Efficacy and Safety of the Combination Therapy of Dabrafenib and Trametinib in Subjects With BRAF V600E- Mutated Rare Cancers

This study is currently recruiting participants. (see Contacts and Locations)

Verified October 2014 by GlaxoSmithKline

Sponsor:
GlaxoSmithKline

Information provided by (Responsible Party):
GlaxoSmithKline

ClinicalTrials.gov Identifier:
NCT02034110

First received: December 5, 2013
Last updated: November 13, 2014
Last verified: October 2014
History of Changes

Purpose

This is a Phase II, open-label, non-randomized, multi-center study of oral Dabrafenib in combination with oral Trametinib in subjects with rare cancers including anaplastic thyroid cancer, biliary tract cancer, gastrointestinal stromal tumor, non-seminomatous germ cell tumor/non-geminomatous germ cell tumor, hairy cell leukemia, World Health Organization (WHO) Grade 1 or 2 glioma, WHO Grade 3 or 4 (high-grade) glioma, multiple myeloma, and adenocarcinoma of the small intestine, with **BRAF V600E** positive-mutations. This study is designed to determine the overall response rate (ORR) of oral Dabrafenib in combination with oral Trametinib in subjects with rare **BRAF V600E** mutated cancers. Subjects will need to have a fresh or frozen tumor tissue sample provided to confirm the **BRAF V600E** mutation status. Only subjects with histologically confirmed advanced disease and no available standard treatment options will be eligible for enrollment. Subjects will undergo screening assessments within 14 days (up to 35 days for ophthalmology exam, echocardiogram or disease assessments) prior to the start of treatment to determine their eligibility for enrollment in the study.

Condition	Intervention	Phase
Cancer	Drug: Dabrafenib Drug: Trametinib	Phase 2

Study Type: Interventional
Study Design: Endpoint Classification: Safety/Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: A Phase II, Open-label, Study in Subjects With **BRAF V600E**-Mutated Rare Cancers With Several Histologies to Investigate the Clinical Efficacy and Safety of the Combination Therapy of Dabrafenib and Trametinib

Resource links provided by NLM:

MedlinePlus related topics: Cancer

Drug Information available for: Trametinib Dabrafenib

U.S. FDA Resources

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measures:

- Overall response rate (ORR) [Time Frame: Possibly up to Week 208] [Designated as safety issue: No]

To determine the ORR as measured radiographically via Response Evaluation Criteria in Solid tumors (RECIST) version 1.1 for solid tumor histologies or established response criteria for specific hematologic malignancies.

Secondary Outcome Measures:

- Duration of response [Time Frame: From the time of first documented evidence of CR or PR until the first documented sign of disease progression or death (approximately up to Week 208)] [Designated as safety issue: No]

  Duration of response is defined as the subset of subjects who show a confirmed clinical response (CR) or partial response (PR), the time from first documented evidence of CR or PR until the first documented sign of disease progression or death.

- Investigator-assessed Progression-free survival (PFS) [Time Frame: Possibly up to Week 208] [Designated as safety issue: No]

  PFS is defined as the time from the date of enrollment to the earliest date of progression or death.

- Overall Survival (OS) [Time Frame: Until death or lost to follow-up (approximately up to Week 208)] [Designated as safety issue: No]

  OS is defined as the time from the date of enrollment to the date of death due to any cause.

- Change from baseline in physical examination findings [Time Frame: Possibly up to Week 208] [Designated as safety issue: No]

  Examination will include assessments of the head and neck, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes, extremities and genitalia. Height (measured only at Screening) and weight will be measured and recorded. Complete physical examinations will also include thorough rectal and genitourinary (pelvic) examinations to assess secondary malignancies.

- Change from baseline in vital signs [Time Frame: Possibly up to Week 208] [Designated as safety issue: No]

  Vital sign measurements will include systolic and diastolic blood pressure, temperature, pulse rate and respiratory rate

- Number of subjects with Adverse events (AEs) [Time Frame: Possibly up to Week 208] [Designated as safety issue: No]

  AE is any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

- Change from baseline in laboratory values [Time Frame: Possibly up to Week 208] [Designated as safety issue: No]

  Laboratory assessments include haematology, clinical chemistry, urinalysis, coagulation and histology-specific tests

- Change from baseline in cardiac assessments [Time Frame: Possibly up to Week 208] [Designated as safety issue: No]

  Cardiac assessments include Electrocardiogram (ECG) and Echocardiograms (ECHOs)

Estimated Enrollment:	135
Study Start Date:	March 2014
Estimated Study Completion Date:	April 2026
Estimated Primary Completion Date:	September 2018 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: Dabrafenib + Trametinib Subjects will receive Dabrafenib 150 mg twice daily orally plus Trametinib 2 mg once daily orally on a continuous basis. Dabrafenib will be administered under fasted conditions, either 1 hour (hr) before or 2 hours (hrs) after a meal with approximately 200 mL of water with an interval of 12 hours. Trametinib will be administered under fasted conditions, either 1 hr before or 2 hrs after a meal with approximately 200 mL of water. Subjects will take their dose of Trametinib concurrently with the morning dose of Dabrafenib. A treatment cycle is 28 days in duration. Subjects will continue treatment until an unacceptable toxicity, disease progression, or death occurs.	Drug: Dabrafenib Dabrafenib is a 150 mg twice daily capsule administered orally on a continuous basis. Drug: Trametinib Trametinib is a 2 mg once daily tablet administered orally on a continuous basis.

Eligibility

Ages Eligible for Study: 18 Years and older

Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Signed, written informed consent.
- Sex: male or female.
- Age: >=18 years of age at the time of providing informed consent.
- Eastern Cooperative Oncology Group (ECOG) performance status: 0, 1 or 2.
- BRAF V600E mutation-positive tumor: Local testing - Local BRAF mutation test results obtained by a Clinical Laboratory Improvement Amendments (CLIA) approved local laboratory may be used to permit enrollment of subjects with positive results. Local BRAF mutation test results will be subject to central verification; Central testing - Local BRAF mutation test results will be confirmed by central testing in a CLIA approved, designated central reference laboratory by the THxID BRAF assay or an alternate GSK designated assay. NOTE: For central testing, Formalin-fixed paraffin-embedded (FFPE) core bone marrow (BM) biopsies are not acceptable from subjects in the Multiple myeloma (MM) cohort.
- Able to swallow and retain orally administered medication. NOTE: Subject should not have any clinically significant gastrointestinal (GI) abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels. For example, subjects should have no more than 50% of the large intestine removed and no sign of malabsorption (i.e., diarrhea).NOTE: If clarification is needed as to whether a condition will significantly affect the absorption of study treatments, contact the GSK Medical Monitor.
- Female Subjects of Childbearing Potential: Subjects must have a negative serum pregnancy test within 7 days prior to the first dose of study treatment and agrees to use effective contraception, throughout the treatment period and for 4 months after the last dose of study treatment.
- French subjects: In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

Exclusion Criteria:

- Prior treatment with: BRAF and/or MEK inhibitor(s); anti-cancer therapy (e.g., chemotherapy with delayed toxicity, immunotherapy, biologic therapy or chemoradiation) within 21 days (or within 42 days if prior nitrosourea or mitomycin C containing therapy) prior to enrollment and/or daily or weekly chemotherapy without the potential for delayed toxicity within 14 days prior to enrolment; Investigational drug(s) within 30 days or 5 half-lives, whichever is longer, prior to enrollment
- Previous major surgery within 21 days prior to enrollment.
- Prior extensive radiotherapy treatment within 21 days prior to enrolment. NOTE: Limited radiotherapy for palliative care is permitted within 14 days prior to enrollment as long as any radiation-related toxicity has resolved prior to enrollment.
- Prior solid organ transplantation or allogenic stem cell transplantation (ASCT). NOTE: Previous autologous bone marrow transplant (ABMT) or autologous peripheral blood stem cell transplant (PBSCT) is permitted.
- History of: Interstitial lung disease or pneumonitis; Another malignancy. NOTE: Subjects with another malignancy are eligible if: (a) disease-free for 3 years, (b) had a history of completely resected non-melanoma skin cancer, and/or (c) have a indolent second malignancy(ies) defined as a slow growing second/concurrent malignancy which is characterized by slow growth, a high initial response rate and a relapsing , progressive disease course. For example, a previously untreated low grade and select intermediate-grade lymphoid malignancy would be allowed as per the available body of evidence. There are no available clinical alternatives to the proposed population. Consult a GSK Medical Monitor if unsure whether second malignancies meet requirements specified above.
- Presence of: cerebral metastases (except for subjects in the WHO Grade 1 or 2 Glioma or WHO Grade 3 or 4 Glioma histology cohorts). NOTE: Subjects with brain metastases may be included if: All known lesions have been previously treated with surgery or stereotactic radiosurgery, and Any remaining cerebral lesion(s) are asymptomatic and confirmed stable disease (i.e., no increase in lesion size) for >=90 days prior to enrollment as documented by two consecutive magnetic resonance imaging (MRI) or computed tomography (CT) scans with contrast, and No treatment with corticosteroids or enzyme-inducing anticonvulsants required for >=30 days prior to enrolment. Approval received from GSK Medical Monitor.
- Presence of symptomatic or untreated leptomeningeal or spinal cord compression. NOTE: Subjects who have been previously treated for these conditions and have stable central nervous system (CNS) disease (documented by consecutive imaging studies) for >60 days, are asymptomatic and currently not taking corticosteroids, or have been on a stable dose of corticosteroids for at least 30 days prior to enrollment, are permitted.
- Presence of pre-existing >= Grade 2 peripheral neuropathy.
- Presence of unresolved treatment-related toxicity of >= Grade 2 (except alopecia) or toxicities listed in the general and histology-specific adequate organ function tables at the time of enrolment.
- Presence of any serious and/or unstable pre-existing medical disorder (aside from malignancy exception above), psychiatric disorder, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures.
- History or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR): History of RVO or CSR, or predisposing factors to RVO or CSR (e.g., uncontrolled glaucoma or ocular hypertension, uncontrolled systemic disease such as hypertension or diabetes mellitus, or history of hyperviscosity or hypercoagulability syndromes); Visible retinal pathology as assessed by ophthalmic examination that is considered a risk factor for RVO or CSR such as evidence of new optic disc cupping, evidence of new visual field defects and intraocular pressure >21 mmHg.

- History or evidence of cardiovascular risk including any of the following: Acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to enrolment; Clinically significant uncontrolled arrhythmias NOTE: Subjects with controlled atrial fibrillation for >30 days prior to enrollment are eligible; Class II or higher congestive heart failure as defined by the New York Heart Association (NYHA) criteria; Left ventricular ejection fraction (LVEF) below the institutional lower limit of normal (LLN). NOTE: If a LLN does not exist at an institution, then use LVEF <50%.; Corrected QT (QTc) interval for heart rate using Bazett-corrected QT interval (QTcB) >=480 millisecond (msec); Intracardiac defibrillator and/or permanent pacemaker; Treatment-refractory hypertension defined as a blood pressure (BP) >140/90 millimeters of mercury (mmHg) which may not be controlled by anti-hypertensive medication(s) and/or lifestyle modifications; Known cardiac metastases.
- Current use of prohibited medication(s) or requirement of prohibited medications during study. NOTE: Use of anticoagulants such as warfarin is permitted; however, international normalization ratio (INR) must be monitored according with local institutional practice.
- Positive for: Hepatitis B surface antigen or Hepatitis C antibody. NOTE: Subjects with laboratory evidence of cleared hepatitis B virus (HBV) and hepatitis C virus (HCV) infection will be permitted. NOTE: False positive subjects may be cleared for enrollment based on RNA-based assays; Human immunodeficiency virus (HIV); testing not required.
- Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to study treatment, or excipients, or to dimethyl sulfoxide and/or sulfonamides (structural component of dabrafenib).
- Female subjects: Pregnant, lactating or actively breastfeeding.
- Subjects enrolled in France: The French subject has participated in any study using an investigational product (IP) within 30 days prior to enrollment in this study.

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT02034110

Contacts

Contact: US GSK Clinical Trials Call Center 877-379-3718 GSKClinicalSupportHD@gsk.com

Show 32 Study Locations

Sponsors and Collaborators

GlaxoSmithKline

Investigators

Study Director: GSK Clinical Trials GlaxoSmithKline

More Information

No publications provided

Responsible Party:	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT02034110 History of Changes
Other Study ID Numbers:	117019
Study First Received:	December 5, 2013
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Health Authority:	United States: Food and Drug Administration

Keywords provided by GlaxoSmithKline:

safety
Dabrafenib
efficacy
trametinib
solid tumors
BRAF V600E mutation

Additional relevant MeSH terms:

Dabrafenib
Trametinib
Antineoplastic Agents
Enzyme Inhibitors
Molecular Mechanisms of Pharmacological Action
Pharmacologic Actions
Protein Kinase Inhibitors
Therapeutic Uses

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