A PHASE I/II, MULTICENTER, OPEN-LABEL, DOSE-ESCALATION STUDY OF THE SAFETY AND PHARMACOKINETICS OF COBIMETINIB IN PEDIATRIC AND YOUNG ADULT PATIENTS WITH PREVIOUSLY TREATED SOLID TUMORS

Published: 15-03-2016
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Safety (Primary) ObjectiveThe primary objective for this study is as follows:- To evaluate the safety and tolerability of cobimetinib in children and young adults, including estimation of the maximum-tolerated dose (MTD) or the maximum administered...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON44717

Source
ToetsingOnline

Brief title
GO29665

Condition

- Other condition

Synonym
abnormal cellular and tumor growth in an organ, Solid tumors

Health condition

solide tumoren

Research involving
Human

Sponsors and support

Primary sponsor: F. Hoffmann-La Roche Ltd.
Source(s) of monetary or material Support: F. Hoffmann-La Roche Ltd

Intervention

Keyword: Pediatric and young adult patients, Phase I/II, Solid tumor

Outcome measures

Primary outcome

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence and nature of DLTs

- Nature, frequency, severity, and timing of adverse events, including serious adverse events and adverse events of special interest

- Changes in vital signs, physical findings, and clinical laboratory results during and following cobimetinib administration

- Growth patterns (relative to age-specific standards for height and weight) accounting for baseline growth of the patient

- Development patterns (relative to onset of menarche [for females] and pubertal changes) accounting for baseline development of the patient

Pharmacokinetic Outcome Measure

The PK outcome measure for this study is as follows:

- To characterize cobimetinib PK in pediatric patients, the following PK

parameters following single and multiple doses will be estimated: maximum plasma concentration observed, time to maximum concentration, total exposure (area under the concentration-time curve from 0 to 24 hours [AUC0-24]), and apparent clearance.

Efficacy Outcome Measures

The co-primary efficacy outcome measures for this study are as follows:

- ORR, defined as the percentage of patients with a complete or partial response for patients with measurable disease or neuroblastoma patients with evaluable disease at baseline, or a complete response for patients with non*measurable but evaluable disease at baseline (except neuroblastoma patients), on two consecutive occasions * 4 weeks apart, as determined by the investigator using mINRC for patients with neuroblastoma, RANO criteria for patients with HGG, and RECIST v1.1 for patients with other tumors
- PFS, defined as the time from initiation of study drug to the first documented occurrence of disease progression, as determined by the investigator using mINRC for patients with neuroblastoma, RANO criteria for patients with HGG, and RECIST v1.1 for patients with other tumors, or death from any cause, whichever occurs first

Secondary outcome

The secondary efficacy outcome measures for this study are as follows:

- DOR, defined as the time from the first tumor assessment that supports the patient*s objective response to the time of disease progression, as determined by the investigator using mINRC for patients with neuroblastoma, RANO criteria

for patients with HGG, and RECIST v1.1 for patients with other tumors, or death from any cause, whichever occurs first

- OS, defined as the time from initiation of study drug to death from any cause

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Levels of potential PD biomarkers (including but not limited to p-MEK, p ERK, and Ki67) measured in tumor tissue collected at baseline, on treatment, and at the time of disease progression
- Correlation between non-inherited and inherited biomarkers in plasma (including but not limited to BRAF mutations, BRAF fusions, RAS mutations, and NF1) and safety, PK, or efficacy outcome measures
- To explore potential relationships between cobimetinib pharmacokinetics and other outcome measures (such as safety or efficacy outcome measures)
- Diffusion activity in tumors before and after cobimetinib treatment, as demonstrated on available MRI scans
- Metabolic activity in tumors before and after cobimetinib treatment, as demonstrated on available PET scans
- Acceptability Survey

Study description

Background summary

see protocol version 3 (05 August 2015), section 1.3 "study rationale and

benefit-risk assessment", pages 45-46

Study objective

Safety (Primary) Objective
The primary objective for this study is as follows:
- To evaluate the safety and tolerability of cobimetinib in children and young adults, including estimation of the maximum-tolerated dose (MTD) or the maximum administered dose (MAD) and characterization of dose-limiting toxicities (DLTs)

Pharmacokinetic Objective
The pharmacokinetic (PK) objective for this study is as follows:
- To characterize the pharmacokinetics of cobimetinib in children and young adults

Efficacy Objective
The efficacy objective for this study is as follows:
- To evaluate the anticancer activity of cobimetinib in children and young adults with solid or brain tumors, as measured by objective response rate (ORR), progression-free survival (PFS), duration of objective response (DOR), and overall survival (OS)

Dose-Finding Objective
An additional objective for this study is as follows:
- To identify recommended Phase II doses for cobimetinib tablet and suspension formulations in pediatric patients on the basis of safety, PK, and efficacy outcome measures

Exploratory Objectives
The exploratory objectives for this study are as follows:
- To explore the relationship between cobimetinib exposure and changes in levels of pharmacodynamic (PD) biomarkers in children and young adults
- To explore non-inherited biomarkers that may be predictive of response to cobimetinib (i.e., predictive biomarkers), may be associated with progression to a more severe disease state (i.e., prognostic biomarkers), acquired resistance to cobimetinib, or susceptibility to developing adverse events, may provide evidence of cobimetinib activity, or may increase the knowledge and understanding of disease biology
- To explore inherited biomarkers (i.e., variants in germline DNA) that may be predictive of response to cobimetinib (i.e., predictive biomarkers), may be associated with progression to a more severe disease state (i.e., prognostic biomarkers), acquired resistance to cobimetinib, or susceptibility to developing adverse events, or may increase the knowledge and understanding of disease biology
- To explore potential relationships between PK parameters for cobimetinib and other outcome measures (such as safety or efficacy outcome measures)
- To evaluate tumor characteristics before and after treatment on the basis of

available magnetic resonance imaging (MRI) and positron emission tomography (PET) scans
- To evaluate specific aspects of the acceptability of the cobimetinib formulations

Study design

This is a Phase I/II, multicenter, open-label, dose-escalation study designed to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of cobimetinib in pediatric and young adult patients with solid tumors with known or potential RAS/RAF/MEK/ERK pathway activation for which standard therapy has proven to be ineffective (i.e., relapsed or refractory tumors) or intolerable or for which no curative standard-of-care treatment options exist.

Patients will be enrolled via an interactive web response system in two stages: a dose escalation stage and an expansion stage at the recommended dose. During the dose escalation stage, cohorts of 3-6 pediatric patients (age * 6 months to < 18 years) will be evaluated at escalating dose levels to determine the MTD or MAD of cobimetinib in pediatric patients with advanced solid tumors. The MTD or MAD of each cobimetinib formulation (tablet or suspension) will be determined in separate dose escalations. Once the MTD or MAD has been established, pediatric patients (age * 6 months to < 18 years) will be enrolled in the expansion stage and treated at the recommended dose, which will be at or below the MTD or MAD, as determined by the Sponsor; adult patients * 18 years of age with pediatric tumor types can be enrolled on this study but only during the expansion stage; these adult patients will be treated at the adult flat dose.

Intervention

The test product (investigational drug) for this study is cobimetinib 20 mg tablets. Cobimetinib will be taken orally once daily on Days 1-21 of each 28-day treatment cycle (21/7 dosing schedule) according to the guidance provided in Appendix 9 until the occurance of disease progression as determined by the investigator, death, unacceptable toxicity, or patient or investigator decision to discontinue treatment. Patients will be assigned to dose levels in the order in which they are enrolled. The starting dose for tablets will be 0.6 mg/kg in the dose-escalation stage. Pediatric patients (< 18 years of age) enrolled in the expansion stage will be treated at or below the MTD or MAD, as determined by the sponsor. Adult patients (* 18 years of age) enrolled in the expansion stage will be treated with the adult recommended dose of 60 mg daily. Cobimetinib should be taken at approximately the same time each day, no earlier than 1 hour before and no later than 4 hours after the usual dosing time.

Patients under 6 years of age or weighing < 20 kg are only eligible to receive

the drug in suspension.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Study burden and risks

An overview of the risks can be found in the informed consent form, Annex 5. Study procedures can be found in the informed consent form, on page 2 under header "How will the study be conducted", and in the protocol under study procedures.

Contacts

Public
F. Hoffmann-La Roche Ltd.

Grenzacherstrasse 124
Basel 4070
CH
Scientific
F. Hoffmann-La Roche Ltd.

Grenzacherstrasse 124
Basel 4070
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)

Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

Patients must meet the following criteria for study entry:
- Signed Informed Consent Form
- Signed Child's Informed Assent, when appropriate as determined by patient's age and individual site and country standards
- For dose-escalation stage, tablets: Age at study entry * 6 years to < 18 years
- For dose-escalation stage, suspension: age at study entry * 6 months to < 18 years
Patients <1 year of age will not be enrolled until * 6 patients *1 year to <18 years of age have received at least one cycle of therapy with suspension and until safety and PK assessment of these patients has been conducted.
- For expansion stage: Age at study entry * 6 months (* 6 years if suspension is not available) to < 30 years
Patients * 6 months to < 1 year of age may not be enrolled until * 6 patients *1 year to <18 years of age have received at least one cycle of therapy with suspension in the dose-escalation phase and until safety and PK assessment of these patients has been conducted.
In exceptional cases of relapsed pediatric tumors in patients * 30 years of age, the Sponsor will consider waiving the age requirement with approval of the Medical Monitor. This waiver is restricted to patients with pediatric-specific diseases (e.g., neuroblastoma) for whom clinical trials are unlikely to be available, and will not be extended to patients with tumors that typically occur both in children and adults (e.g., HGG). The Sponsor may decide to stop enrollment of patients * 18 years of age at any time during the study to ensure adequate enrollment of patients < 18 years of age.
- Able to comply with the requirements of the study protocol, in the investigator*s judgment
- Tumor for which prior treatment has proven to be ineffective (i.e., relapsed or refractory) or intolerable or for which no standard therapy exists.
- Tumor with known or expected RAS/RAF/MEK/ERK pathway involvement. Diagnosis MUST be one of the following tumor types:
Central nervous system gliomas, including high- and low-grade gliomas, and diffuse intrinsic pontine glioma (DIPG)
Embryonal rhabdomyosarcoma and other non-rhabdomyosarcoma soft tissue sarcomas
Neuroblastoma
Melanoma
Malignant peripheral nerve sheath tumor
Rhabdoid tumors, including atypical teratoid/rhabdoid tumor
Tumors from the following groups that, in the judgment of the investigator, are life threatening, resulting in severe symptoms (including severe pain), or are in close proximity to vital structures:
Neurofibromatosis 1 (NF1)-associated tumors (including plexiform neurofibroma)
Schwannoma
Any solid tumor or brain tumor that occurs in a patient with another RASopathy (such as Noonan syndrome)

Any solid or brain tumor that has been molecularly profiled and shown to have RAS/RAF/MEK/ERK pathway activation, with approval of the Medical Monitor.
- Tumor diagnosis must be histologically or cytologically confirmed either at the time of diagnosis or at the time of relapse, except in the following scenario:
DIPG and optic pathway gliomas do not require histologic confirmation if radiographic findings are sufficient to make diagnosis and institutional standard of care does not mandate biopsy for diagnosis.
- Current disease state for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life
- Disease that is measurable as defined by mINRC, RANO criteria, or RECIST v1.1 (as appropriate) or evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers, or other reliable measures
- Availability of tumor tissue at study enrollment is mandatory. Archival tumor tissue block or 15 freshly cut, unstained, serial slides available for submission, and/or willingness to undergo a core or excisional biopsy prior to enrollment (fine-needle aspiration, brush biopsy, and lavage samples are not acceptable)
For patients submitting archival tissue, a minimum of 15 slides are required. Patients with fewer than 15 slides available may be eligible for study entry following approval of the Medical Monitor.
- Lansky Performance Status or Karnofsky Performance Status * 50%
- Life expectancy * 3 months, in the investigator's judgment
- For female patients of childbearing potential: Agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 3 months after the last dose of study drug
True abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
Examples of contraceptive methods with a failure rate of <1% per year include, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a spermicide.
- For male patients with a female partner of childbearing potential or a pregnant female partner: Agreement to remain abstinent or use a condom during the treatment period and for at least 3 months after the last dose of study drug
True abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For male patients: agreement to refrain from donating sperm during the treatment period and for at least 3 months after the last dose of study drug
- Adequate hematologic and end organ function, defined by the following laboratory results obtained within 28 days prior to initiation of study drug:
ANC * 0.75 x 10 9/L (unsupported)
Platelet count * 75 x 10 9/L (unsupported)
Hemoglobin * 8 g/dL (transfusion is acceptable to meet this criterion)
Bilirubin * 1.5 x the upper limit of normal (ULN) for age
AST and ALT * 2.5 x ULN for age

Serum creatinine * 1.5 x ULN for age or creatinine clearance (or radioisotope glomerular filtration rate) > 70 mL/min/1.73 m2
- Fractional shortening (FS) * 30% and left ventricular ejection fraction (LVEF) * 50% at baseline, as determined by echocardiography or multigated acquisition scan within 28 days prior to initiation of study drug
Depending on institutional standard, either FS or LVEF is adequate for enrollment if only one value is measured; if both values are measured, then both values must meet criteria above.
- Body weight must be * 20 kg if suspension is not available

Exclusion criteria

Patients who meet any of the following criteria will be excluded from study entry:
- Pregnant or lactating, or intending to become pregnant during the study
Females of childbearing potential must have a negative serum pregnancy test result within 1 week prior to initiation of study drug.
- Prior treatment with cobimetinib or other MEK inhibitor (prior sorafenib use is permissible)
- Treatment with high-dose chemotherapy and stem-cell rescue (autologous stem cell transplant) within 3 months prior to initiation of study drug
- Treatment with chemotherapy (other than high-dose chemotherapy as described above) or differentiation therapy (such as retinoic acid) or immunotherapy (such as anti-GD2 antibody treatment) within 4 weeks prior to initiation of study drug or, if treatment included nitrosoureas, within 6 weeks prior to initiation of study drug. This requirement may be waived at the investigator*s request if the patient has recovered from therapeutic toxicity to the degree specified in the protocol, with approval of the Medical Monitor.
- with thoracic or mediastinal radiotherapy within 6 weeks prior to initiation of study drug
- Treatment with hormonal therapy (except hormone replacement therapy or oral contraceptives), immunotherapy, biologic therapy, or herbal cancer therapy within 4 weeks or < 5 half-lives, whichever is shorter, prior to initiation of study drug
- Treatment with a long-acting hematopoietic growth factor within 2 weeks prior to initiation of study drug or a short-acting hematopoietic growth factor within 1 week prior to initiation of study drug
- Treatment with investigational therapy (with the exception of cancer therapies as described above) within 4 weeks prior to initiation of study drug
- Requirement for initiation of corticosteroids or an increase in the dose of corticosteroids within 1 week prior to initiation of study drug
- Treatment with St. John's wort or hyperforin or drugs that are strong inhibitors or inducers of CYP3A within 1 week prior to initiation of study drug
- Ingestion of grapefruit juice within 1 week prior to initiation of study drug
- Any toxicity (excluding alopecia and ototoxicity) from prior treatment that has not resolved to Grade * 1 (per NCI CTCAE v4.0) at screening except as otherwise permitted in the inclusion/exclusion criteria
- Major surgical procedure or significant traumatic injury within 4 weeks prior to initiation of study drug, or anticipation of need for major surgical procedure during the course of the study
Placement of a vascular access device or minor surgery is permitted if the site has healed

prior to initiation of study drug.
- Known active infection (excluding fungal infection of the nail beds) within 28 days prior to initiation of study drug that has not completely resolved
- History of Grade * 2 CNS hemorrhage.
- History of CNS hemorrhage within 28 days of study entry. This criterion may be waived at the investigator*s request if the CNS hemorrhage was asymptomatic, with approval of the Medical Monitor.
- For brain tumor patients, use of anticoagulants within 1 week of study drug initiation.
- History or evidence of retinal pathology on ophthalmologic examination that is considered to be a risk factor for or indicative of neurosensory retinal detachment, central serous chorioretinopathy, neovascular retinopathy, or retinopathy of prematurity
- Known hypersensitivity to any component of the study drug
- Inability to swallow oral medications
- Impaired gastrointestinal absorption
- Prior allogenic bone marrow transplantation or prior solid organ transplantation
- Any other disease, metabolic or psychological dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or places the patient at unacceptable risk from treatment complications
- Current drug or alcohol use or dependence that would interfere with adherence to study requirements, in the opinion of the investigator

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Cobimetinib
Generic name:	Cotellic
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	15-03-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-09-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-04-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-11-2017
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-004685-25-NL
ClinicalTrials.gov	NCT02639546
CCMO	NL52503.078.16

Study results

Summary results
Trial never started

First publication
01-12-2021