ISRCTN18043777 https://doi.org/10.1186/ISRCTN18043777

# MEK and MET Inhibition in Colorectal Cancer

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| **Submission date**<br>04/02/2015 | **Recruitment status**<br>No longer recruiting | [_] Prospectively registered<br>[_] Protocol<br>[_] Statistical analysis plan<br>[X] Results<br>[_] Individual participant data |
| **Registration date**<br>04/02/2015 | **Overall study status**<br>Completed | |
| **Last Edited**<br>23/05/2022 | **Condition category**<br>Cancer | |

**Plain English summary of protocol**
http://www.cancerresearchuk.org/about-cancer/trials/a-trial-looking-crizotinib-pd0325901-binimetinib-for-bowel-cancer-mercuric1

**Study website**
http://www.oncology.ox.ac.uk/trial/mercuric1

## Contact information

**Type(s)**
Scientific

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## Additional identifiers

**EudraCT/CTIS number**
2014-000463-40

**IRAS number**

**ClinicalTrials.gov number**
NCT02510001

### Secondary identifying numbers
17363

# Study information

### Scientific Title
A Sequential Phase I study of MEK1/2 inhibitors PD0325901 or Binimetinib combined with c-MET inhibitor PF02341066 in KRAS Mutant and RAS Wild Type (with aberrant c-MET) Colorectal Cancer

### Acronym
MErCuRIC1

### Study objectives
Combined MEK/MET inhibitor treatment is well tolerated and results in superior survival of patients with RASMT CRC and RASWT CRC with aberrant c-MET signalling (overexpression, amplification or mutation; RASWT/c-MET+) compared to standard chemotherapy treatment. (added 07/09/2016)

There are two phases of the study:
1. Dose escalation phase in patients with solid tumours to discover the maximum tolerated drug doses
2. Dose expansion phase in two particular patient groups who have advanced colorectal cancer to study the treatment responses in each of those groups.
Both drugs have shown beneficial activity in studies treating patients with advanced cancer and it is believed that using this combination will inhibit the chemical pathways that are involved in colorectal cancer.

### Ethics approval required
Old ethics approval format

### Ethics approval(s)
14/SC/1010; First MREC approval date 06/08/2014

### Study design
Non-randomised; Interventional; Design type: Treatment

### Primary study design
Interventional

### Secondary study design
Non randomised study

### Study setting(s)
Hospital

### Study type(s)
Treatment

## Participant information sheet
Not available in web format, please use contact details to request a patient information sheet

## Health condition(s) or problem(s) studied
Topic: Cancer; Subtopic: Colorectal Cancer; Disease: Colon

## Interventions
Current interventions as of 19/09/2017:
PD-0325901:
1. This is a highly specific non-ATP competitive inhibitor of MEK1 and MEK2.
2. Dose escalation phase (in combination with PF-02341066) started at 4mg BD up to maximum levels of 8mg BD which is known to inhibit the target of MEK1 and MEK2.
Binimetinib (MEK162):
1. An orally bioavailable, selective and potent mitogen-activated protein (MAP) kinase kinase (MEK) 1 and MEK 2 inhibitor.
2. Dose escalation phase (in combination with PF-02341066) will start at 30mg BD up to maximum level of 45mg BD.
PF-02341066 (Crizotinib):
1. A selective ATP-competitive small molecule oral inhibitor of ALK, c-Met/hepatocyte growth factor receptor(HGFR), RON and ROS RTKs and their oncogenic variants. It is both a CYP3A substrate and inhibitor. The extent and duration of inhibition of c-MET activity is directly linked to its anti-tumour efficacy.
2. Dose escalation phase (in combination with PD-0325901) started at 250mg OD.
3. Dose escalation phase (in combination with Binimetinib) started at 250mg OD up to maximum level of 200mg BD.

Previous interventions:
1. PD-0325901: This is a highly specific non-ATP competitive inhibitor of MEK1 and MEK2. Dose start will be at 4mg BD up to maximum levels of 8mg BD which is known to inhibit the target of MEK1 and MEK2.
2. Binimetinib is a selective and potent mitogen-activated protein (MAP) kinase (MEK) 1 and MEK 2 inhibitor. Dose start will be at 30mg BD up to maximum level of 45mg BD.(added 07/09/2016)
3. PF-02341066 (Crizotinib): A selective ATP-competitive small molecule oral inhibitor of ALK, cMet/hepatocyte growth factor receptor(HGFR), RON and ROS RTKs and their oncogenic variants. PF-02341066 has a long half life, takes 15 days to reach steady state and is excreted by the fecal route. It is both a CYP3A substrate and inhibitor. The extent and duration of inhibition of c-MET activity is directly linked to its anti-tumour efficacy.

## Intervention Type
Drug

## Phase
Phase I

## Drug/device/biological/vaccine name(s)
PD-0325901 Binimetinib PF-02341066 (Crizotinib)

## Primary outcome measure
As of 07/09/2016:
Dose Expansion phase; Time point(s): Clinical & radiological response to PD-0325901 or Binimetinib with PF-02341066 using RECIST v1.1

Initial:
Dose Expansion phase; Timepoint(s): Clinical & radiological response to PD-0325901 with PF-02341066 using RECIST v1.1

### Secondary outcome measures
As of 07/09/2016:Dose Escalation Phase; Time point(s): Maximal tolerated dose of PD-0325901 or Binimetinib with PF-02341066 according to toxicities in cycle 1.

Initial:
Dose Escalation Phase; Timepoint(s): Maximal tolerated dose of PD-0325901 with PF-02341066 according to toxicities in cycle 1.

### Overall study start date
14/11/2014

### Completion date
30/09/2019

## Eligibility

### Key inclusion criteria
Participant inclusion criteria as of 21/11/2018:
All patients
1. Age at least 16 years
2. ECOG performance status 0-1
3. Adequate respiratory and cardiac function on clinical assessment
4. Left ventricular ejection fraction (LVEF) ≥ 50% as determined by a multigated acquisition (MUGA) scan or echocardiogram
5. Able to give informed consent prior to any screening procedures being performed and be capable of complying with the protocol and its requirements
6. Haematological and biochemical indices within the ranges shown below:
6.1. Haemoglobin (Hb) =9g/dl (transfusion to achieve this allowed),
6.2. Neutrophils= 1,500/µl,
6.3. Platelet count = 100,000/µl,
6.4. AST or ALT ≤2.5 x ULN, patient with liver metastases <5 x ULN, alkaline phosphatase ≤5 x ULN,
6.5. Serum Bilirubin ≤1.5 x ULN,
6.6. Creatinine Clearance ≥50ml/min
7. Able to swallow oral medication
8. Life expectancy of at least 3 months

Dose escalation phase:
1. Patients with any advanced solid tumours
2. Patients for whom the combination of PF-02341066 with Binimetinib is a reasonable option.

Dose expansion phase:
Patients will be eligible for pre-screening for MErCuRIC provided that:
1. They have given informed consent to screening.
2. They are willing to undergo a biopsy for assessment of tumour RAS mutation status and c-MET assessment.

3. 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:
1. Histologically confirmed colon adenocarcinoma that is either a) RASMT (KRAS codon 12, 13, 61, 117, 146; NRAS codon 12, 13, 61, 117, 146 mutations) or b) RASWT/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.
2. Prior treatment with an EGFR targeted monoclonal antibody for patients with RASWT/c-MET mutated or amplified CRC or RASWT/c-MET over-expressed.
3. No evidence for a mutation in BRAF at codon600
4. Metastases accessible for biopsy on at least 2-3 occasions
5. At least one other measurable lesion (according to RECIST v1.1).
6. Unsuitable for potential curative resection.

Participant inclusion criteria as of 19/09/2017:
All patients
1. Age at least 16 years
2. ECOG performance status 0-1
3. Adequate respiratory and cardiac function on clinical assessment
4. Left ventricular ejection fraction (LVEF) ≥ 50% as determined by a multigated acquisition (MUGA) scan or echocardiogram
5. Able to give informed consent prior to any screening procedures being performed and be capable of complying with the protocol and its requirements
6. Haematological and biochemical indices within the ranges shown below:
6.1. Haemoglobin (Hb) =9g/dl (transfusion to achieve this allowed),
6.2. Neutrophils= 1,500/µl,
6.3. Platelet count = 100,000/µl,
6.4. AST or ALT = <2.5 x ULN, patient with liver metastases <5 x ULN, alkaline phosphatase = <5 x ULN,
6.5. Serum Bilirubin = 1.5 x ULN,
6.6. Creatinine Clearance = 50ml/min
7. Able to swallow oral medication
8. Life expectancy of at least 3 months

Dose escalation phase:
1. Patients with any advanced solid tumours
2. Patients for whom the combination of PF-02341066 with Binimetinib is a reasonable option.

Dose expansion phase:
Patients will be eligible for pre-screening for MErCuRIC provided that:
1. They have given informed consent to screening.
2. They are willing to undergo a biopsy for assessment of tumour RAS mutation status and c-MET assessment.
3. 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:
1. Histologically confirmed colon adenocarcinoma that is either a) RASMT (KRAS codon 12, 13, 61, 117, 146; NRAS codon 12, 13, 62, 227, 146 mutations) or b) RASWT/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.
2. Prior treatment with an EGFR targeted monoclonal antibody for patients with RASWT/c-MET mutated or amplified CRC or RASWT/c-MET over-expressed.
3. No evidence for a mutation in BRAF at codon600
4. Metastases accessible for biopsy on at least 2-3 occasions
5. At least one other measurable lesion (according to RECIST v1.1).
6. Unsuitable for potential curative resection.

As of 07/09/2016:
1. Age at least 16 years
2. ECOG performance status 0-1
3. Adequate respiratory and cardiac function on clinical assessment
4. Left ventricular ejection fraction (LVEF) ≥ 50% as determined by a multigated acquisition (MUGA) scan or echocardiogram.
5. Able to give informed consent prior to any screening procedures being performed and be capable of complying with the protocol and its requirements
6. Haematological and biochemical indices within the ranges shown below:
6.1. Haemoglobin (Hb) =9g/dl (transfusion to achieve this allowed),
6.2. Neutrophils= 1,500/µl,
6.3. Platelet count = 100,000/µl,
6.4. AST or ALT = <2.5 x ULN, patient with liver metastases <5 x ULN, alkaline phosphatase = <2 x ULN,
6.5. Serum Bilirubin = 1.5 x ULN,
6.6. Creatinine Clearance = 50ml/min
7. Able to swallow oral medication
8. Life expectancy of at least 3 months

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

Dose expansion
Patients will be eligible for pre-screening for MErCuRIC provided that:
1. They have given informed consent to screening
2. They are willing to undergo a biopsy for assessment of tumour KRAS mutation status and c-MET assessment
3. 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 pr-e-screening, requires:
1. Histologically confirmed colon adenocarcinoma that is RASMT (KRAS codon 12, 13, 61, 117, 146; NRAS codon 12, 13, 61, 117, 146)) or RASWT/c-MET+, with progressive disease on or within 6 months of completion of adjuvant therapy or after chemotherapy and/or targeted therapies for metastatic disease.
2. No evidence for a mutation in BRAF at codon600
3. Metastases accessible for biopsy on at least 2-3 occasions
4. At least one other measurable lesion (according to RECIST v1.1).
5. Unsuitable for potential curative resection

Initial:
All patients

1. Age at least16 years
2. ECOG performance status 0-1
3. Adequate respiratory and cardiac function
4. Able to give informed consent to co-operate with the protocol
5. Haematological and biochemical indices within the ranges shown below:
5.1. Haemoglobin (Hb) =9g/dl (transfusion to achieve this allowed),
5.2. Neutrophils= 1,500/µl,
5.3. Platelet count = 100,000/µl,
5.4. AST or ALT = 3 x ULN, alkaline phosphatase = 2 x ULN,
5.5 Serum Bilirubin = 1.5 x ULN,
5.6. Creatinine Clearance = 30ml/min
6. Able to swallow oral medication
7. Only well-controlled

CNS metastatic disease
1. Life expectancy of at least 3 months

Dose escalation phase
1. Patients with any advanced solid tumours
2. Patients for whom PF-02341066
with PD_0325901 is a reasonable option.

Dose expansion
Patients will be eligible for prescreening for MErCuRIC provided that:
1. They have given informed consent to screening.
2. They are willing to undergo a biopsy for assessment of tumour KRAS mutation status and c-MET assessment.
3. The Investigator anticipates that they are likely to satisfy the eligibility criteria for the trial. Formal screening should not be performed until the tumour prescreening result is known.

Eligibility for the trial, in patients passing pr-escreening, requires:
1. Histologically confirmed colon adenocarcinoma KRASMT (codon 12, 13, 61 mutations) or KRASWT/c-MET+, with progressive disease on or within 6 months of completion of adjuvant therapy or after chemotherapy and/or targeted therapies for metastatic disease.
2. Metastases accessible for biopsy
3. At least one other measurable lesion (according to RECIST v1.1).
4. Unsuitable for potential curative resection.

## Participant type(s)
Patient

## Age group
Adult

## Lower age limit
18 Years

## Sex
Both

## Target number of participants

Planned Sample Size: 92-148 ; UK Sample Size: 52 Description: Actual UK sample size expected to be less for the UK as the study is also recruiting from 4 European sites.

## Key exclusion criteria

Exclusion criteria as of 21/11/2018:
1. Unstable ischemic heart disease, cardiac dysrhythmias, coronary/peripheral artery bypass graft or cerebrovascular accident within 6 months prior to starting treatment.
2. Uncontrolled arterial hypertension despite medical treatment.
3. Ongoing congestive heart failure or cardiac dysrhythmias of NCI CTCAE Grade >2 or uncontrolled atrial fibrillation.
4. 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.
5. 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.
6. Patients who have neuromuscular disorders that are associated with elevated CK (e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy);
7. 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.
8. Spinal cord compression unless treated with the patient attaining good pain control and stable or recovered neurologic function.
9. Carcinomatous meningitis or leptomeningeal disease.
10. History of hypoalbuminaemia, or patients with peritoneal disease or pleural disease, where there is a requirement for ascitic or pleural taps.
11. History of retinal vein occlusion, intraocular pressure > 21 mmHg or patient considered at risk of retinal vein thrombosis.
12. History of retinal degenerative disease.
13. History of Gilbert's syndrome.
14. Active infections (including chronic hepatitis type B or C and HIV infection if status known), severe immunologic defect, compromised bone marrow function
15. Other severe acute or chronic medical conditions
16. Patients who have undergone major surgery ≤ 3 weeks prior to starting study drug or who have not recovered from side effects of such procedure
17. Use of drugs or foods that are known potent CYP3A4 inhibitors or inhibitors or are CYP3A4 substrates with narrow therapeutic indices
18. Radiotherapy (except for palliative reasons), endocrine therapy, immunotherapy or chemotherapy during the previous four weeks (six weeks for nitrosoureas, Mitomycin-C)
19. Resting ECG with QTc >480msec at 2 or more time points within a 24h period.
20. Requirement for medication known to prolong QT interval.
21. History of other malignancy less than 3 years before the diagnosis of current cancer
22. 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 one highly effective form of contraception (oral, injected or implanted hormonal contraception or intrauterine 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.
23. Male patients with partners of childbearing 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 intrauterine device) in addition tocondom 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.
24. Prior exposure to a HGF or c-MET inhibitor and/or a MEK inhibitor.

Exclusion criteria as of 19/09/2017:
1. Unstable ischemic heart disease, cardiac dysrhythmias, coronary/peripheral artery bypass graft or cerebrovascular accident within 6 months prior to starting treatment.
2. Uncontrolled arterial hypertension despite medical treatment.
3. Ongoing congestive heart failure or cardiac dysrhythmias of NCI CTCAE Grade >2 or uncontrolled atrial fibrillation.
4. 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.
5. 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.
6. Patients who have neuromuscular disorders that are associated with elevated CK (e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy);
7. 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.
8. Spinal cord compression unless treated with the patient attaining good pain control and stable or recovered neurologic function.
9. Carcinomatous meningitis or leptomeningeal disease.
10. History of hypoalbuminaemia, or patients with peritoneal disease or pleural disease, where there is a requirement for ascitic or pleural taps.
11. History of retinal vein occlusion, intraocular pressure > 21 mmHg or patient considered at risk of retinal vein thrombosis.
12. History of retinal degenerative disease.
13. History of Gilbert's syndrome.
14. Active infections (including chronic hepatitis type B or C and HIV infection if status known), severe immunologic defect, compromised bone marrow function
15. Other severe acute or chronic medical conditions
16. Patients who have undergone major surgery ≤ 3 weeks prior to starting study drug or who have not recovered from side effects of such procedure
17. Use of drugs or foods that are known potent CYP3A4 inhibitors or inhibitors or are CYP3A4 substrates with narrow therapeutic indices
18. Radiotherapy (except for palliative reasons), endocrine therapy, immunotherapy or chemotherapy during the previous four weeks (six weeks for nitrosoureas, Mitomycin-C)
19. Resting ECG with QTc >480msec at 2 or more time points within a 24h period.
20. Requirement for medication known to prolong QT interval.
21. History of other malignancy less than 3 years before the diagnosis of current cancer
22. 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, have a intrauterine device and condom, diaphragm with spermicidal

gel and condom) for four weeks before entering the trial, during the trial and for six months afterwards are considered eligible.
23. Male patients with partners of childbearing potential (unless they agree to take measures not to father children by using two forms of highly effective contraception [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 (for example, condom plus spermicidal gel) to prevent exposure to the foetus or neonate.
24. Prior exposure to a HGF or c-MET inhibitor and/or a MEK inhibitor.

As of 07/09/2016:
1. Unstable ischemic heart disease, cardiac dysrhythmias, coronary/peripheral artery bypass graft or cerebrovascular accident within 6 months prior to starting treatment.
2. Uncontrolled arterial hypertension despite medical treatment.
3. Ongoing congestive heart failure or cardiac dysrhythmias of NCI CTCAE Grade =>2 or uncontrolled atrial fibrillation.
4. 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.
5. 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.
6. Patients who have neuromuscular disorders that are associated with elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy);
7. 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
8. Spinal cord compression unless treated with the patient attaining good pain control and stable or recovered neurologic function
9. Carcinomatous meningitis or leptomeningeal disease
10. History of hypoalbuminaemia, or patients with peritoneal disease or pleural disease, where there is a requirement for ascitic or pleural taps.
11. History of retinal vein occlusion, intraocular pressure > 21 mmHg or patient considered at risk of retinal vein thrombosis.
12. History of retinal degenerative disease.
13. History of Gilbert's syndrome.
14. Active infections (including chronic hepatitis type B or C and HIV infection if status known), severe immunologic defect, compromised bone marrow function
15. Other severe acute or chronic medical conditions
16. Patients who have undergone major surgery ≤ 3 weeks prior to starting study drug or who have not recovered from side effects of such procedure
17. Use of drugs or foods that are known potent CYP3A4 inhibitors or inhibitors or are CYP3A4 substrates with narrow therapeutic indices
18. Radiotherapy (except for palliative reasons), endocrine therapy, immunotherapy or chemotherapy during the previous four weeks (six weeks for nitrosoureas, Mitomycin-C)
19. Resting ECG with QTc >480msec at 2 or more time points within a 24h period.
20. Requirement for medication known to prolong QT interval.
21. History of other malignancy less than 3 years before the diagnosis of current cancer
22. 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, have a intrauterine device and condom, diaphragm with spermicidal gel and condom) for four weeks before entering the trial, during the trial and for six months afterwards are considered eligible.
23. Male patients with partners of childbearing potential (unless they agree to take measures not to father children by using two forms of highly effective contraception [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 (for example, condom plus spermicidal gel) to prevent exposure to the foetus or neonate
24. Prior exposure to a HGF or cMET inhibitor and/or a MEK inhibitor

Initial:
All patients
1. Unstable ischemic heart disease, cardiac dysrhythmias, coronary/peripheral artery bypass graft or cerebrovascular accident within 6 months prior to starting treatment.
2. Ongoing congestive heart failure or cardiac dysrhythmias of NCI CTCAE Grade =2 or uncontrolled atrial fibrillation.
3. 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.
4. Spinal cord compression unless treated with the patient attaining good pain control and stable or recovered neurologic function.
5. Carcinomatous meningitis or leptomeningeal disease.
6. History of retinal vein occlusion, intraocular pressure > 21 mmHg or patient considered at risk of retinal vein thrombosis.
7. Active infections (including chronic hepatitis type B or C and HIV infection if status known), severe immunologic defect, compromised bone marrow function
8. Other severe acute or chronic medical conditions
9. Use of drugs or foods that are known potent CYP3A4 inhibitors or inhibitors or are CYP3A4 substrates with narrow therapeutic indices
10. Radiotherapy (except for palliative reasons), endocrine therapy, immunotherapy or chemotherapy during the previous four weeks (six weeks for nitrosoureas, Mitomycin-C)
11. Resting ECG with QTc >480msec at 2 or more time points within a 24h period.
12. Requirement for medication known to prolong QT interval.
13. History of other malignancy less than 5 years before the diagnosis of current cancer
14. 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, have a intrauterine device and condom, diaphragm with spermicidal gel and condom) for four weeks before entering the trial, during the trial and for six months afterwards are considered eligible.
15. Male patients with partners of childbearing potential (unless they agree to take measures not to father children by using one form of highly effective contraception [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 (for example, condom plus spermicidal gel) to prevent exposure to the foetus or neonate.
16. Prior exposure to a HGF or cMET inhibitor and/or a MEK inhibitor.

## Date of first enrolment
14/11/2014

**Date of final enrolment**
31/10/2018

# Locations

**Countries of recruitment**
Belgium

England

France

Ireland

Northern Ireland

Spain

United Kingdom

Wales

**Study participating centre**
**Churchill Hospital**
Old Rd
Headington
Oxford
United Kingdom
OX3 7LE

**Study participating centre**
**Belfast Health and Social Care Trust**
Knockbracken Healthcare
Saintfield Rd
Belfast
United Kingdom
BT8 8BH

**Study participating centre**
**Velindre Cancer Centre**
Velindre Rd
Cardiff
United Kingdom
CF14 2TL

**Study participating centre**
**University Hospital Antwerp**
Wilrijkstraat 10
Edegem
Belgium
2650

**Study participating centre**
**Vall d'Hebron University Hospital**
Passeig de la Vall d'Hebron, 119-129
Barcelona
Spain
08035

**Study participating centre**
**Beaumont Hospital**
Beaumont Rd
Dublin 9
Ireland
-

**Study participating centre**
**St Antoine Hospital**
184 Rue du Faubourg Saint-Antoine
Paris
France
75012

**Study participating centre**
**European Georges Pompidou Hospital**
20 Rue Leblanc
Paris
France
75015

**Study participating centre**
**University of Oxford**
Department of Oncology
Oncology Clinical Trials Office (OCTO)

Old Road Campus Research Builiding
Roosevelt Drive
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OX3 7DQ

# Sponsor information

**Organisation**
University of Oxford

**Sponsor details**
Joint Research Office
Block 60, Churchill Hospital
Oxford
England
United Kingdom
OX3 7LE

**Sponsor type**
University/education

**ROR**
https://ror.org/052gg0110

# Funder(s)

**Funder type**
Government

**Funder Name**
European Commission

**Alternative Name(s)**
European Union, Comisión Europea, Europäische Kommission, EU-Kommissionen, Euroopa Komisjoni, Ευρωπαϊκής Επιτροπής, Европейската комисия, Evropské komise, Commission européenne, Choimisiúin Eorpaigh, Europskoj komisiji, Commissione europea, La Commissione europea, Eiropas Komisiju, Europos Komisijos, Európai Bizottságról, Europese Commissie, Komisja Europejska, Comissão Europeia, Comisia Europeană, Európskej komisii, Evropski komisiji, Euroopan komission, Europeiska kommissionen, EC, EU

**Funding Body Type**
Government organisation

### Funding Body Subtype
National government

### Location

## Results and Publications

### Publication and dissemination plan
Not provided at time of registration

### Intention to publish date

### Individual participant data (IPD) sharing plan
Not provided at time of registration

### IPD sharing plan summary
Not provided at time of registration

### Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Basic results | EU Clinical Trials Register results | 05/01/2020 | 20/05/2022 | No | No |
| Basic results | ClinicalTrials.gov results | 26/04/2021 | 23/05/2022 | No | No |