A Phase IA, multicenter, open-label dose escalation study of BKM120, administered orally in adult patients with advanced solid malignancies

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Primary objectiveTo determine the maximum-tolerated dose (MTD) of BKM120 as a single agent when administered orally to adult patients with advanced solid tumorsSecondary objectives* To assess the safety and tolerability of BKM120* To characterize...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON35139

Source
ToetsingOnline

Brief title
Phase I study with BKM120 in advanced solid malignancies

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Advanced and/or metastatic cancer

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Financiering door de sponsor Novartis Pharma BV (farmaceutisch bedrijf)

Intervention

Keyword: BKM120, Dose escalation, Phase I, Solid tumor

Outcome measures

Primary outcome

Phase I: to determine the MTD of BKM120 as a single agent, administered orally

daily. Estimation of the MTD will be based upon the estimation of the

probability of DLT in cycle 1.

Secondary outcome

* Safety: Type, frequency and severity of adverse events (CTCAE Version 3.0)

* Efficacy: In the dose-escalation arm response will be also assessed by RECIST.

* Pharmacokinetics

* PD: PET response, blood and tumor biomarkers at baseline and post-BKM120

dosing.

Study description

Background summary

Patients with advanced solid malignancies often have limited therapeutic options beyond institutional standard of care. In addition in some malignancies, the cancer pathology can be driven by, or be largely dependent on oncogenes and tumor suppressors, whose transforming potential is mediated by constitutive PI3K activation. In addition resistance to a variety of therapeutic interventions, can be linked to constitutive activation of the PI3K pathway. The use of BKM120 for such tumors therefore addresses an unmet medical need by giving new hope to patients whose cancer has become refractory to all

available treatments.

Study objective

Primary objective
To determine the maximum-tolerated dose (MTD) of BKM120 as a single agent when administered orally to adult patients with advanced solid tumors

Secondary objectives
* To assess the safety and tolerability of BKM120
* To characterize the single and multiple-dose pharmacokinetic (PK) profile of oral BKM120
* To characterize the safety and tolerability, pharmacokinetics and biologic activity profile of BKM120 at the MTD dose (MTD-dose including MTD dose-expansion arm)
* To obtain preliminary evidence of efficacy of BKM120
* To assess changes in Pharmacodynamic markers as a measure of PI3K inhibition pre- vs. post-treatment
* To investigate a potential anti-angiogenic effect of BKM120, by assessing changes in circulating angiogenic markers (pre- vs. posttreatment)
* To obtain preliminary data on cellular anti-tumor activity of BKM120 by assessing presence of apoptosis and cellular proliferation in tumor tissue and blood (pre- vs. post-treatment)
* To assess molecular status of markers related to PI3K signaling in tumor tissue.
* To understand relationship with any clinical responses if possible 18F-FDG PET changes reflecting inhibition of tumor metabolic activity as a marker of early efficacy
* To assess changes in tumor markers (as relevant for the respective cancer type), if applicable, as potential surrogate indicators of efficacy

Study design

The study has been designed as a Phase IA dose-escalation trial including a MTD dose expansion arm in patients with advanced solid tumors, in which oral BKM120 will be administered once daily on a continuous schedule.

One to 3 patients will be enrolled at the initial dose level of 12,5 mg /day.
If only one evaluable patients is available for assessment and has not experienced clinically relevant * CTCAE grade 2 toxicity, then one patient will be considered sufficient for decision making. Once the 2nd patient experiences CTCAE * grade 2 toxicity or the first
CTCAE * grade 3 toxicity has occurred in the study, a minimum of 3 patients will be enrolled for all further cohorts.
Before a drug dosage can be declared to be the MTD, at least 6 patients will have to be treated at this dose level for one treatment cycle.

Once MTD has been declared, the MTD cohort will be expanded to enroll a total of at least 22 patients with advanced solid tumors including at least 8 patients with paired fresh biopsies
Patients will be treated until disease progression, unacceptable toxicity or until investigator*s decision or patient refusal.

Intervention

BKM120 - orally, starting dose 12,5 mg / day

Study burden and risks

The risks and side effects of treatment with BKM120 in humans are not known. In animal studies conducted in different species, e.g. rats and dogs, the main adverse events observed were related to the mode of action of BKM120
- changes in pancreas: glucose and insuline level changes
- increase in bloodpressure
- low risk on photoxicity
- changes in bonemarrow and lymphatic system
- diarrhea
- effects on male (testes, sperm cells) and female sexual organs (ovaries).

Taking blood, skinbiopsies and tumorbiopsies may cause pain, bleeding, and/or bruising.

Patients will be exposed to radiation (CT-scan, PET-scan and MUGA-scan). The radiation exposure will not exceed the maximum ranges that are set within the Netherlands.

Contacts

Public
Novartis

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Scientific
Novartis

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Patients with advanced solid tumors who have progressed on standard therapy or for whom no standard anticancer therapy exists
2. At least one measurable or non-measurable lesion as defined by RECIST
3. Patients who fulfill the following criteria will be eligible for FDG-PET:
* tumor types known to have a high FDG uptake, such as breast, lung, GIST, melanoma, colorectal, lymphoma
* To be eligible for follow-up scans, patients should have FDG uptake with a tumor background ratio * 2 in at least one lesion * 2cm at baseline.
4. Availability of a representative tumor tissue specimen.
5. WHO Performance Status of * 2 and life expectancy of * 12 weeks
6. Patients must have the following laboratory values:
* Absolute Neutrophil Count * 1.5 x 109/L
* Hemoglobin * 9 g/dl <= 5.58 mmol/l
* Platelets * 100 x 109/L
* Potassium and totsal calcium within normal limits
* Magnesium * the lower limit of normal
* AST/SGOT and ALT/SGPT * 2.5 x Upper Limit of Normal (ULN) or * 5.0 x ULN if liver metastases are present
* Serum bilirubin * 1.5 x ULN
* Serum creatinine * 1.5 x ULN or 24-hour clearance * 50 mL/min
* Serum amylase and lipse * ULN
* Serum triglycerides * 500 mg/dL
* Fasting plasma glucose * 140 mg/dL (7.8 mmol/L)
7. Negative serum pregnancy test within 72 hours before starting study treatment

Exclusion criteria

1. Presence of brain metastases. Exception for MTD part: Patients with treated brain metastases that are asymptomatic and have been clinically stable for 3 months
2. Prior treatment with a PI3K inhibitor
3. Presence of acute or chronic liver disease, renal disease or pancreatitis
4. Patients with any peripheral neuropathy * CTCAE grade 2
5. Patients with unresolved diarrhea * CTCAE grade 2
6. Impaired cardiac function or clinically significant cardiac diseases, including any of the following: LVEF < 45%, ST depression or elevation of * 1.5 mm, congenital long QT syndrome and QTc > 480 msec, ventricular arrhythmias or atrial fibrillation, clinically significant bradycardia, complete left bundle branch block, right bundle branch block + left anterior hemiblock (bifascicular block), unstable angina pectoris or acute myocardial infarction * 3 months prior to studystart, congestive heart failure, uncontrolled hypertension.
7. Clinically manifest diabetes mellitus, history of gestational diabetes mellitus, or steroid-induced diabetes mellitus
8. Uncontrolled hypertriglyceridemia, active or uncontrolled infection
9. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of BKM120
10. Treatment with any hematopoietic colony-stimulating growth factors * 2 weeks prior to starting study drug.
11 Treatment with medication that has the potential to prolong the QT interval or inducing Torsades de Pointes
12. Therapeutic doses of warfarin sodium (Coumadin®) - for the Netherlands acenocoumarol and fenprocoumon
13. Corticosteroids * 2 weeks prior to starting study drug;Amendment 4: patients with the following mood disorders as judged by the Investigator or a psychiatrist:
* history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of suicidal attempt or ideation, or homicidal ideation
* * CTCAE grade 3 anxiety

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):	29-06-2009
Enrollment:	19
Type:	Actual

Ethics review

Approved WMO Date:	15-12-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-05-2009
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-06-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-07-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-07-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-11-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	11-11-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-02-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-02-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-12-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-12-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-01-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-01-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-06-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	20-07-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-09-2012
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	EUCTR2008-002652-17-NL
CCMO	NL25226.078.08