# Clinical Trials Data BRAF - Document 5

# BRAF/MEK/EGFR Inhibitor Combination Study in Colorectal Cancer (CRC)

## Clinical Trial: https://clinicaltrials.gov/study/NCT01750918

"eligibilityCriteria": "Inclusion Criteria: Subjects eligible for enrolment in this study must meet all of the following criteria\n\n\* Provided written informed consent,\n\* Male or female \\>=18 years of age and able to swallow and retain orally administered study treatment and does not have any clinically significant gastrointestinal (GI) abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach and/or bowels.\n\* Part 1 and Part 2: Histologically- or cytologically-confirmed diagnosis of advanced or metastatic BRAF V600E mutation positive CRC\n\* Part 4A and 4B ONLY: Histologically- or cytologically-confirmed diagnosis of advanced or metastatic CRC that either harbours the BRAF V600E -mutation, as determined by relevant genetic testing OR has developed secondary resistance to anti-EGFR therapy, defined as patients that derived benefit (disease control based on investigator assessment for \\>6 months OR partial response \\[confirmed or unconfirmed\\] based on RECIST 1.1) from prior anti-EGFR-containing therapy (as defined below) and then subsequently progressed on therapy. The anti-EGFR therapy must have been the most recent therapy and the patient must have progressed based on investigator assessment within 3 months of screening. Acceptable prior anti-EGFR-containing therapies include: a. Monotherapy anti-EGFR, including cetuximab or panitumumab OR b. irinotecan/anti-EGFR combo after previously having disease progression (based on investigator assessment) on an irinotecan-containing regimen\n\* Part 3: Histologically- or cytologically-confirmed diagnosis of BRAFV600E mutation positive advanced or metastatic colorectal cancer (CRC who are eligible to receive fluoropyrimidine-containing chemotherapy regimen that have experienced documented radiographic progression on one prior line of fluoropyrimidine-containing chemotherapy (previous anti-EGFR therapy is excluded), Second-line for advanced/metastatic disease, having failed or been intolerant to at least one regimen of fluoropyrimidine-containing chemotherapy including irinotecan or oxaliplatin in the advanced/metastatic setting. Enrollment in Part 3 may only occur following confirmation of KRAS wild-type cancer.\n\* Archival tissue is required; if archival tissue is not available or found to not contain tumor tissue, a fresh biopsy is required.\n\* Measurable disease per RECIST version 1.1.\n\* Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.\n\* Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use one of the contraception methods listed in protocol.\n\* Female subjects are eligible if: Non-childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or post-menopausal female defined as 12 months of spontaneous amenorrhea to be verified with a follicle-stimulating hormone (FSH) level \\>40 Milli-international units per milliliter (MIU/mL) and estradiol level \\<40 picogram per milliliter (pg/mL). Child-bearing potential and agrees to use one of the contraceptive methods listed in protocol.\n\* Female subjects must agree to use contraception from 7 days prior to the first dose of study drug(s) until 6 months after the last dose of panitumumab, until 4 months after the last dose of trametinib, or 4 weeks after the last dose of dabrafenib, whichever is longer. Additionally, women of childbearing potential must have had a negative serum pregnancy test within 7 days prior to the first dose of study drug(s).\n\* Adequate organ system function as defined in absolute neutrophil count greater than or equal to 1.2X10\\^9/Liter (L), hemoglobin greater than or equal to 9 grams per deciliter (g/dL) or 5.6 millimoles per litre (mmol/L), platelets greater than or equal to 75 \u00d7 10\\^9/L, Prothrombin Time / International Normalized Ratio (PT/INR) and Partial Thromboplastin Time (PTT) less than or equal to 1.5X upper limit of normal (ULN); serum magnesium greater than or equal to the lower limit of normal (LLN); albumin greater than or equal to 2.5 g/dL or 25 grams per liter (g/L), total bilirubin less than or equal to 1.5XULN, and Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) less than or equal to 2.5X ULN; creatinine less than or equal to 1.5XULN or calculated creatinine clearance greater than or equal to 50mL/min; left ventricular ejection fraction (LVEF) greater than or equal to the LLN by echocardiography (ECHO) or multigated acquisition scan (MUGA).\n\* Subjects enrolled in France or Italy: In France or Italy, a subject will be eligible for inclusion in this study only if either affiliated to, or a beneficiary of, a social security category.\n\nExclusion Criteria: Subjects meeting any of the following criteria must not be enrolled in the study\n\n\* History of prior malignancy, other than colorectal cancer.\n\* Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures.\n\* Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases or otherwise stable chronic liver disease per investigator's assessment).\n\* History of sensitivity to heparin or heparin-induced thrombocytopenia.\n\* Currently receiving cancer therapy (chemotherapy, radiation therapy, immunotherapy or biologic therapy).\n\* Prior exposure to a MEK inhibitor.\n\* Part 1, Part 2 and BRAF-mutant patients in Part 4 ONLY: Prior exposure to a BRAF inhibitor.\n\* Part 1, Part 2 and BRAF-mutant patients in Part 4 ONLY: Known presence of KRAS-mutation based on previous KRAS-testing. Note: Prospective KRAS testing is not required. However, if the results of previous KRAS testing are known, they must be used in assessing eligibility. KRAS testing will be performed retrospectively for all patients.\n\* Part 3: Prior exposure to EGFR inhibitors or an anti-EGFR antibody\n\* Received an investigational or approved anti-cancer drug within 4 weeks, or within 5 half-lives (whichever is shorter) of the first dose of study drug(s). At least 14 days must have passed between the last dose of prior investigational agent and the first dose of study drug(s).\n\* Part 3: Received more than one prior anti-cancer therapy in the metastatic setting, exclusive of previous adjuvant regimens. Previous investigational anti-cancer therapy in the metastatic setting is prohibited.\n\* Current use of a prohibited medication or requirement to dose with any of these medications during treatment with study drug(s).\n\* Known Hepatitis B, or Hepatitis C infection.\n\* Any major surgery, radiotherapy or immunotherapy within the 4 weeks prior to first dose of study drug(s). Limited radiotherapy with in the 2 weeks prior to first dose of study drug(s).\n\* Chemotherapy regimens with delayed toxicity within the 3 weeks prior to first dose of study drug(s). Chemotherapy regimens given continuously or on a weekly basis with limited potential for delayed toxicity within 2 weeks prior to first dose of study drug(s).\n\* Unresolved toxicity greater than National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4 Grade 1 from previous anti-cancer therapy, with the exception of Grade 2 alopecia, Grade 2 neuropathy, or laboratory values that are allowed per inclusion criteria.\n\* History of retinal vein occlusion (RVO).\n\* Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism or excretion of drugs. Previous colectomy is acceptable.\n\* Subjects with brain metastases are excluded, unless: All known lesions must be previously treated with surgery or stereotactic radio-surgery, and Brain lesion(s), if present, must be confirmed stable (i.e., no increase in lesion size) for \\>=90 days prior to first dose of study drug(s). This must be documented with two consecutive MRI or CT scans using contrast, and Asymptomatic with no corticosteroids requirement for \\>=30 days prior to first dose of study drug(s), and No enzyme-inducing anticonvulsants for \\>=14 days prior to first dose of study drug(s). In addition, for subjects that had brain metastases but currently have no evidence of disease (NED), NED for \\>=12 weeks is required and must be confirmed by two consecutive MRI or CT scans (using contrast) separated by \\>=6 weeks, prior to randomization. Enrollment of a subject with brain metastases who meet the above criteria requires approval of a GlaxoSmithKline (GSK) Medical Monitor.\n\* Psychological, familial, sociological or geographical conditions that do not permit compliance with the protocol.\n\* History or evidence of cardiovascular risk including any of the following: LVEF\\<LLN; A QT interval corrected for heart rate using the Bazett's formula (QTcB;) \u2265 480 milliseconds (msec);.History or evidence of current clinically significant uncontrolled arrhythmias. Exception: Subjects with controlled atrial fibrillation for \\>30 days prior to randomization are eligible. History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to randomization. History or evidence of current \\>= Class II congestive heart failure as defined by New York Heart Association (NYHA). Treatment refractory hypertension defined as a blood pressure of systolic\\> 140 millimeter of mercury (mm Hg) and/or diastolic \\> 90 mm Hg which cannot be controlled by anti-hypertensive therapy; Subjects with intra-cardiac defibrillators or permanent pacemakers; Known cardiac metastases\n\* Unstable pulmonary embolism, deep vein thrombosis, or other significant arterial/venous thromboembolic event \\<=30 days before randomization. If on anticoagulation, subject must be on stable therapeutic dose prior to randomization.\n\* Subjects with a history of pneumonitis or interstitial lung disease (ILD).\n\* Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study drug(s) or their excipients.\n\* Pregnant or lactating female.\n\* Unwillingness or inability to follow the procedures outlined in the protocol.\n\* Uncontrolled diabetes or other medical condition that may interfere with assessment of toxicity.",  
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Question:  
Based on the following clinical trial information, would a patient with a BRAF gene mutation be eligible for the clinical trial?

Answer:  
A patient with \*any\* BRAF gene mutation is \*\*not\*\* automatically eligible for this trial. The inclusion criteria specify either \*\*BRAF V600E mutation positive CRC\*\* (for Parts 1, 2, and 3) or, for Part 4A and 4B only, \*\*BRAF V600E mutation positive CRC \*or\* CRC with acquired resistance to anti-EGFR therapy\*\*. Therefore, having a BRAF mutation other than V600E would exclude the patient from parts 1, 2, and 3. Only in Part 4A and 4B could a patient with a non-V600E BRAF mutation potentially be eligible if they also met the criteria for acquired resistance to anti-EGFR therapy.