Phase Ib trial of the combination of PI3K inhibitor BAY 80-6946 and allosteric-MEK inhibitor BAY 86-9766 in subjects with advanced cancer

Published: 24-05-2011
Last updated: 29-04-2024

The purpose of this study is to find the answers to the following research questions:1. What are the side effects of the combination of BAY 80-6946 and BAY 86-9766 when given together at different dose levels?2. What dose level of BAY 80-6946 and...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON39510

Source
ToetsingOnline

Brief title
Phase Ib PI3K plus MEKi

Condition

- Other condition
- Miscellaneous and site unspecified neoplasms benign

Synonym
Malignant solid tumor / advanced cancer

Health condition

gevorderde kanker

Research involving
Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: Bayer Healthcare

Intervention

Keyword: - advanced cancer, - BAY 80-6946 and BAY 86-9766, - combination of PI3K inhibitor and allosteric-MEK inhibitor, - Open-label

Outcome measures

Primary outcome

The primary variables being evaluated include, safety, tolerability,

pharmacokinetics and recommended Phase II dose for the combination of BAY

80-6946 and BAY 86-9766. (protocol page 47)

Secondary outcome

Not applicable

Study description

Background summary

Phase I studies with BAY 80-6946 and BAY 86-9766 have been conducted (and are currently ongoing) using these study drugs in a monotherapy setting. The rationale for conducting this study is that the majority of cancers exhibit increased signaling through either the RAS/RAF/MEK/ERK (MAPK) or the PI3/AKT/mTOR pathway, or both. In the past decade, numerous small molecule agents have been developed which inhibit signaling proteins in either pathway, but the presence of feedback loops and crosstalk between the two pathways poses a difficult barrier to the successful use of these drugs. One approach to this problem is to use two agents, one an inhibitor of the MAPK pathway, BAY 86-9766 and the other an inhibitor of the PI3K pathway, BAY 80-6946.

Study objective

The purpose of this study is to find the answers to the following research questions:
1. What are the side effects of the combination of BAY 80-6946 and BAY 86-9766 when given together at different dose levels?
2. What dose level of BAY 80-6946 and BAY 86-9766 should be tested in future clinical research studies?
3. How much BAY 80-6946 is in the blood at specific times after administration and does adding BAY 86-9766 have an affect?
4. How much BAY 86-9766 is in the blood at specific times after administration and does adding BAY 80-6946 have an affect?
5. Does the combination of BAY 86-9766 and BAY 80-6946 have an effect on tumors?
6. Are there specific biomarkers that might be able to explain why some patients respond to treatment and others do not?

Study design

Study 12876 is a Phase Ib, open-label, dose-escalation study of the combination of BAY 80-6946 (PI3K inhibitor) and BAY 86 -9766 (allosteric MEK inhibitor) in subjects with advanced cancer.

Intervention

Treatment on this study will follow a 4-week schedule and each 4-week period is known as a *cycle*. Patients will be taking different dose strengths of each drug depending on when they start treatment and what side effects have been seen so far during the study.

The first drug is called BAY 80-6946. This drug is given as an IV infusion. You will receive treatment on days 1, 8 and 15 of each cycle. Some patients will also receive the drug on Day 22 of each cycle. If you are treated at the lowest dose level and do not have bad side effects, and the patients at the next highest dose level do not have serious side effects, your dose may be increased. However, if you have bad side effects, your dose of BAY 80-6946 may also be lowered at future visits.

The second drug is called BAY 86-9766. This drug is given by mouth. You will start taking this drug on Day 4 of your first cycle and will take it twice a day, either at home or in the clinic. You will be asked to keep a record of what time and how many pills you take each day. Your dose of BAY 86-9766 will not increase during the study, but may be lowered if you have bad side effects. Some patients will be assigned to a schedule where they take the drug for 4 days (twice a day) and then do not take it for the next 3 days before starting again for 4 days. If you are assigned to this schedule, you will begin taking the drug on Day 6 of your first cycle.

Please see protocol Table 4-1: Dose escalation scheme page 42

Study burden and risks

The patient will visit the hospital minimum 10 times. In the first cycle, this will be on day 1, 8, 15 and 22 where the patient will receive an IV with BAY 80-6946 (time: +/- 1h) with the accompanied standard procedures: blood test, urine sample, physical exam. On Day 1, 14 and 15, the patient will spend 12h minimum in the hospital for blood sampling. The patient will receive a morning dose of BAY 86-9766 day 4, 8, 14 and 22 after blood sampling.

During the cycle 2, day 1: Concomitant medical review, full physical exam, blood tests, urine sampling, ECG and MUGA-scans, ophthalmologic exam, IV with BAY 80-6949 (time: +/- 1h), blood pressure measurement, morning dose of BAY89-9766. On day 8 and 15: brief physical exam, blood tests, IV with BAY 80-6946 (time: +/-1h), blood pressure measurement, morning dose of BAY 86-9766. Day 22: scans are made to assess the affliction, morning dose BAY 86-9766, IV with BAY 80-6946 (time= +/- 1h)

Patients in cohorts 2A, 2B, 2C and the expansion cohorts, will have a FDG-PET scan during the screening and on day 22 of Cyclus 1. Patients in the expansion cohorts will also have a paired tumor biopsy during the screening and day 17 of Cyclus 1.

The patient will have a risk on side effects of both experimental drugs (BAY 80-6946 and BAY 86-9766). For an extensive description, see section E9 in this ABR-form

Contacts

Public
Bayer

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US
Scientific
Bayer

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Whippany 07981
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- The informed consent must be signed before any study specific tests or procedures are initiated
- Subjects, at least 18 years of age, with incurable and refractory advanced or metastatic solid tumors that have progressed on or failed to respond to therapies known to provide clinical benefit
- Histological or cytological documentation of non-hematologic, malignant solid tumor, excluding primary brain or spinal tumors, with no current involvement in the central nervous system. Subjects who have brain metastases that have been treated and have been stable for > 3 months may be included in the study
- At least one measurable lesion or evaluable disease, as per RECIST 1.1
- ECOG Performance Status of 0 or 1
- Life expectancy of at least 12 weeks
- LVEF >= LLN (Lower Limit of Normal) for the Institution
- Women of childbearing age and men enrolled in this study must use adequate birth control measures prior to, during the course of the study and 30 days after the last administration of either BAY 80-6946 or BAY 86-9766. An adequate contraception includes a hormonal contraception with implants or combined oral, transdermal, or injectable contraceptives, certain intrauterine devices, bilateral tubal ligation, hysterectomy, or vasectomy of the partner. In addition the use of condoms for subjects or their partners is required unless the woman has had a hysterectomy
- ALT and AST <= 2.5 x ULN (<= 5 x ULN for subjects with liver involvement of their cancer)
- Total bilirubin <= 1.5 x ULN
- Serum creatinine <= 1.5 x ULN
- PT-INR/PTT < 1.5 x upper limit of normal (Subjects who are being therapeutically anti-coagulated with an agent such as coumadin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in these parameters exists).Low-dose aspirin is permitted (<= 100 mg daily)
- Adequate bone marrow function as assessed by the following:
- Hemoglobin >= 9.0 g/dL (transfusion permitted)

- Absolute neutrophil count (ANC) >= 1,500/mm3
- Platelet count >= 100,000/mm3
- Ability to understand and follow study-related instructions
- Only for subjects enrolled into the expansion cohort(s): Presence of a tumor mutation in one or more of the following genes: KRAS, NRAS, BRAF, or PI3KCA

Exclusion criteria

• Ability to understand andfollow study related instructions;Subjects are to be excluded from the study if they display any of the following criteria:;•History of Retinal Vein Occlusion or eye exam showing risk factor;•History of cardiac disease congestive heart failure(CHF)>NYHA Class II; active coronary artery disease, myocardial infarction within 6 months prior to study entry; new onset angina within 3 months prior to study entry or unstable angina or ventricular cardiac arrhythmias requiring anti-arrhythmic therapy. ;•Current diagnosis of Type 1 or 2 Diabetes Mellitus, or fasting blood glucose > 125 mg/dL, or HgBA1c > = 7.0;•Use of systemic corticosteroid medication within 2 weeks of the start of study treatment (topical or inhaled steroids are permitted). Single doses of systemic corticosteroids given as pre-medication for procedures or nonstudy drugs may be administered up to 24 hours of first dosing of BAY 80-6946 ;•Active clinically serious infections, including viral hepatitis, > Grade 2 (NCI CTCAE Version 4.0) ;•Uncontrolled seizure disorder;•Uncontrolled hypertension defined as systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg, despite optimal medical management.;•Known human immunodeficiency virus (HIV) infection;•Subjects undergoing renal dialysis;•Known bleeding diathesis;•Ongoing substance abuse, medical, psychological or social conditions that may interfere with the subject*s participation in the study or evaluation of the study results;•Pregnant or breast feeding women. Women of childbearing potential must have a negative serum or urine pregnancy test performed within 7 days before the start of treatment.;•Women of childbearing age and men enrolled in this study must use adequate birth control measures prior to, during the course of the study and 30 days after the last administration of either BAY 80-9766 or BAY 86-9766. An adequate contraception includes a hormonal contraception with implants or combined oral, transdermal or injectable contraceptives, certain intrauterine devices, bilateral tubal ligation, hysterectomy, or vasectomy of the partner. In addition the use of condoms for subjects or their partners is required unless the woman has had a hysterectomy.;•Use of strong inhibitors of CYP3A4, (eg, ketoconazole, itraconazole, clarithromycin, ritonavir, indinavir, nelfinavir and saquinavir), and strong inducers of CYP3A4 (eg, St. John*s Wort, rifampin) are prohibited within 2 weeks of starting study treatment and for the duration of the study.;• Known G6PD deficiency

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-02-2012
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BAY 80-6766
Product type:	Medicine
Brand name:	BAY 80-6946

Ethics review

Approved WMO Date:	24-05-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-07-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-12-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	17-04-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-05-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-09-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-10-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-03-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-04-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-10-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-11-2013
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	EUCTR2010-024082-45-NL
CCMO	NL36437.078.11