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BRIM-P Study

Investigator Reference Guide

A Study of RO5185426 in Pediatric Patients with Surgically Incurable and Unresectable Stage IIIC or Stage IV Melanoma Harboring BRAF^{V600} Mutations

Sponsor:	F. Hoffmann-La Roche LTD
Protocol:	NO25390
www.ClinicalTrials.gov Identifier:	NCT01519323
EUDRACT No.	2011-000874-67

Study Description

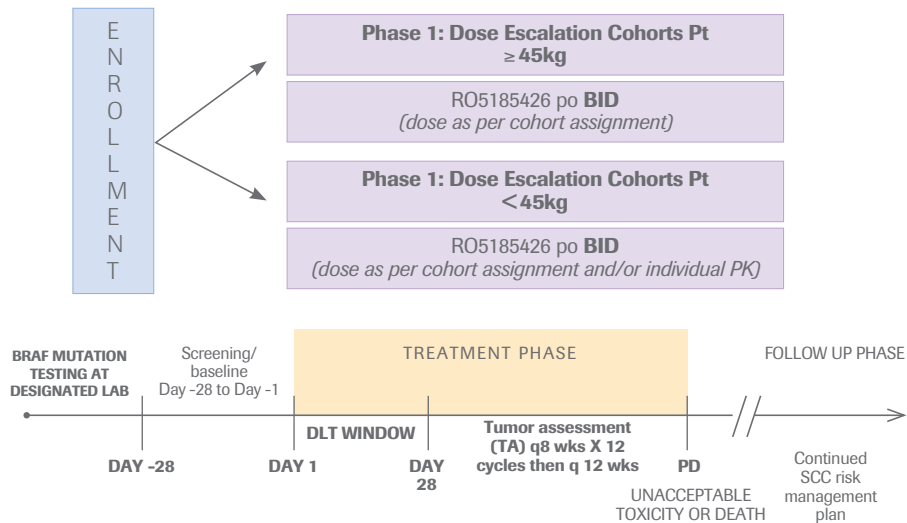
Open-label, multicenter (approximately 18 sites across 5 countries – Germany, UK, Italy, UK, USA), single-arm, Phase I dose-escalation with efficacy tail extension study of RO5185426 in pediatric patients (aged 12 through 17) with surgically incurable and unresectable Stage IIIC or Stage IV melanoma harboring BRAF^{V600} mutations

Estimated Enrollment: 27 subjects

Study Start Date: 19th December 2011

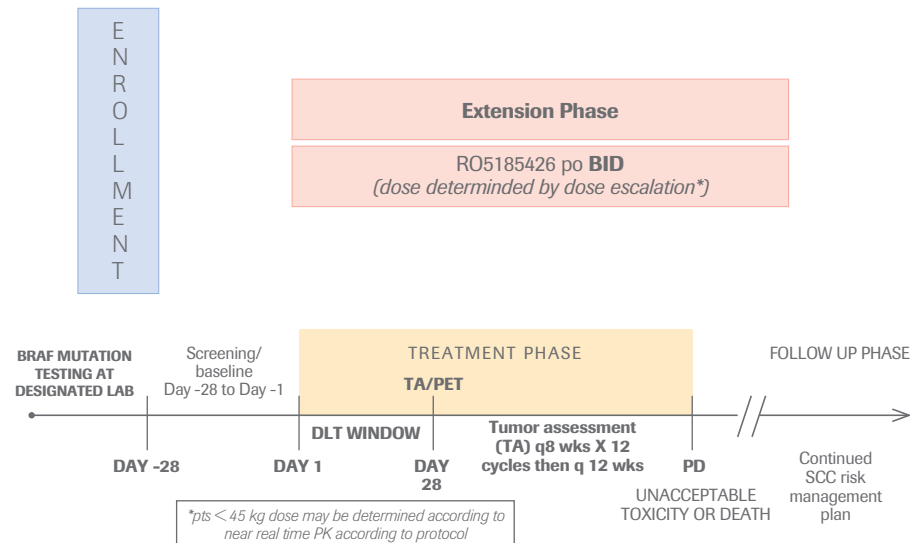
Estimated Recruitment End: April 2015

Study Design of the Dose-Escalation Phase



BID = twice daily; DLT = dose-limiting toxicity; PD = progressive disease; PO = oral; q = every; SCC = squamous cell carcinoma.

Study Design of the Extension Phase



BID = twice daily; PD = progressive disease; PET = positron emission tomography; PO = oral; q = every; SCC = squamous cell carcinoma.

Study Objectives

Primary Objective:

Dose-escalation phase: To estimate the maximum tolerated dose (MTD) and to identify the recommended dose of RO5185426 in pediatric patients ages 12 through 17 years with newly diagnosed or recurrent unresectable Stage IIIC or Stage IV BRAF mutation-positive melanoma.

Secondary Objectives:

- Dose-escalation and extension phases:
 - To describe the pharmacokinetics of RO5185426 in pediatric patients aged ≥ 12 to ≤ 17 years with BRAF mutation-positive newly diagnosed unresectable Stage IIIC or Stage IV or recurrent melanoma.
 - To evaluate the safety and tolerability of RO5185426 using NCI CTCAE* v4.0 in pediatric patients aged 12 through 17 years with newly diagnosed or recurrent BRAF mutation-positive unresectable Stage IIIC or Stage IV melanoma.
 - To evaluate the efficacy of RO5185426 in patients treated at the recommended dose using investigator-assessed best overall response rate (BORR), based on Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v.1.1), progression-free survival (PFS), overall survival (OS), and clinical benefit rate.

* NCI CTCAE = National Cancer Institute Common Toxicity Criteria for Adverse Events

Exploratory Objectives:

- To evaluate the molecular characteristics of cutaneous squamous cell carcinomas (cuSCCs) and other suspicious lesions that may be observed in patients treated with RO5185426.
- To explore the relationship of potential biomarkers on the efficacy and safety of RO5185426.

Investigational Drug

RO5185426 is a low molecular weight, orally available, inhibitor of oncogenic BRAF kinase. It is not currently approved for use in this patient population.

Dose-Escalation and Extension Phases

After completion of the dose-escalation window, all patients will continue to receive RO5185426 at their assigned dose until the maximum tolerated dose (MTD) for the extension phase is defined. After the recommended dose is established, all patients will be eligible to receive the recommended dose.

Patients will receive an oral dose of RO5185426 BID on a continuing basis until disease progression, death due to any cause, unacceptable toxicity, discontinuation from the study, or other criteria set forth in the protocol. All patients who withdraw from treatment for any reason (including progression) will be followed for survival until death, withdrawal of consent, loss to follow-up, or the end of the study. Additionally, these

patients will be followed for SCC according to a Risk Management Plan for a maximum of 6 months after the last dose of study drug.

Patients who withdraw from treatment for any reason other than progression will be followed for progression of disease during the follow-up period.

Eligibility Criteria

Inclusion Criteria

Disease-Specific

1. Histologically confirmed, surgically incurable and unresectable Stage IIIC or Stage IV American Joint Committee on Cancer (AJCC) melanoma (NOTE: Unresectable Stage IIIC disease must have confirmation from a surgical oncologist.)
2. Positive BRAF mutation result determined by a Genetech/Roche-designated central laboratory using the cobas® 4800 BRAF V600 Mutation Test prior to administration of RO5185426.
3. Newly diagnosed melanoma or completed and failed prior standard of care regimen (eg, DTIC, temozolomide, etc.)
4. Measurable disease according to RECIST v1.1 criteria.
5. Head CT/MRI to evaluate for CNS metastasis within 28 days prior to treatment. Patients with radiographically stable, asymptomatic previously treated lesions are eligible provided:
 - Patient has received prior treatment (including radiation therapy [whole brain radiotherapy is not allowed with the exception of patients who have also had definitive resection of stereotactic therapy of all radiologically detectable parenchymal lesions], stereotactic radiosurgery, surgical resection), to the site(s) of CNS metastatic disease >3 months prior to starting study treatment.

- Patient has no requirement for glucocorticoids, and glucocorticoids discontinued >21 days prior to starting study treatment.
- Patient is not taking anticonvulsants (discontinued at least 3 weeks prior to treatment).

General

6. Male and female patients aged ≥ 12 to ≤ 17 years.
7. Performance status: Karnofsky (for patients ≥ 16 years of age) or Lansky (for patients < 16 years of age) score of ≥ 60 .
8. Patients must have recovered from effects of any major surgery or significant traumatic injury at least 14 days prior to administration of the first dose of study drug.
9. Life expectancy > 3 months.
10. Patient and/or parent/legal guardian (per local regulation) is willing to provide written informed consent prior to performing any study-related procedures.
11. Able to swallow pills.
12. Patients must have adequate organ and marrow functions based on laboratory values performed within 28 days prior to initiation of dosing:
 - a. Bone marrow function: ANC $\geq 1.5 \times 10^9/L$; Platelet count $\geq 100 \times 10^9/L$; Hemoglobin ≥ 9 g/dL; Patient must not have required transfusion within 2 weeks prior to start of treatment.

- b. Hepatic function: AST, ALT, and ALP $\leq 2.5 \times$ ULN for age ($\leq 5 \times$ ULN for age in patients with concurrent liver metastases); Bilirubin $\leq 1.5 \times$ ULN for age; Albumin ≥ 3 g/dL.
 - c. Renal function: Creatinine clearance or radioisotope glomerular filtration rate ≥ 70 mL/min/1.73 m² or serum creatinine based on age (12 to ≤ 15 yrs, 1.2mg/dL; >15 yrs, 1.5 mg/dL).
13. Negative serum or urine pregnancy test within 7 days prior to commencement of dosing for female patients of childbearing potential.
 14. Birth control: Patients of childbearing or child-fathering potential must be willing to use a medically acceptable form of birth control, which includes abstinence, while being treated in this study and for at least 6 months after completion of treatment as directed by their physician (in accordance with local requirements).
 15. Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before trial entry.
 16. Completed baseline skin examination by a dermatologist for cuSCC; examination must be negative or if suspected cuSCC lesions are identified, they must be excised, and there must be adequate wound healing prior to study treatment.

Prior Therapy

17. Patients must have fully recovered from the acute toxic effects of all prior therapy prior to first administration of study drug.
18. Myelosuppressive chemotherapy must have been completed at least 14 days (28 days for nitrosureas) prior to first administration of study drug.
19. Biologic (anti-neoplastic) therapy must have been completed at least 14 days prior to first administration of study drug.
20. Radiation therapy: Patients must have completed local radiation therapy at least 14 days prior to first administration of study drug, craniospinal radiation therapy (> 24Gy) and whole pelvis RT at least 3 months prior, and bone marrow RT at least 6 weeks prior.
21. Investigational agents: Patients must not have received an investigational agent within 28 days of study entry.
22. Prior surgery must have occurred at least 14 days prior to first dose of study drug, and patients must have recovered from any effects from surgery and have adequate wound healing prior to first dose of study drug.

Exclusion Criteria

Disease-Specific

1. Patients with active or untreated CNS lesions.
2. History of or known spinal cord compression or carcinomatous meningitis.
3. Negative result for BRAF mutation as determined using the Genentech/Roche cobas® 4800 BRAF V600 Mutation Test.
4. Anticipated or ongoing administration of anti-cancer therapies other than those administered in this study.
5. Patients with a previous malignancy within the past 5 years are excluded except for patients with basal or squamous cell carcinoma of the skin, melanoma in-situ, and carcinoma in-situ of the cervix.
6. Patients who have been previously treated with a selective/specific BRAF or MEK inhibitor (previous treatment with sorafenib is allowed).
7. Patients who have had any previous treatment with study drug (RO5185426) or participated in a clinical trial that includes RO5185426.

General

8. QTc \geq 450 msec on screening or baseline ECG, history of congenital long QT syndrome, or uncorrectable electrolyte abnormalities.

9. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate absorption of study drug.
10. Pregnant or lactating females.
11. NCI CTCAE v4.0 Grade 3 hemorrhage within 4 weeks of starting the study treatment.
12. Any of the following within the 6 months prior to study drug administration: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, serious cardiac arrhythmia requiring medication, uncontrolled hypertension, cerebrovascular accident or transient ischemic attack, or symptomatic pulmonary embolism.
13. Known clinically significant active infection at the time of study drug treatment start, at the time of screening, or within 14 days of study drug start.
14. History of allogeneic bone marrow transplantation or organ transplantation.
15. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results, which in the judgment of the investigator, would make the patient inappropriate for entry into this study.
16. Known HIV positivity or AIDS-related illness, active hepatitis B virus, or active hepatitis C virus.

Contact Us

If you are likely to see patients that fit the above mentioned criteria who you believe may be eligible to participate in this study or have any questions regarding this study, please contact us at:

**PLEASE ATTACH LABEL
WITH SITE CONTACT DETAILS**

Alternatively please send an email with your contact details to contact@brim-pstudy.com and you will be provided with access to our Study Investigator Portal which you can use to check patient eligibility and refer a patient(s) to your nearest Investigator Site.

We look forward to hearing from you.