his/her partner whilst taking part in the trial or during a stage where the foetus could have been exposed to the medicinal product. Following inclusion of the Binimetinib into this trial, Array Biopharma should also be informed by OCTO of any pregnancy arising in a study participant or his/her partner whilst taking part in the trial or during a stage where the foetus could have been exposed to the medicinal product.

14 DEFINING THE END OF TRIAL

For this study the end of the trial is defined as the last visit of the last patient undergoing the trial (LPLV).

The study will be stopped when:

- The stated number of patients to be recruited is reached.

AND

- All patients have discontinued treatment with either PD-0325901 in combination with PF-02341066 or Binimetinib in combination with PF-02341066.

The sponsor, Chief Investigator in consultation with the trial committee, reserve the right to terminate the study earlier at any time. In terminating the study, they must ensure that adequate consideration is given to the protection of the participants' best interests.

15 STATISTICAL CONSIDERATIONS

15.1 Sample size

Phase I dose escalation using PF-02341066 in combination with PD-0325901
Between 2 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 earlier sections of the protocol. The dose escalation is agreed between the CI's at the recruiting centres based on the definitions in this protocol.

Phase I dose escalation using PF-02341066 in combination with Binimetinib
Up to 25 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 earlier sections of the protocol. The dose escalation is agreed between the CI's at the four recruiting centres based on the definitions in this protocol.

Dose expansion

a) *RAS*MT expansion phase statistical plan:

A Simon Minimax design was proposed for the *RAS*MT patients, as these patients should be easier to recruit as they comprise 50% of the total CRC population and there is a shortage of competing therapeutic options. If 7/40 responders are observed in the *RAS*MT group, we will continue to the randomised phase II trial (WP2).

b) RAS WT/cMET amplified or mutated expansion phase statistical plan

c) RAS WT/cMET overexpressed expansion phase statistical plan

A Simon optimal design will be used for both the *RAS*WT/cMET+ groups. This design will give a rapid indication if an effect is not observed, allowing a timely decision to stop that group continuing in the trial (thereby involving fewer patient) or continue the trial (motivating further recruitment). *RAS*WT/cMET patients are rare, hence recruitment to this group will be slower than *RAS*MT. Due to the rarity of *RAS*WT/cMET patients and delays in the project timelines due to replacement of PD-0325901 with Binimetinib with , consequential delays due to protocol amendment, ethics/regulatory approval, Binimetinib supply delay) and lengthy phase Ia dose escalation for Binimetinib/Crizotinib (higher than anticipated number of patients requiring replacement), inclusion of *RAS*WT/cMET patients in the randomised phase II trial is not achievable. Nonetheless, this design will be the first study that aims to: (a) find these *RAS*WT MET aberrant cases, and (b) define the role of MET inhibition in these two separate MET-dependent groups.

Table 1 Sample size calculation for dose expansion phase design

RAS MT	RAS WT/cMET amplified	RAS WT/cMET overexpressed
Simon minimax: response *then* (conditionally) RCT: primary: PFS, secondary: OS	Simon optimal: response	Simon optimal: response
p1=0.1 p2=0.25 Power=80% Alpha=5% Stage 1: If at least 2 responder in first 22 patients, then continue to stage 2 Stage 2: If at least 7 responders in 40 patients, then continue to phase II	p1*=0.1 p2*=0.3 Power=80% Alpha=5% Stage 1: If 2/10 responders, then continue to Stage 2 Stage 2: If 6/29 responders, then continue to collect samples for MErCuRIC translational WPs and generate evidence for future clinical trials after MErCuRIC	p1*=0.1 p2*=0.3 Power=80% Alpha=5% Stage 1: If 2/10 responders, then continue to Stage 2 Stage 2: If 6/29 responders, then continue to collect samples for MErCuRIC translational WPs and generate evidence for future clinical trials after MErCuRIC
40 patients	29 patients	29 patients

15.2 Statistical analysis plan

A statistical analysis plan written adhering to the current OCTRU standard operating procedures will be signed off for this trial prior to analysis of primary or secondary aims.

Inclusion in analysis
Toxicity analysis will be on all patients who received at least some of at least one of the treatments in the combination.

Dose escalation for both combination IMPs
All evaluable patients will be analysed for dose escalation, which is those completing cycle 1 or who withdraw early for experiencing a DLT. 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
All patients recruited to the dose expansion phase will be analysed as intention to treat.
This means that patients will be analysed as they are consented irrespective of the amount of treatment actually received. 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. Results will be given separately for the three genetic subgroups.

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

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

Procedures for reporting any deviation(s) from the original statistical plan
Sites must report any deviations/violations to OCTO according to the procedure outlined during site initiation. These will be noted in the statistical report.

Final analysis

All patients enrolled in the study, will be accounted for. 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-free and overall survival will be performed.

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, study drug accountability and other data that impact on the general conduct of the study.

Baseline characteristics will be summarised for all evaluable patients. Treatment related toxicity will be tabulated by type and grade of toxicity for cycle 1 alone and all cycles. All trial treatment and efficacy information will be summarised.

Primary objectives:

Dose Escalation
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 patients with and without DLTs will also be presented according to dose level.

Dose Expansion
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.

Secondary Objectives:

Analysis will be specified in the analysis plan.

16 TRIAL COMMITTEES

16.1 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) (see section 16.2). 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
- Principal Investigators from participating sites.

16.2 Data and Safety Monitoring

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

16.3 Trial Steering Committee

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

17 DATA MANAGEMENT

17.1 Database considerations

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 Investigator will act as Data Custodian 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.

17.2 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). Please 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, i.e. within 7-14 days of the study visit or reported event..
- 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.

17.3 Accounting for missing, unused, or spurious data.

Missing data found will be chased up and supplemented where possible after consultation with the investigator. The control of the correctness of the data is performed with ranking tests, validity tests and consistency checks. Unused data will be retained as for used data.

18 CLINICAL STUDY REPORT

All clinical data will be presented at the end of the study as data listings. These will be checked to confirm the lists accurately represents the data collected during the course of the study. The trial data will then be locked and a final data listing produced. The clinical study report will be based on the final data listings. The locked trial data may then be used for analysis and publication.

19 STUDY SITE MANAGEMENT

19.1 Study site responsibilities

The Principal Investigator (the PI or lead clinician for the study site) has overall responsibility for conduct of the study, but may delegate responsibility where appropriate to suitably experienced and trained members of the study site team (e.g. drug supplies will be monitored by the on-site pharmacist, trial forms completed by the Data Manager, etc.). All members of the study site team must complete the delegation log or the Staff Contact Responsibility Sheet provided prior to undertaking any study duties. The PI must counter sign and date each entry in a timely manner, authorising staff to take on the delegated responsibilities. The Principal Investigator must ensure that all staff involved in the study are adequately trained and their duties have been logged on the forms provided. All Principal Investigators and Co-Investigators must have valid and up to date GCP training.
For further information on trial responsibilities, please refer to the ICH GCP guideline (E6).

19.2 Study site set up and activation

A Principal Investigator should lead the study at each site, providing the local study office with all core documentation and attend 'Site Training Call' organized by the trial office or visit before the site becomes activated (usually carried out as a telephone conference call or personal visit). The Trial Office will call to check that the site has all the required study information/documentation and is ready to recruit. The site will then be notified once they are activated on the MErCuRIC database and able to recruit.

19.3 Arrangements for sites outside the UK

Within each country (except the UK) the lead site will co-ordinate the applications to the necessary competent authority and other bodies (e.g. ethics) in line with national regulations. Each participating centre will be responsible for obtaining any local approvals needed. Any changes to the protocol or other supporting documents must be agreed with the Sponsor. Agreements will be put in place with each site/country which includes an appropriate delegation of responsibilities which will include producing translations into local language(s) of all patient documents.

19.4 Study documentation

OCTO will provide an Investigator File and Pharmacy File (where applicable) to each investigational site including: contact details, study procedures and all other documents required for completion of the study. Further copies of documents are available from OCTO as appropriate.

The trial office must review and approve any local changes made to any study documentation including patient information and consent forms prior to use. Additional documentation generated during the course of the trial, including relevant communications must be retained in the site files as necessary to reconstruct the conduct of the trial.

A screening log must be kept of all patients considered for the study and subsequently excluded; the reason for exclusion must be recorded on this form. A copy of the screening log without patient identifiers should be sent through to OCTO on a monthly basis, or as requested by OCTO. The original must be retained on site.

20 REGULATORY AND ETHICAL CONSIDERATIONS

The Sponsor and Investigators will ensure that this protocol will be conducted in compliance with the European Clinical Trials Regulations, the Principles of Good Clinical Practice (GCP)[3] and the applicable policies of the sponsoring organisation. Together, these implement the ethical principles of the Declaration of Helsinki (1996) and the regulatory requirements for clinical trials of an investigational medicinal product under the European Union Clinical Trials Directive.

[3] GCP Directive 2005/28/EC.

20.1 Ethical conduct of the trial and ethics approval

The protocol, patient information sheet, consent form and any other information that will be presented to potential trial patients (e.g. advertisements or information that supports or supplements the informed consent) will be reviewed and approved by an appropriately constituted, independent Research Ethics Committee (REC) or equivalent for non-UK countries (IRB etc.). Principal Investigators will be approved by the relevant national and/or local body.

20.2 Regulatory Authority approval

Approval to conduct the study will be obtained from the relevant Competent Authority in each participating country prior to initiating the study. In the UK the study will be conducted under a Medicines and Healthcare products Regulatory Agency (MHRA) Clinical Trial Authorisation (CTA).

20.3 Local Approvals

Investigators are responsible for ensuring they obtain appropriate local approvals to conduct the trial in accordance with local arrangements and policies.

20.4 Protocol amendments

Amendments are changes made to the research following initial approval. A 'substantial amendment' is an amendment to the terms of the Responsible Authority application (if applicable), the REC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of the investigational medicinal product(s) used in the trial.

Non-substantial amendments are those where the change(s) involve only minor logistical or administrative aspects of the study.

All amendments will be generated and managed according to the trial office standard operating procedures to ensure compliance with applicable regulation and other requirements. Written confirmation of all applicable REC, regulatory and local approvals must be in place prior to implementation by Investigators. The only exceptions are for changes necessary to eliminate an immediate hazard to study patients (see below).

It is the Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the trial. The Investigator must ensure this is documented in the patient's medical notes and the patient is re-consented if appropriate.

20.5 Urgent safety measures

The sponsor or Investigator may take appropriate urgent safety measures to protect trial participants from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorisation. The trial may continue with the urgent safety measures in place. **The Investigator must inform the Oxford MErCuRIC team IMMEDIATELY if the study site initiates an urgent safety measure:**

Tel: +44 (0)1865 227194
Email: octo-MERCURIC@oncology.ox.ac.uk

The notification must include:

- Date of the urgent safety measure;
- Who took the decision; and
- Why the action was taken.

The Investigator will provide any other information that may be required to enable the trial office to report and manage the urgent safety measure in accordance with the current regulatory and ethical requirements for expedited reporting and close out.
The Trials office will follow written procedures to implement the changes accordingly.

20.6 Temporary halt

The sponsor and Investigators reserve the right to place recruitment to this protocol on hold for short periods for administrative reasons **or** to declare a temporary halt. A temporary halt is defined as a formal decision to:

- interrupt the treatment of subjects already in the trial for safety reasons;
- stop recruitment on safety grounds; or
- stop recruitment for any other reason(s) considered to meet the substantial amendment criteria, including possible impact on the feasibility of completing the trial in a timely manner.

The trial office will report the temporary halt via an expedited substantial amendment procedure. The trial may not restart after a temporary halt until a further substantial amendment to re-open is in place. If it is decided not to restart the trial this will be reported as an early termination.

20.7 Serious Breaches

The Medicines for Human Use (Clinical Trials) Regulations require the Sponsor to notify any "serious breaches" to the MHRA within 7 days of the sponsor becoming aware of the breach. A serious breach is defined as “A breach of GCP or the trial protocol which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial”

Investigators must notify the trials office at once if any serious breach of GCP is suspected.

20.8 Reports: Progress, Safety and End of Study Reports

This protocol will comply with all current applicable Regulatory Authority, Research Ethics Committee and Sponsor requirements for the provision of periodic study safety and progress reports. Any additional reports will be provided on request. Reporting will be managed by the trials office according to internal SOPs. Sites will be urged to return as much data as possible before each database lock point.

The trial office will determine which reports need to be circulated Principal Investigators and other interested parties according to internal SOPs. Study sites are responsible for forwarding trial reports they receive to their local Institutions as required.

21 EXPENSES AND BENEFITS

Each participating centre will follow local regulations and policy on reimbursement of travel expenses.

22 QUALITY ASSURANCE

22.1 Risk assessment and monitoring

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 (on-site and central) will be performed according to the plan and trial office 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. Study staff will be in regular contact with site personnel to check on progress and deal with any queries that they may have including those arising from queries raised by OCTO.

22.2 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.

23 RECORDS RETENTION & ARCHIVING

During the clinical trial and after trial closure the Investigator must maintain adequate and accurate records to enable the conduct of a clinical trial and the quality of the research data to be evaluated and verified. These essential documents, detailed in the trial office SOP must be stored in such a way that ensures that they are readily available, upon request, to the sponsor or the Regulatory Agency, for the minimum period required by national legislation or for longer if needed. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the host institution policy. It is the University of Oxford's policy to store research data for a minimum of 5 years. Retention and storage of laboratory records for clinical trial samples will follow national guidelines.

Retention and storage of central laboratory records supporting PK or PD endpoints and the disposition of samples donated via the trial must also comply with applicable legislation and Sponsor requirements.

It is the University of Oxford's policy to store data for a minimum of 5 years. Investigators may not archive or destroy study essential documents or samples without written instruction from the trial office.

24 PATIENT CONFIDENTIALITY

Personal data recorded on all documents will be regarded as confidential, and to preserve each patient's anonymity, only their patient study number, initials and date of birth (or other identified as appropriate to country regulations and agreed with the Sponsor) will be recorded on the CRFs.

The Investigator site must maintain the patient's anonymity in all communications and reports related to the research. The Investigator site team must keep a separate log of enrolled patients' personal identification details as necessary to enable them to be tracked. These documents must be retained securely, in strict confidence. They form part of the Investigator Site File and are not to be released externally.

25 STUDY FUNDING

This trial is being organised by the Oncology Clinical Trials Office (OCTO) at the University of Oxford and is being funded by the European Commission. The trial is part of the NIHR portfolio, and any additional NHS clinical service support costs of patient care while on study should be met by the host study site.

26 SPONSORSHIP AND INDEMNITY

26.1 Sponsorship

The Sponsor will provide written confirmation of Sponsorship and authorise the trial commencement once satisfied that all arrangements and approvals for the proper conduct of the trial are in place. A separate study delegation agreement, setting out the responsibilities of the Chief Investigator and Sponsor will be put in place between the parties.

26.2 Insurance

The University has a specialist insurance policy in place: - Newline Underwriting Management Ltd, at Lloyd's of London - which would operate in the event of any participant suffering harm as a result of their involvement in the research.

26.3 Contracts/Agreements

This trial is subject to the Sponsor's policy requiring that written contracts/agreements are agreed formally by the participating bodies as appropriate. A Clinical Trial Agreement (CTA) will be placed between the Sponsor and participating sites prior to site activation. The Sponsor will also set up written agreements with any other external third parties involved in the conduct of the trial as appropriate.

27 PUBLICATION POLICY

Ownership and publication policy will be as per the MErCuRIC consortium agreement.
Authors shall acknowledge that the study was sponsored by the University of Oxford and funded by the MErCuRIC EU 7th Framework Programme (Grant agreement number 602901-2).

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APPENDIX 1: ECOG PERFORMANCE SCALE

Activity Performance Description	Score
Fully active, able to carry out all on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.	1
Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.	4

APPENDIX 2: COCKCROFT AND GAULT FORMULATION ESTIMATE GFR

The estimated GFR is given by:

Males: $\frac{1.25 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{serum creatinine (µmol/l)}}$

Females: $\frac{1.05 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{serum creatinine (µmol/l)}}$

- This formula usually under-estimates GFR by 10-30% compared with EDTA or measured 24-hour creatinine clearance, so is used in this trial as a screening test.
-
- A Cockcroft and Gault estimate of ≥50 ml/min is accepted as evidence of adequate renal function.
-
- Patients with a Cockcroft and Gault estimate of <50 ml/min prior to randomisation should have formal GFR measurement with EDTA or 24 urinary creatinine, which must be within the normal range. The corrected EDTA clearance should be ≥50ml/min.
-
- After the start of treatment, if the Cockcroft and Gault estimate falls by >25% from baseline or to below 50 ml/min, the EDTA measurement or 24 hour urinary creatinine should be re-checked.

APPENDIX 3: NCI-CTCAE V4.0 CRITERIA NEUROLOGIC DISORDERS

Toxicity Grade	1	2	3	4
Neurological				
Neuro-sensory	mild paresthesias, loss of deep tendon reflexes	mild or moderate objective sensory loss; moderate paresthesias	severe objective sensory loss or paresthesias that interfere with function	-
Neuro-motor	subjective weakness; no objective findings	mild objective weakness without significant impairment of function	objective weakness with impairment of function	paralysis
Neuro-cortical	mild somnolence or agitation	moderate somnolence or agitation	severe somnolence, agitation, confusion, disorientation, or hallucinations	coma, seizures, toxic psychosis
Neuro-cerebellar	slight incoordination, dysdiadochokinesia	intention tremor, dysmetria, slurred speech, nystagmus	locomotor ataxia	cerebellar necrosis
Neuro-mood	mild anxiety or depression	moderate anxiety or depression	severe anxiety or depression	suicidal ideation
Neuro -- headache	mild	moderate or severe but transient	unrelenting and severe	-
Neuro-constipation	mild	moderate	severe	ileus >96 hrs
Neuro-hearing	asymptomatic, hearing loss on audiometry only	tinnitus	hearing loss interfering with function but correctable with hearing aid	deafness not correctable
Neuro-vision	-	-	symptomatic subtotal loss of vision	blindness

APPENDIX 4: MEASUREMENT OF DISEASE - RECIST 1.1 CRITERIA

RESPONSE EVALUATION CRITERIA IN SOLID TUMOURS

Objective tumour response and time of progression will be measured according to the RECIST (Response Evaluation Criteria In Solid Tumours) criteria (version 1.1).
Response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions, and – together with other lesions that are denoted as non-target lesions – followed until disease progression.
The following paragraphs are a quick reference to the RECIST criteria (version 1.1). The complete criteria are included in the published RECIST document:

Eisenhauer, EA, Therasse, P, Bogaerts, J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-247

Up to date details are available at: http://www.eortc.be/RECIST

APPENDIX 5: MEDICATIONS TO BE AVOIDED OR USED WITH CAUTION WITH PF-02341066

NB. This list is not exhaustive and the absence of a drug from the list does not imply that its combination with PF-02341066 is safe. Please contact the Trials office if further clarification is required.

DRUGS AFFECTING CYTOCHROME P450

Potent inhibitors of CYP3A4/5: may increase exposure to PF-02341066 by more than 3-fold
The following drugs should not be combined with PF-02341066. Recommended withdrawal periods for patients who have recently received treatment with these agents are indicated in the table. For example, it is recommended that patients should not have received clarithromycin for at least 7 days before treatment with PF-02341066 is started.

Contra-indicated		
Drug	**Inhibits**	**Minimum washout period prior to PF-02341066 administration**
Ketoconazole, Ritonavir, Atazanavir, Saquinavir, Indinavir, Nefazodone, Nelfinavir	CYP3A4/5	2 days
Itraconazole, Clarithromycin, Erythromycin*, Fluconazole>400 mg	CYP3A4/5	7 days
Diltiazem	CYP3A4/5	2 Weeks

* Topical use of erythromycin is permitted during treatment with PF-02341066

Moderate Inhibitors of CYP3A4/5: may increase exposure to PF-02341066
Caution should be exercised in combining the following drugs with PF-02341066.

Warning of possible interaction		
Drug	**Inhibits**	
Verapamil	CYP3A4	These drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions.
Grapefruit juice	CYP3A4	Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits, e.g. grapefruit juice or marmalade) during the study. Please do not have more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1-2 teaspoons (15 g) of Seville orange marmalade daily.
Seville oranges (and other products containing Seville oranges)	CYP3A4	

Potent Inducers of CYP3A4/5: may reduce exposure to PF-02341066 by more than 3-fold
The following drugs should not be combined with PF-02341066. Recommended withdrawal periods for patients who have recently received treatment with these agents are indicated in the table. For example; it is recommended that patients should not have received carbamazepine for at least 2 weeks before treatment with PF-02341066 is started

Contra-indicated	
Drug	**Minimum washout period prior to PF-02341066 administration**
Barbiturates,Carbamazepine, Phenytoin, Rifampicin, Rifabutin, St John's Wort	2 Weeks

Substrates of CYP3A4/5: PF-02341066 may increase exposure
The following drugs should not be given with PF-02341066

Contra-indicated	
Drug	
Dihydroergotamine, Ergotamine Pimozide, Astemizole, Cisapride Terfenadine	**CYP3A4/5 substrates with narrow therapeutic indices associated with life-threatening arrhythmias, and must be avoided during PF-02341066 administration**

The following drugs may be given with PF-02341066, but caution is advised

Contra-indicated	
Drug	
Alfentanil, Cyclosporin, Fentanyl, Quinidine, Sirolimus, Tacrolimus	**CYP3A4/5 substrates with narrow therapeutic indices, caution must be exercised**

The following bradycardic agents (e.g. beta-blockers, non-dihydropyridine calcium channel blockers) should not be given with PF-02314066

Contra-indicated	
Drug	
Verapamil, Diltiazem Clonidine, Digoxin	**Increased risk of symptomatic bradycardia**

DRUGS THAT MAY PROLONG QT INTERVAL

The drugs listed in this section are taken from information provided by The Arizona Center for Education and Research on Therapeutics and The Critical Path Institute, Tucson, Arizona and Rockville, Maryland.
http://www.arizonacert.org/medical-pros/drug-lists/drug-lists.htm

The following drugs are known to prolong QT interval or induce Torsades de Pointes and **should not be combined with PF-02341066**. Recommended withdrawal periods for patients who have recently received treatment with these agents are indicated in the following table.

Contraindicated drug	Withdrawal period
Droperidol, Procainamide	2 days
Cisapride Clarithromycin, Disopyramide, Dofetilide, Domperidone, Erythromycin**, Ibutilide, Quinidine, Sotalol, Sparfloxacin, Thioridazine	7 days
Bepridil, Chlorpromazine, Halofantrine, Haloperidol, Mesoridazine	14 days
Levomethadyl, Methadone, Pimozide	4 weeks
Arsenic trioxide	6 weeks*
Pentamidine	8 weeks
Amiodarone, Chloroquine	1 year

* Estimated value as pharmacokinetics of arsenic trioxide has not been studied

** Topical use of erythromycin is permitted during treatment with PF-02341066

APPENDIX 6: RECOMMENDED DOSE MODIFICATIONS FOR BINIMETINIB (MEK 162)

Guidelines – Binimetinib (MEK162)

Recommended Dose Modifications
Version 2 11 November 2015

Binimetinib (MEK162) Dose Modifications

Patients will be monitored for adverse events at each visit with the NCI CTCAE version 4.03 used for all grading. Doses of MEK162 should be adjusted for AEs throughout the study. In general, doses should not be reduced or interrupted for Grade 1 AEs unless the AE is a specific treatment-related ocular AE. Treatment to control symptoms should be provided as appropriate. All dose modifications should be based on the worst preceding toxicity (CTCAE version 4.03).

An individual patient may have their dose of MEK162 reduced to the dose levels specified in Table 6. When the AE that resulted in a dose reduction improves to and remains stable at the patient's Baseline for a minimum of 14 days, the dose can be re-escalated to the next dose level at the discretion of the Investigator, provided there are no other concomitant MEK162-related toxicities that would prevent drug re-escalation. There is no limit to the number of times the patient can have their dose reduced or re escalated (in 15 mg increments); however, no dose re escalation is allowed after a dose reduction due to LVEF dysfunction or prolonged QTcF $\geq$ 501 msec.

A dose reduction below 30 mg BID is not allowed (Table 6). Patients requiring additional reductions must be discontinued from study treatment. Dose interruptions of more than 21 days are not allowed.

Eye disorders should be graded according to CTCAE version 4.03 as described below in Table 1.

Table 1 CTCAE grading for eye disorders

Grade	Description
1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL
3	Severe or medically significant but not immediately sight threatening; Hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL
4	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye
ADL= activities of daily living	

Retinal detachment should be graded according to the CTCAE version 4.03 as described below in Table 2.

Table 2 CTCAE grading for retinal detachment

Grade	Description
1	Asymptomatic
2	Exudative and visual acuity 20/40* or better
3	Rhegmatogenous or exudative detachment; operative intervention indicated; decline in vision (worse than 20/40*but better than 20/200*)
4	Blindness (20/200* or worse) in the affected eye
* Please refer to Appendix 7 for Snellen Equivalence (Visual Acuity Conversion Chart).	

Uveitis should be graded according to the CTCAE version 4.03 as described below in Table 3.

Table 3 CTCAE grading for uveitis

Grade	Description
1	Asymptomatic; clinical or diagnostic observations only
2	Anterior uveitis; medical intervention indicated
3	Posterior or pan-uveitis
4	Blindness (20/200* or worse) in the affected eye

* Please refer to Snellen Equivalence (Visual Acuity Conversion Chart).

Hand Foot Skin Reaction should be graded according to CTCAE version 4.03 as described below in Table 4.

Table 4 CTCAE grading of Hand foot skin reaction (HFSR)[a]

Grade	Description[b]
1	Minimal skin changes or dermatitis (e.g., erythema, edema, numbness, dysesthesia, paresthesia, tingling or hyperkeratosis) without pain
2	Skin changes (e.g.,peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL
3	Severe skin changes (e.g., peeling, ulceration, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL

ADL=activities of daily living
[a]HFSR or palmar-plantar erythrodysaesthesia syndrome, a disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet;
[b]More specifics examples to grade 1 and grade 3 are added to facilitate proper grading [from the sorafenib package insert (West Haven, CT: Bayer Pharmaceuticals Corporation; 2007); Porta et al 2007].

Diarrhea should be graded according to CTCAE version 4.03 as described below in Table 5.

Table 5 CTCAE grading of diarrhea

Grade	Description
1	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline
1-2 Complicated	Definition as above with the following complicating signs/symptoms: • Moderate to severe cramping • Grade ≥ 2 nausea/vomiting • Decreased performance status • Fever • Sepsis • Neutropenia • Frank bleeding • Dehydration • Unresolved diarrhea after 48 hours of treatment with loperamide (including high dose administration) and initiation of second-line treatment
3	Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL
4	Life threatening consequences; urgent intervention indicated

ADL=activities of daily living

Dose modification and dose delay for MEK162

Table 6 Dose reduction for MEK162

Dose reduction*		
	Dose (level - 0)	**Dose level - 1****
Binimetinib (MEK162)	45 mg BID	30 mg BID

*Dose reduction should be based on the highest AE grade

**Dose reduction below 30 mg bid is not allowed

Missed/skipped doses will not be made up (i.e. the patient should not double their dose if the previous dose was missed). When the toxicity that resulted in a dose reduction improves to and remains stable at Grade 1 or less for a minimum of 21 days, the dose can be re-escalated at the investigator's discretion provided there are no other concomitant toxicities.

No dose re-escalation is allowed after dose reduction due to left ventricular dysfunction or prolonged QTcF > 500 msec.

Dose reduction/interruption/discontinuation decisions should be based on the CTCAE grade of the toxicity and the guidelines provided below. All AEs should be followed weekly or as clinically appropriate until stabilization or resolution.

Please refer to the tables below for dose adjustment recommendations for MEK162 induced toxicities.

MEK162 – Recommended dose modifications associated with treatment-related adverse events

Worst Toxicity **CTCAE v4.03 Grade (unless otherwise specified)**	**Dose Modification for Binimetinib**
Eye Disorder – Serous Detachment of the Retina Events[b,c]	
Grade 1	• Maintain dose level of binimetinib and increase frequency of ophthalmic monitoring to at least every 14 days until stabilization or resolution
Grade2	• Maintain dose level of binimetinib and refer the patient to ophthalmologist within 1 week: o If resolved to Grade ≤ 1 in ≤ 21 days, maintain dose of binimetinib o If not resolved to Grade ≤ 1 in ≤ 21 days, reduce 1 dose level[d] of binimetinib or maintain dose of binimetinib based upon the Investigator's discretion after consultation with the ophthalmologist
Grade 3	• Interrupt binimetinib and refer the patient to ophthalmologist within 1 week: o If resolved to Grade ≤ 1 in ≤ 21 days, reduce 1 dose level[d] of binimetinib o If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue binimetinib and close follow-up with ophthalmic monitoring until stabilization or resolution
Grade 4	• Permanently discontinue binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution
Eye Disorder – RVO[c]	
RVO of any grade	• Permanently discontinue binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution
Other Eye Disorders (i.e., Non-retinal Events)[c]	
Grade 1-2	• Maintain dose level of binimetinib and increase frequency of ophthalmic monitoring to at least every 14 days until stabilization or resolution
Grade 3	• Interrupt binimetinib and refer patient to ophthalmologist within 1 week: o If resolved to Grade ≤ 1 in ≤ 21 days, reduce 1 dose level[d] of binimetinib o If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue binimetinib and close follow-up with ophthalmic monitoring until stabilization or resolution
Grade 4	• Permanently discontinue binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified[a])	Dose Modification for Binimetinib
Liver-related Adverse Events	
Grade 1 ALT or AST > ULN to 3 × ULN	• Maintain dose level of binimetinib
Grade 2 *For patients with Baseline ALT/AST values ≤ ULN:* ALT or AST > 3.0 to 5.0 × ULN and blood bilirubin[f] ≤ 2.0 × ULN *For patients with liver metastases or ALT/AST Baseline values >ULN:* ALT or AST 3 × Baseline value to 5.0 × ULN and blood bilirubin[f] ≤ 2.0 × ULN *For all patients:* ALT or AST > 3.0 to 5.0 × ULN and blood bilirubin[f] > 2.0 × ULN	• Interrupt binimetinib until resolved to Grade ≤ 1, then: o If resolved in ≤ 14 days, maintain dose level of binimetinib o If not resolved in ≤ 14 days, reduce 1 dose level[d] of binimetinib • Interrupt binimetinib until resolved to Grade ≤ 2, then: o If resolved in ≤ 14 days, maintain dose level of binimetinib o If not resolved in ≤ 14 days, reduce 1 dose level[d] of binimetinib • Interrupt binimetinib until resolved to Grade ≤ 1, then: o If resolved in ≤ 7 days, reduce 1 dose level[d] of binimetinib o If not resolved in ≤ 7 days, permanently discontinue binimetinib
Grade 3 ALT or AST > 5.0 to 8.0 × ULN and blood bilirubin[f] ≤ 2.0 × ULN ALT or AST > 8.0 ×ULN and blood bilirubin[f] ≤ 2.0 × ULN ALT or AST > 5.0 × ULN and blood bilirubin[f] > 2.0 × ULN	• Interrupt binimetinib until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then: o If resolved in ≤ 14 days, maintain dose level of binimetinib o If not resolved in ≤ 14 days, reduce 1 dose level[d] of binimetinib • Permanently discontinue binimetinib • Permanently discontinue binimetinib
Grade 4 ALT or AST > 20.0 × ULN	• Permanently discontinue binimetinib
QTc Prolongation	
Grade 3 mean triplicate QTcF ≥ 501 msec (confirmed by a separate mean triplicate ECG)	First Occurrence: • Interrupt binimetinib. Electrolyte abnormalities (if applicable) should be corrected and any concomitant medication that could potentially prolong QT should be discontinued • Monitor patient until resolution of the AE. Include a consultation with a cardiologist, if indicated • Once resolved to Grade ≤ 1, resume binimetinib at 1 reduced dose level[d] Second Occurrence: • If second occurrence is attributed to binimetinib, permanently discontinue binimetinib

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified[a])	Dose Modification for Binimetinib
Cardiac Disorders - Left Ventricular Systolic Dysfunction[a]	
Asymptomatic absolute decrease of > 10% in LVEF compared to Baseline and the LVEF is below the institution's LLN (e.g., a decrease of 60% to 48% is an absolute decrease of 12%)	• Interrupt binimetinib and repeat evaluation of LVEF within 2 weeks: o If the LVEF recovers (defined as LVEF ≥ 50% or ≥ LLN and absolute decrease ≤ 10% compared to Baseline) in ≤ 21 days, reduce 1 dose level[d] after approval of the Medical Monitor. Monitor LVEF 2 weeks after resuming binimetinib, every 4 weeks for 12 weeks and subsequently as per protocol o If the LVEF does not recover in ≤ 21 days, permanently discontinue binimetinib. Closely monitor LVEF until resolution or for up to 16 weeks
Grade 3-4	• Permanently discontinue binimetinib. Closely monitor LVEF until resolution or for up to 16 weeks Note: Copies of ECHO and/or MUGA scans may be requested to be available to the Sponsor for patients with absolute decrease of > 10% in LVEF compared to Baseline and LVEF < LLN
CK Elevations	
Grade 1-2	• Maintain dose level of binimetinib o If total CK ≥ 3 × ULN, measure CK, CK isoenzymes and myoglobin in blood or urine weekly for 3 weeks and if total CK remains ≤ Grade 2, continue to assess CK, CK isoenzymes and myoglobin along with regularly scheduled clinical chemistry assessments
Grade 3 > 5.0 to 10.0 × ULN	• If asymptomatic, maintain dose of binimetinib and monitor closely o Measure CK, CK isoenzymes and myoglobin in blood or urine weekly for 3 weeks and if total CK remains ≤ Grade 3, continue to assess CK, CK isoenzymes and myoglobin along with regularly scheduled clinical chemistry assessments • If symptomatic (muscle pain/spasms), interrupt binimetinib until resolved to Grade ≤ 1 and monitor closely, then: o If resolved in ≤ 21 days, reduce 1 dose level[d] of binimetinib o If not resolved in ≤ 21 days, permanently discontinue binimetinib
Grade 4	• If asymptomatic, interrupt binimetinib until resolved to Grade ≤ 1 and monitor closely, then: o If resolved in ≤ 21 days, reduce 1 dose level[d] of binimetinib o If not resolved in ≤ 21 days, permanently discontinue binimetinib • If symptomatic, permanently discontinue binimetinib

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified[a])	Dose Modification for Binimetinib
Rash	
Grade 1	• Maintain dose level of binimetinib • Initiate Initial Rash Treatment Regimen if it was not already started and rash should be closely monitored
Grade 2	First Occurrence: • Maintain dose level of binimetinib and rash should be closely monitored • Initiate Initial Rash Treatment if it was not already started • Reassess within ≤ 14 days. If rash worsens or does not improve, interrupt binimetinib until resolved to Grade ≤ 1. Resume binimetinib at current dose level Second Occurrence: • Reassess within ≤ 14 days. If rash worsens or does not improve, interrupt binimetinib until resolved to Grade ≤ 1. Resume binimetinib at 1 reduced dose level[d]
Grade 3	First Occurrence: • Interrupt binimetinib until resolved to Grade ≤ 1. Reassess weekly. Resume binimetinib at current dose level • Consider referral to dermatologist and manage rash per dermatologist's recommendation Second Occurrence: • Interrupt binimetinib until resolved to Grade ≤ 1. Reassess weekly. Resume binimetinib at 1 reduced dose level[d] • Consider referral to dermatologist and manage rash per dermatologist's recommendation
Grade 4	• Permanently discontinue binimetinib
Diarrhea	
Uncomplicated Grade 1-2	• Consider temporary interruption of binimetinib until resolved to Grade ≤ 1. Resume binimetinib at current dose level
Complicated Grade 1-2	• Temporarily interrupt binimetinib until resolved to Grade ≤ 1. Resume binimetinib at 1 reduced dose level[d]
Grade 3	• Temporarily interrupt binimetinib until resolved to Grade ≤ 1. Resume binimetinib at 1 reduced dose level[d]
Grade 4	• Temporarily interrupt binimetinib until resolved to Grade ≤ 1. Resume binimetinib at 1 reduced dose level[d]

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified[a])	Dose Modification for Binimetinib
All Other Binimetinib Treatment-related Adverse Events	
Grade 1-2	• If the event is Grade 1 or non-persistent Grade 2, maintain dose level of binimetinib and monitor until stabilization or resolution • If the event is a persistent Grade 2 AE not responsive to a specific therapy, consider binimetinib dose interruption or reduction[d]
Grade 3	• Interrupt binimetinib until resolved to Grade ≤1 or to pretreatment/Baseline level. If the event resolves ≤ 21 days, then binimetinib may be resumed at 1 reduced dose level[d] based upon the Investigator's discretion
Grade 4	• Permanently discontinue binimetinib [e]

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; CK = creatine kinase; CTCAE = Common Terminology Criteria for Adverse Events; ECHO = echocardiogram; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; mg = milligram(s); MUGA = multi-gated acquisition; OCT = optical coherence tomography; RVO = retinal vein occlusion; ULN = upper limit of normal

[a] Not according to CTCAE.

[b] Further evaluation with specialized retinal imaging (e.g., OCT [spectral domain OCT recommended] of the macula for non-vascular abnormalities; and color fundus photography of the central 30 degrees and/or fluorescein angiography for vascular abnormalities) is recommended.

[c] Images/results of the ophthalmic examinations (at a minimum, OCT, color fundus photography and/or fluorescein angiography) must be made available upon Sponsor request.

[d] The lowest recommended dose level of MEK162 is 15 mg BID. When the AE that resulted in a dose reduction improves to and remains stable at ≤ Grade 1 for a minimum of 14 days, the dose can be re-escalated to the next dose level at the discretion of the Investigator, provided there are no other concomitant toxicities. There is no limit to the number of times the patient can have their dose reduced or re-escalated (in 15 mg increments); however, no dose re escalation is allowed after a dose reduction due to LVEF dysfunction or prolonged QTcF > 500 msec.

[e] A patient with a Grade 4 AE may resume treatment at the lower dose level if the AE recovers to Grade ≤ 1 within 21 days of interrupting drug and, if in the opinion of the Investigator and Medical Monitor, the event is not life-threatening, and the patient can be managed and monitored for recurrence of AE. Dose interruptions of more than 21 days are not allowed unless approved by the Investigator, and the Array BioPharma Medical Monitor or designee.

[f] Refers to total bilirubin.

APPENDIX 6A: UPDATED RECOMMENDED DOSE MODIFICATIONS FOR BINIMETINIB (MEK 162)

Guidelines – Binimetinib (MEK162)

Recommended Dose Modifications
Version 2 11 November 2015 – updated to guidelines Mar 2017

Binimetinib (MEK162) Dose Modifications

Patients will be monitored for adverse events at each visit with the NCI CTCAE version 4.03 used for all grading. Doses of MEK162 should be adjusted for AEs throughout the study. In general, doses should not be reduced or interrupted for Grade 1 AEs unless the AE is a specific treatment-related ocular AE. Treatment to control symptoms should be provided as appropriate. All dose modifications should be based on the worst preceding toxicity (CTCAE version 4.03).

An individual patient may have their dose of MEK162 reduced to the dose levels specified in Table 6. When the AE that resulted in a dose reduction improves to and remains stable at the patient's Baseline for a minimum of 14 days, the dose can be re-escalated to the next dose level at the discretion of the Investigator, provided there are no other concomitant MEK162-related toxicities that would prevent drug re-escalation. There is no limit to the number of times the patient can have their dose reduced or re escalated (in 15 mg increments); however, no dose re escalation is allowed after a dose reduction due to LVEF dysfunction or prolonged QTcF $\geq$ 501 msec.

A dose reduction below 30 mg BID is not allowed (Table 6). Patients requiring additional reductions must be discontinued from study treatment. Dose interruptions of more than 21 days are not allowed.

Eye disorders should be graded according to CTCAE version 4.03 as described below in Table 1.

Table 1 CTCAE grading for eye disorders

Grade	Description
1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL
3	Severe or medically significant but not immediately sight threatening; Hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL
4	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye
ADL= activities of daily living	

Retinal detachment should be graded according to the CTCAE version 4.03 as described below in Table 2.

Table 2 CTCAE grading for retinal detachment

Grade	Description
1	Asymptomatic
2	Exudative and visual acuity 20/40* or better
3	Rhegmatogenous or exudative detachment; operative intervention indicated; decline in vision (worse than 20/40*but better than 20/200*)

Grade	Description
4	Blindness (20/200* or worse) in the affected eye
* Please refer to Appendix 7 for Snellen Equivalence (Visual Acuity Conversion Chart).	

Uveitis should be graded according to the CTCAE version 4.03 as described below in Table 3.

Table 3 CTCAE grading for uveitis

Grade	Description
5	Asymptomatic; clinical or diagnostic observations only
6	Anterior uveitis; medical intervention indicated
7	Posterior or pan-uveitis
8	Blindness (20/200* or worse) in the affected eye
* Please refer to Snellen Equivalence (Visual Acuity Conversion Chart).	

Hand Foot Skin Reaction should be graded according to CTCAE version 4.03 as described below in Table 4.

Table 4 CTCAE grading of Hand foot skin reaction (HFSR)[a]

Grade	Description[b]
1	Minimal skin changes or dermatitis (e.g., erythema, edema, numbness, dysesthesia, paresthesia, tingling or hyperkeratosis) without pain
2	Skin changes (e.g.,peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL
3	Severe skin changes (e.g., peeling, ulceration, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL

ADL=activities of daily living
[a]HFSR or palmar-plantar erythrodysaesthesia syndrome, a disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet;
[b]More specifics examples to grade 1 and grade 3 are added to facilitate proper grading [from the sorafenib package insert (West Haven, CT: Bayer Pharmaceuticals Corporation; 2007); Porta et al 2007].

Diarrhea should be graded according to CTCAE version 4.03 as described below in Table 5.

Table 5 CTCAE grading of diarrhea

Grade	Description
1	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline
1-2 Complicated	Definition as above with the following complicating signs/symptoms: • Moderate to severe cramping • Grade ≥ 2 nausea/vomiting • Decreased performance status • Fever • Sepsis • Neutropenia • Frank bleeding • Dehydration • Unresolved diarrhea after 48 hours of treatment with loperamide (including high dose administration) and initiation of second-line treatment

Grade	Description
3	Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL
4	Life threatening consequences; urgent intervention indicated

ADL=activities of daily living

Dose modification and dose delay for MEK162

Table 6 Dose reduction for MEK162

Dose reduction*		
	Dose (level - 0)	**Dose level - 1****
Binimetinib (MEK162)	45 mg BID	30 mg BID

*Dose reduction should be based on the highest AE grade

**Dose reduction below 30 mg bid is not allowed

Missed/skipped doses will not be made up (i.e. the patient should not double their dose if the previous dose was missed). When the toxicity that resulted in a dose reduction improves to and remains stable at Grade 1 or less for a minimum of 21 days, the dose can be re-escalated at the investigator's discretion provided there are no other concomitant toxicities.

No dose re-escalation is allowed after dose reduction due to left ventricular dysfunction or prolonged QTcF > 500 msec.

Dose reduction/interruption/discontinuation decisions should be based on the CTCAE grade of the toxicity and the guidelines provided below. All AEs should be followed weekly or as clinically appropriate until stabilization or resolution.

Please refer to the tables below for dose adjustment recommendations for MEK162 induced toxicities.

MEK162 – Recommended dose modifications associated with treatment-related adverse events

Worst Toxicity **CTCAE v4.03 Grade (unless otherwise specified)**	**Dose Modification for Binimetinib**
Eye Disorder – Serous Detachment of the Retina Events[b,c]	
Grade 1	• Maintain dose level of binimetinib and increase frequency of ophthalmic monitoring to at least every 14 days until stabilization or resolution
Grade2	• Maintain dose level of binimetinib and refer the patient to ophthalmologist within 1 week: o If resolved to Grade ≤ 1 in ≤ 21 days, maintain dose of binimetinib o If not resolved to Grade ≤ 1 in ≤ 21 days, reduce 1 dose level[d] of binimetinib or maintain dose of binimetinib based upon the Investigator's discretion after consultation with the ophthalmologist
Grade 3	• Interrupt binimetinib and refer the patient to ophthalmologist within 1 week: o If resolved to Grade ≤ 1 in ≤ 21 days, reduce 1 dose level[d] of binimetinib o If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue binimetinib and close follow-up with ophthalmic monitoring until stabilization or resolution
Grade 4	• Permanently discontinue binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution
Eye Disorder – RVO[c]	
RVO of any grade	• Permanently discontinue binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution
Other Eye Disorders (i.e., Non-retinal Events)[c]	
Grade 1-2	• Maintain dose level of binimetinib and increase frequency of ophthalmic monitoring to at least every 14 days until stabilization or resolution
Grade 3	• Interrupt binimetinib and refer patient to ophthalmologist within 1 week: o If resolved to Grade ≤ 1 in ≤ 21 days, reduce 1 dose level[d] of binimetinib o If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue binimetinib and close follow-up with ophthalmic monitoring until stabilization or resolution
Grade 4	• Permanently discontinue binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified[a])	**Dose Modification for Binimetinib**
Liver-related Adverse Events	
Grade 1 ALT or AST > ULN to 3 × ULN	• Maintain dose level of binimetinib
Grade 2 *For patients with Baseline ALT/AST values ≤ ULN:* ALT or AST > 3.0 to 5.0 × ULN and blood bilirubin[f] ≤ 2.0 × ULN *For patients with liver metastases or ALT/AST Baseline values >ULN:* ALT or AST 3 × Baseline value to 5.0 × ULN and blood bilirubin[f] ≤ 2.0 × ULN *For all patients:* ALT or AST > 3.0 to 5.0 × ULN and blood bilirubin[f] > 2.0 × ULN	• Interrupt binimetinib until resolved to Grade ≤ 1, then: o If resolved in ≤ 14 days, maintain dose level of binimetinib o If not resolved in ≤ 14 days, reduce 1 dose level[d] of binimetinib • Interrupt binimetinib until resolved to Grade ≤ 2, then: o If resolved in ≤ 14 days, maintain dose level of binimetinib o If not resolved in ≤ 14 days, reduce 1 dose level[d] of binimetinib • Interrupt binimetinib until resolved to Grade ≤ 1, then: o If resolved in ≤ 7 days, reduce 1 dose level[d] of binimetinib o If not resolved in ≤ 7 days, permanently discontinue binimetinib
Grade 3 ALT or AST > 5.0 to 8.0 × ULN and blood bilirubin[f] ≤ 2.0 × ULN ALT or AST > 8.0 ×ULN and blood bilirubin[f] ≤ 2.0 × ULN ALT or AST > 5.0 × ULN and blood bilirubin[f] > 2.0 × ULN	• Interrupt binimetinib until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then: o If resolved in ≤ 14 days, maintain dose level of binimetinib o If not resolved in ≤ 14 days, reduce 1 dose level[d] of binimetinib • Permanently discontinue binimetinib • Permanently discontinue binimetinib
Grade 4 ALT or AST > 20.0 × ULN	• Permanently discontinue binimetinib
QTc Prolongation	
Grade 3 mean triplicate QTcF ≥ 501 msec (confirmed by a separate mean triplicate ECG)	First Occurrence: • Interrupt binimetinib. Electrolyte abnormalities (if applicable) should be corrected and any concomitant medication that could potentially prolong QT should be discontinued • Monitor patient until resolution of the AE. Include a consultation with a cardiologist, if indicated • Once resolved to Grade ≤ 1, resume binimetinib at 1 reduced dose level[d] Second Occurrence: • If second occurrence is attributed to binimetinib, permanently discontinue binimetinib

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified[a])	Dose Modification for Binimetinib
Cardiac Disorders - Left Ventricular Systolic Dysfunction[a]	
Asymptomatic absolute decrease of > 10% in LVEF compared to Baseline and the LVEF is below the institution's LLN (e.g., a decrease of 60% to 48% is an absolute decrease of 12%)	• Interrupt binimetinib and repeat evaluation of LVEF within 2 weeks: o If the LVEF recovers (defined as LVEF ≥ 50% or ≥ LLN and absolute decrease ≤ 10% compared to Baseline) in ≤ 21 days, reduce 1 dose level[d] after approval of the Medical Monitor. Monitor LVEF 2 weeks after resuming binimetinib, every 4 weeks for 12 weeks and subsequently as per protocol o If the LVEF does not recover in ≤ 21 days, permanently discontinue binimetinib. Closely monitor LVEF until resolution or for up to 16 weeks
Grade 3-4	• Permanently discontinue binimetinib. Closely monitor LVEF until resolution or for up to 16 weeks Note: Copies of ECHO and/or MUGA scans may be requested to be available to the Sponsor for patients with absolute decrease of > 10% in LVEF compared to Baseline and LVEF < LLN
CK Elevations	
Grade 1-2	• Maintain dose level of binimetinib o If total CK ≥ 3 × ULN, measure CK, CK isoenzymes and myoglobin in blood or urine weekly for 3 weeks and if total CK remains ≥ Grade 2, continue to assess CK, CK isoenzymes and myoglobin along with regularly scheduled clinical chemistry assessments
Grade 3 > 5.0 to 10.0 × ULN	• If asymptomatic, maintain dose of binimetinib and monitor closely o Measure CK, CK isoenzymes and myoglobin in blood or urine weekly for 3 weeks and if total CK remains ≥ Grade 3, continue to assess CK, CK isoenzymes and myoglobin along with regularly scheduled clinical chemistry assessments • If symptomatic (muscle pain/spasms), or asymptomatic with an increase in creatinine ≥ 1,5 x the patient's Baseline screening creatinine, interrupt binimetinib until resolved to Grade ≤ 1 and monitor closely, then: o If resolved in ≤ 21 days, reduce 1 dose level[d] of binimetinib o If not resolved in ≤ 21 days, permanently discontinue binimetinib
Grade 4	• If asymptomatic, interrupt binimetinib until resolved to Grade ≤ 1 and monitor closely, then: o If resolved in ≤ 21 days, reduce 1 dose level[d] of binimetinib o If not resolved in ≤ 21 days, permanently discontinue binimetinib • If symptomatic, or asymptomatic with an increase in creatinine ≥ 1,5 x the patient's Baseline screening creatinine , permanently discontinue binimetinib

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified[a])	Dose Modification for Binimetinib
Rash	
Grade 1	• Maintain dose level of binimetinib • Initiate Initial Rash Treatment Regimen if it was not already started and rash should be closely monitored
Grade 2	First Occurrence: • Maintain dose level of binimetinib and rash should be closely monitored • Initiate Initial Rash Treatment if it was not already started • Reassess within ≤ 14 days. If rash worsens or does not improve, interrupt binimetinib until resolved to Grade ≤ 1. Resume binimetinib at current dose level Second Occurrence: • Reassess within ≤ 14 days. If rash worsens or does not improve, interrupt binimetinib until resolved to Grade ≤ 1. Resume binimetinib at 1 reduced dose level[d]
Grade 3	First Occurrence: • Interrupt binimetinib until resolved to Grade ≤ 1. Reassess weekly. Resume binimetinib at current dose level • Consider referral to dermatologist and manage rash per dermatologist's recommendation Second Occurrence: • Interrupt binimetinib until resolved to Grade ≤ 1. Reassess weekly. Resume binimetinib at 1 reduced dose level[d] • Consider referral to dermatologist and manage rash per dermatologist's recommendation
Grade 4	• Permanently discontinue binimetinib
Diarrhea	
Uncomplicated Grade 1-2	• Consider temporary interruption of binimetinib until resolved to Grade ≤ 1. Resume binimetinib at current dose level
Complicated Grade 1-2	• Temporarily interrupt binimetinib until resolved to Grade ≤ 1. Resume binimetinib at 1 reduced dose level[d]
Grade 3	• Temporarily interrupt binimetinib until resolved to Grade ≤ 1. Resume binimetinib at 1 reduced dose level[d]
Grade 4	• Temporarily interrupt binimetinib until resolved to Grade ≤ 1. Resume binimetinib at 1 reduced dose level[d]

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified[a])	Dose Modification for Binimetinib
All Other Binimetinib Treatment-related Adverse Events	
Grade 1-2	• If the event is Grade 1 or non-persistent Grade 2, maintain dose level of binimetinib and monitor until stabilization or resolution • If the event is a persistent Grade 2 AE not responsive to a specific therapy, consider binimetinib dose interruption or reduction[d]
Grade 3	• Interrupt binimetinib until resolved to Grade ≤1 or to pretreatment/Baseline level. If the event resolves ≤ 21 days, then binimetinib may be resumed at 1 reduced dose level[d] based upon the Investigator's discretion
Grade 4	• Permanently discontinue binimetinib [e]

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; CK = creatine kinase; CTCAE = Common Terminology Criteria for Adverse Events; ECHO = echocardiogram; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; mg = milligram(s); MUGA = multi-gated acquisition; OCT = optical coherence tomography; RVO = retinal vein occlusion; ULN = upper limit of normal

[a] Not according to CTCAE.

[b] Further evaluation with specialized retinal imaging (e.g., OCT [spectral domain OCT recommended] of the macula for non-vascular abnormalities; and color fundus photography of the central 30 degrees and/or fluorescein angiography for vascular abnormalities) is recommended.

[c] Images/results of the ophthalmic examinations (at a minimum, OCT, color fundus photography and/or fluorescein angiography) must be made available upon Sponsor request.

[d] The lowest recommended dose level of MEK162 is 15 mg BID. When the AE that resulted in a dose reduction improves to and remains stable at ≤ Grade 1 for a minimum of 14 days, the dose can be re-escalated to the next dose level at the discretion of the Investigator, provided there are no other concomitant toxicities. There is no limit to the number of times the patient can have their dose reduced or re-escalated (in 15 mg increments); however, no dose re escalation is allowed after a dose reduction due to LVEF dysfunction or prolonged QTcF > 500 msec.

[e] A patient with a Grade 4 AE may resume treatment at the lower dose level if the AE recovers to Grade ≤ 1 within 21 days of interrupting drug and, if in the opinion of the Investigator and Medical Monitor, the event is not life-threatening, and the patient can be managed and monitored for recurrence of AE. Dose interruptions of more than 21 days are not allowed unless approved by the Investigator, and the Array BioPharma Medical Monitor or designee.

[f] Refers to total bilirubin.

APPENDIX 7: INCLUSION AND EXCLUSION CRITERIA FOR DOSE ESCALATION PHASE USING PF-02341066 WITH PD-0325901

INCLUSION CRITERIA

- **Age ≥ 16 years**
- **ECOG performance status 0-1 (Appendix 1)**
- **Adequate respiratory and cardiac function (left ventricular function WNL on echocardiography)**
- **Able to give informed consent and be capable of co-operating with the protocol**
- **Haematological and biochemical indices within the ranges shown below:**
  - **Haemoglobin (Hb) ≥9g/dl (transfusion to achieve this allowed),**
  - **Neutrophils≥ 1,500/µl,**
  - **Platelet count ≥ 100,000/µl,**
  - **AST or ALT ≤ 3 x ULN, alkaline phosphatase ≤ 2 x ULN,**
  - **Serum Bilirubin ≤ 1.5 x ULN,**
  - **Creatinine Clearance ≥ 30ml/min (Calculated by Cockcroft Gault equation, or by EDTA) (Appendix 2)**
- **Able to swallow oral medication**
- **Only well-controlled CNS metastatic disease ie stable for at least 12 weeks after therapy (surgery, radiotherapy) for brain metastases.**
- **Life expectancy of at least 3 months.**
- **Patients with any advanced solid tumours**
- **Patients for whom the combination of PF-02341066 with PD-0325901 is a reasonable option.**

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.**
- **Ongoing congestive heart failure or cardiac dysrhythmias of NCI CTCAE Grade ≥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.**
- **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, with peritoneael disease or pleural disease, where patient has requirement for ascites or pleural taps.**
- **History of retinal vein occlusion, intraocular pressure > 21 mmHg or patient considered at risk of retinal vein thrombosis.**
- **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 e.g. 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 inhibitors 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.**
- **Requirement for medication known to prolong QT interval (see appendix 5).**
- **History of other malignancy less than 5 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 with 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 two forms of highly effective contraception including oral, injected or implanted hormonal contraception 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) to prevent exposure to the foetus or neonate.**
- Prior exposure to a HGF or cMET inhibitor and/or a MEK inhibitor.

APPENDIX 8: STUDY EVALUATIONS FOR DOSE ESCALATION PHASE USING PF-02341066 WITH PD-0325901

1. Main screening: pre-dosing evaluations

The following must be performed/obtained within the 28 days before the patient receives the first administration of study drug.

- **Written informed consent**
- **Demographic details**
- **Medical history (including prior diagnosis, prior treatment, concomitant diseases, concomitant medications, therapies received by patient within 28 days prior to cycle 1, day minus 7, known ophthalmologic medical history).**
- **ECOG Performance Status (PS)**
- **Full physical examination**
- **Clinical and radiological (CT chest/abdomen/pelvis or CT chest with MRI abdomen/pelvis) disease assessment**
- **Vital signs (systolic/diastolic blood pressure, pulse, body temperature), height and weight.**
- **Ophthalmic assessment, including visual acuity, pressure, perimetry, slit lamp examination, fundoscopy with digital photography, optical coherence tomography and fluorescin angiography.**
- **Safety blood laboratory examination [Haematology: haemoglobin, white blood cells (WBC) with differential count and platelets; Clinical chemistry: sodium, potassium, calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (alk phos), AST and/or ALT and LDH; Coagulation screen: APTT, PT)**
- **Serum or urine Human Chorionic Gonadotropin (HCG) pregnancy test for women of childbearing potential.**
- **12-lead electrocardiogram**
- **Echocardiography**
- **Review of inclusion and exclusion criteria**
- **Obtain archived tumour tissue for biomarker analysis**
- **Draw blood sample for germline DNA**
- **Obtain fresh skin biopsy for PD assessment**
- **Obtain fresh tumour biopsy for PD assessment, where additional consent has been given.**

2. Evaluations during dosing

Cycle 1 day minus 7

ECOG PS
Record of concomitant medications
Full physical examination
Vital signs (systolic/diastolic blood pressure, pulse, body temperature) and weight.
ECG (12-lead)
Blood for assessment of haematology, clinical chemistry, and coagulation status
Blood for assessment of Carcinoembryonic Antigen (CEA)
PD assessment of ERK phosphorylation according to timings in section 7.4.
PD assessment of soluble c-MET and HGF according to timings in section 7.4
Assessment of adverse events
Dosing with PD-0325901.

Cycle 1 day minus 6

Blood for PD assessment (24 hour sample)
Dosing with PD-0325901.

Cycle 1 day minus 1

Blood for PK assessment: blood draws as per section 7.3.
Dosing with PD-0325901.

Cycle 1 day 1

ECOG PS

Record of concomitant medications
Full physical examination
Vital signs (systolic/diastolic blood pressure, pulse, body temperature) and weight.
ECG (12-lead)
Blood for assessment of haematology, clinical chemistry, and coagulation status
Blood for assessment of Carcinoembryonic Antigen (CEA)
PK sampling (24 hour sample)
PD assessments according to timings in section 7.4.
Plasma samples for biomarkers; blood draws as per section 7.4.
Assessment of adverse events
Start PF-02341066 and PD-0325901.
Obtain blood sample for ctDNA as per section 7.5.

Cycle 1 day 2

Blood for PD assessment (24 hour sample) as per section 7.4.
Dosing with PD-0325901 and PF-02341066.

Cycle 1 day 8

ECOG PS
Record of concomitant medications
Full physical examination
Vital signs (systolic/diastolic blood pressure, pulse, body temperature) and weight.
Assessment of adverse events
Dosing with PD-0325901 and PF-02341066.

Cycle 1 day 15

ECOG PS
Record of concomitant medications
Full physical examination
Vital signs (systolic/diastolic blood pressure, pulse, body temperature) and weight.
ECG (12-lead)
Blood for assessment of haematology, clinical chemistry, and coagulation status
Blood for assessment of Carcinoembryonic Antigen (CEA)
PD assessments according to timings in section 7.4.
Plasma samples for biomarkers; blood draws as per section 7.4.
Assessment of adverse events
Dosing with PD-0325901 and PF-02341066
4-6 hours post-dose fresh skin biopsy for PD assessment
4-6 hours post-dose fresh tumour biopsy for PD assessment (for patients in the dose expansion phase and those patients who have consented to the biopsy in the escalation phase).

Cycle 1 day 16

Blood for PD assessment (24 hour sample)
Dosing with PD-0325901 and PF-02341066.

Cycle 1 day 21

ECOG PS
Record of concomitant medications
Full physical examination
Vital signs (systolic/diastolic blood pressure, pulse, body temperature) and weight.
PK sampling: blood draws as per section 7.3.
Ophthalmic assessment, including visual acuity, pressure, perimetry, slit lamp examination, fundoscopy with digital photography, optical coherence tomography and fluorescin angiography.
Assessment of adverse events
Dosing with PD-0325901 and PF-02341066

Cycle 1 day 22

PK sampling (24 hour sample)
Dosing with PF-02341066 only

Cycle 1 day 28

ECOG PS
Record of concomitant medications
Full physical examination
Vital signs (systolic/diastolic blood pressure, pulse, body temperature) and weight.
PK sampling: blood draws as per section 7.3
ECG (12-lead)
Blood for assessment of haematology, clinical chemistry, and coagulation status
Blood for assessment of Carcinoembryonic Antigen (CEA)
Assessment of adverse events
Dosing with PF-02341066 only

Cycle 2 day 1 (Day 29)

PK sampling (24 hour sample)
Plasma samples for biomarkers; blood draws as per section 7.4.
Blood sample for ctDNA (dose expansion phase only)

Dosing with PF-02341066 and restart PD-0325901

Cycle 2 onwards, day 8

ECOG PS
Record of concomitant medications
Full physical examination
Vital signs (systolic/diastolic blood pressure, pulse, body temperature).
Assessment of adverse events
Dosing with PD-0325901 and PF-02341066

Cycle 2 onwards, day 15

ECOG PS
Record of concomitant medications
Full physical examination
Vital signs (systolic/diastolic blood pressure, pulse, body temperature).
Assessment of adverse events
Dosing with PD-0325901 and PF-02341066
Plasma samples for biomarkers; blood draws as per section 7.4 (cycle 2 only).

Cycle 2 onwards, day 21

ECOG PS
Record of concomitant medications
Full physical examination
Vital signs (systolic/diastolic blood pressure, pulse, body temperature).
PK sampling: blood draws as per section 7.3 (trough level and 2h after dosing, cycles 2, 4, 6, 8, 10 and 12).
Assessment of adverse events
Dosing with PD-0325901 and PF-02341066

Cycle 3 onwards day 1

ECOG PS
Record of concomitant medications
Full physical examination
Clinical and radiological (CT chest/abdomen/pelvis or CT chest with MRI abdomen/pelvis) disease assessment

Vital signs (systolic/diastolic blood pressure, pulse, body temperature) and weight.
ECG (12-lead)
Blood for assessment of haematology, clinical chemistry, and coagulation status
Blood for assessment of Carcinoembryonic Antigen (CEA)
Plasma samples for biomarkers; blood draws as per section 7.4.
Blood sample for ctDNA (dose expansion phase only)
Assessment of adverse events
Dosing with PF-02341066 and re-start PD-0325901

3. End of treatment evaluations

ECOG PS
Record of concomitant medications
Full physical examination
Vital signs (systolic/diastolic blood pressure, pulse, body temperature) and weight.
Blood for assessment of haematology, clinical chemistry, and coagulation status
Blood for assessment of Carcinoembryonic Antigen (CEA)
Blood for ctDNA (dose expansion phase only)
Ophthalmic assessment, including visual acuity, pressure, perimetry, slit lamp examination, fundoscopy with digital photography, optical coherence tomography and fluorescin angiography.
Assessment of adverse events
ECG (12-lead)
Tumour assessment: CT scan chest/abdomen/pelvis (or CT chest with MRI abdomen/pelvis) using RECIST v1.1.
Biopsy of representative metastases for molecular profiling (dose expansion phase only: optional)

4. Post treatment follow-up - evaluations

- **Assessment of adverse events**
- **Patients will be followed up every 3 months for survival status until death or study closure, whichever happens first.**

5. Evaluations on early withdrawal

If the patient is withdrawn from treatment, for any of the reasons indicated in section 6, a final off-study visit assessment should be performed 28 - 30 days after the last administration of PF-02341066 and PD-0325901. The following assessments will be done:

- **ECOG PS**
- **Record of concomitant medications**
- **Full physical examination**
- **Vital signs (systolic/diastolic blood pressure, pulse, body temperature) and weight.**
- **Blood for assessment of haematology, clinical chemistry, and coagulation status**
- **Assessment of adverse events**
- **ECG (12-lead)**

If the patient is withdrawn from the trial and declines attendance for a final off-study visit, then a withdrawal assessment should be performed, if possible on the day the decision is made to take the patient off-study or as soon as possible. Telephone review is permitted in these circumstances. These patients will be followed up for progression and overall survival.

APPENDIX 9: SCHEDULE OF EVENTS FOR DOSE ESCALATION PHASE USING PF-02341066 WITH PD-0325901

Visit Description	Screening	Cycle 1											Cycle 2				Cycle 3				Cycle 4				Cycle 5 onwards	End of Treatment [o]	Post end of treatment follow-up
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 [a]	X	X			X		X	X		X		X		X	X	X	X	X	X	X	X	X	X	X		X	
Tumour Assessment [b]	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 [c]	X	X			X		X	X		X		X					X				X					X	
Ophthalmic Exam [d]	X									X																X	
Haem & Clin Chem Bloods [e]	X	X			X			X				X					X				X				Repeat cycle 3 and 4	X	
Pregnancy test	X																										
12 lead ECG	X	X			X			X				X					X				X					X	
Echocardiography [f]	X																										
Inclusion/exclusion criteria	X																										
CEA [g]		X										X					X									X	
PK 24 hours profile [h]				X	X					X	X	X	X														
PK trough [i]																X								X			
PD PBMC/plasma [j]		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
PD-0325901 administration [k]		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 [l]	X							X																			
PD tumour biopsy [m]	X							X																			
Plasma soluble biomarkers [n]		X			X			X					X		X		X				X						

[a] To include vital signs (pulse and systolic/diastolic blood pressure, body temperature) and neurological examination.
[b] 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.
[c] Height to measured only at screening.
[d] Ophthalmic exam on Cycle 1 Day 21 time window of +/- 2 days
[e] 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).
[f] ECHO will only be repeated as clinically indicated.
[g] At same time as CT scan (optional at every cycle) plus Cycle 1 Day 28.
[h] Serum PK measurements will be taken as specified in the protocol (section 7.3).
[i] PK trough sample pre-dose (morning) and 2 hours post dose day 21 of cycles 2, 4, 6, 8, 10 and 12.
[j] PD PBMC/Plasma samples will be taken as specified in the protocol (section 7.4)
[k] Run-in day -7 to day -1 then days 1-21 of each 28 day cycle.
[l] Day 15 +/- 7 days.
[m] At Screening and Day 15 +/- 7 days. Optional biopsy if separate consent obtained.
[n] At each sampling point 4ml of plasma obtained.
[o] Disease progression, intolerance or withdrawal.

APPENDIX 10: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
001 substantial	2.0	29Jul2014	Mark Middleton (CI) Sharon Love (Stats) OCTO Pfizer	In response to MHRA NFGNA: clarification re MTD and dose modification; Protocol and PIS inclusion of MHRA contraception guidelines; IMP information correction to CTA.
004 substantial	3.0	27Jan2015	Mark Middleton (CI) Sharon Love (Stats) OCTO Pfizer	Amend IRAS Dataset updated with changes. Protocol; Dose Escalation and Dose Expansion PIS/CFs; Patient Diary Card; Patient Study Card Belfast site PI - notice of change of status.
007 substantial	4.0	14Jul2015	Mark Middleton (CI) Sharon Love (Stats) OCTO Pfizer	Inclusion of interim dose level. Additional exclusion criteria. Removal of Ondansetron as recommended treatment for Vomiting. Correction to ECG event Cycle 1 Day 15
008 substantial	5.0	13Apr2016	Mark Middleton (CI) Sharon Love (Stats) OCTO Pfizer Array Biopharma	Include new study drug, MEK inhibitor Binimetinib as replacement for the MEK inhibitor PD-0325901. Inclusion of an extra short dose escalation phase using the new combination study drug Binimetinib with PF-02341066. Change to the study design of the dose expansion phase to incorporate specific cohorts of RAS wild type colorectal patients. Additional Investigator Brochure for Binimetinib Notification of change of investigator at an existing site, European St Georges Pompidou Hospital, Paris.
011 substantial	6.0	14Mar2017	Mark Middleton (CI) OCTO	Clarification to CPK DLT criteria and dose modification guidelines in Protocol secs 8.5 and 8.5.1
012 substantial	7.0	11May2017	Mark Middleton (CI) Sharon Love (Stats) OCTO Pfizer Array Biopharma	Amendment to protocol, doe expansion phase patient information and screening consent form and GP letter.. Update to patient numbers required for escalation phase as well as total patient numbers. Update of dose escalation phase site numbers from 4to 5. Update to dose expansion phase site numbers from 8 to 8-10 sites. To capture early phase Ib dose expansion objective responses to study treatment in a) *RAS*MT CRC and b) *RAS*WT/c-METmut/amplified CRC and c) RASWT/c-MET over-expressed CRC. This also requires an increase in patient number target. Update to eligibility and exclusion criteria. Update to contraception guidelines. Correction to the sec 3.0 dose expansion phase secondary endpoints where CT scanning was listed in addition to the primary

				endpoint. Revision of dose expansion phase sample collection to exclude pERK sample collection in PBMCs and reduction in skin biopsy samples to include a limited cohort of 10 patients. Change of lab information for processing of skin biopsies. Dose Expansion Schedule changes for: i) clarification of post end of treatment and follow up and (ii) removal of C1 day 2 and C1 day 16 as no longer required for PD pERK samples. Update to dose modification guidelines for AEs (pneumonitis and LVEF) Change to PI at the Vall d'Hebron, Barcelona site.
013 substantial	8.0	11Sep2017	Mark Middleton (CI) OCTO Sandra Van Schaeybroeck (Project coordinator)	Amendment to sec 7.2 to include PDUM facility for evaluation of amplification and c-MET expression Clarifications to sec 15.1 and correction to sample size typographical error Typographical corrections and clarifications to ensure consistency throughout the protocol. Screening PIS – clarification to reporting timeline for RAS genotype
014	8.0	29Aug2018	Mark Middleton (CI) OCTO	Update to IBs - binimetinib (v Mar2018 and crizotinib (v Oct2017)
015	9.0	29Oct2018	Mark Middleton (CI) OCTO	Change of trial statistician details. Change in protocol design to include early patient recruitment closure – protocol synopsis and sec 2.1 and sec 2.3. Clarification of CPK dose modification guidelines in sec 8.5.1 and Appendix 6A. Removal of ctDNA sample collection time-point in Summary Schedule of Events at screening – dose expansion phase and alsp sec 5.4 as not required.