A phase Ib, open-label, multi-center, dose escalation and expansion study of an orally administered combination of BKM120 plus MEK162 in adult patients with selected advanced solid tumors

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Primary:To determine the MTD and/or RP2D of BKM120 and MEK162 in combination when administered orally to adult patients with selected advanced solid tumors. Secondary:• To characterize the safety and tolerability of the oral combination of BKM120...

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

Summary

ID

NL-OMON43645

Source
ToetsingOnline

Brief title
A phase Ib study with MEK162 in combination with BKM120

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
cancer, Solid tumors

Research involving
Human

Sponsors and support

Primary sponsor: Array BioPharma Inc.
Source(s) of monetary or material Support: Farmaceutische Industrie

Intervention

Keyword: BKM120, MEK162, Phase I, Solid tumors

Outcome measures

Primary outcome

Determine the MTD and/or RP2D of BKM120: Incidence of Dose Limiting Toxicities

Secondary outcome

Safety and tolerability: Adverse and serious adverse drug reactions, changes in hematology and chemistry values and assessment of physical and neurological examinations, vital signs and electrocardiograms.

Preliminary anti-tumor activity of the combination: ORR (Overall Response Rate), DOR (Duration of Response), TTR (Time To Response) and PFS (Progression Free Survival) according to RECIST.

PK profile of the combination: Time vs. plasma concentration profiles; basic PK parameters of BKM120 and MEK162 and its primary active metabolite.

Effects of BKM120 and MEK162 on PI3K and MAPK signaling in skin and tumor tissue: Pharmacodynamic: ΔCT values of DUSP6, SPRY4 and BMF gene expression and H-scores for phospho-Akt/S6/4E-BP1, phospho-MEK/ERK, Ki-67 and PARP pre- vs. post-dose

Study description

Background summary

Signaling through the RAS/RAF/MEK/ERK and PI3K/AKT pathway is triggered by extracellular stimulation and regulates a variety of biological processes, such as proliferation, differentiation and cell death. Both pathways are often activated in many human cancers by mutations or overexpression of upstream molecules. These pathways interact with each other to regulate tumor growth and are thus considered high value targets in treating cancer. Human cancers with PIK3CA mutations often harbor other known oncogenic mutations such as mutations in KRAS in colorectal cancer and HER2 amplification in breast cancer. These concomitant oncogenic changes may affect the tumors* responsiveness to PI3K inhibitors and, possibly, may necessitate combinations of treatments.
The complex and extensive interaction of the PI3K pathway with the MEK/ERK pathway, activation by oncogenic RAS and the reported compensatory signaling when one pathway is inhibited, provide for a strong rationale for the combination therapy of PI3K- and MEK- inhibitors in patients with RAS/BRAF dependent tumors for whom no further effective standard anticancer therapy exists.
Studies in basal-like breast cancer and lung cancer cell lines and tumor models demonstrated synergistic anti-tumor efficacy by dual PI3K and MAPK pathway. Similarly, in EGFR mutant lung cancers with acquired resistance to EGFR TKIs, there is strong preclinical evidence supporting the use of a combination of PI3K/mTOR plus MEK inhibitors to effectively shrink lung tumor volumes.

Study objective

Primary:
To determine the MTD and/or RP2D of BKM120 and MEK162 in combination when administered orally to adult patients with selected advanced solid tumors.

Secondary:
• To characterize the safety and tolerability of the oral combination of BKM120 and MEK162.
• To assess preliminary anti-tumor activity of the combination.
• To determine the single and multiple- dose PK profile of the combination.
• To assess the effects of BKM120 and MEK162 on PI3K and MAPK signaling:
1. Pharmacodynamic changes of pAkt, pS6, p4EBP1, pMEK, pERK, DUSP6, SPRY4 and BMF in pre- vs. post- dose tumor and skin biopsies.
2. Cell proliferation/survival markers (Ki-67, PARP) in pre- vs. post- dose tumor and skin biopsies.
• To characterize baseline status of molecules relevant to PI3K and MAPK signaling in tumor tissue (PIK3CA, PTEN, p53, cMET) and potential correlation with clinical outcome

Study design

A multi-center, open-label, dose finding, phase Ib study to determine the MTD and/or RP2D for the combination of BKM120 and MEK162, followed by an expansion

phase to further assess safety and preliminary efficacy of the combination in selected patient populations.

Intervention

BKM120, capsules. Starting dose is 50 mg once daily.
MEK162, caplets. Starting dose 30 mg twice daily.

Study burden and risks

Based on what has been seen in patients treated with BKM120 and MEK162, the risks and side effects of treatment with the combination in humans may include, but are not limited to, skin rash, diarrhea, nausea and vomiting.

The side effects of MEK162 may include and are not limited to: skin irritation such as rash, acne-like rash or redness which may be itchy, diarrhea, nausea, edema (water retention), fatigue, abdominal pain, mucositis (sores in your mouth or throat), loss of appetite, heartburn or indigestion, muscle aches and formation of small dark spots during the healing process after rash. Some patients who received MEK162 experienced elevation in a protein that is present in muscular tissues (creatine phosphokinase, CPK). Creatine phosphokinase (also known as CK or CPK) may indicate muscle inflammation or damage. Sometimes elevated CPK can lead to more serious problems including kidney damage. MEK162 has also caused mild to moderate visual changes, such as *floaters* or swelling in and around the eye, in subjects treated with the study drug. While this type of visual impairment may improve, there is a risk that it may continue.

The side effects of BKM120 may include but are not limited to: decreased appetite, nausea, constipation, diarrhoea, fatigue, rash, high blood sugar, general weakness, abdominal pain, vomiting, anxiety, depression, mucosal inflammation, itchiness, shortness of breath, elevated liver enzymes, dry skin, indigestion, fever, tiredness and pneumonitis (inflammation of lung tissue) Some patients treated with BKM120 have also shown changes of their mood status, for which the treatment with BKM120 had to be stopped temporarily or permanently.

Other risks and inconveniences are: taking blood, skin and tumorbiopsies may cause pain, bleeding, and/or bruising. Patients will be exposed to radiation (CT-scan, and X-rays). The radiation exposure will not exceed the maximum ranges that are set within the Netherlands.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients with the following histologically/cytologically confirmed, advanced solid tumor for whom no standard therapy exists:
• Advanced pancreatic cancer (irrespective of KRAS or B-RAF mutation status).
• Advanced colorectal with KRAS, NRAS or BRAF mutations.
• Advanced melanoma with NRAS or BRAF mutations.
• Advanced NSCLC with KRAS mutation.
• Other advanced solid tumors with documented KRAS, NRAS or BRAF mutations.
• Triple negative breast cancer.
• Advanced NSCLC patients with EGFR activating mutations, who have progressed on a prior EGFR TKI based regimen and NSCLC patients known to have documented T790M activating mutations (expansion-arm only)
Measurable or non-measurable, but evaluable disease as determined by RECIST.
ECOG (WHO) performance status 0-2.
Adequate organ function and laboratory parameters:
• Absolute Neutrophil Count >= 1.5 x 109/L

• Hemoglobin >= 10 g/dl (=6.2 mmol/L)
• Platelets >= 100 x 109/L
• AST/SGOT and/or ALT/SGPT <= ULN (upper limit of normal) or <= 3.0 x ULN if liver metastases are present.
• Serum bilirubin <= ULN (or <= 1.5 x ULN if liver metastases are present; or total bilirubin <= 3.0 x ULN with direct bilirubin within normal range in patients with well documented Gilbert Syndrome)
• Serum lipase <= ULN
• Fasting glucose levels < 7.0 mmol/L (126 mg/dL) or 2-hrs glucose < 11.1 mmol/L (200 mg/L) during OGTT
• Calculated or directly measured Creatinin Clearance * 50% LLN
Recovery from all adverse events of previous anti-cancer therapies, including surgery and radiotherapy, to baseline or to Grade <= 1, except for alopecia and < Grade 2 sensory peripheral neuropathy.
Adequate cardiac function
• LVEF >= 50%
• NYHA Class <= 2
• QTc interval <= 480ms

Exclusion criteria

Patients with primary CNS tumor. Patients with clinically stable metastatic CNS tumors, not receiving steroid therapy and is not receiving anti-convulsive medications are eligible.
Prior systemic anti-cancer treatment:
• cyclical chemotherapy within a period of time that is shorter than the cycle length used for that treatment (e.g., 6 weeks for nitrosourea, mitomycin-C) prior to starting study treatment.
• biologic therapy (e.g., antibodies) within a period of time which is <= 5 t1/2 or <= 4 weeks prior to starting study treatment.
• continuous or intermittent small molecule therapeutics within a period of time which is <= 5 t1/2 or <= 4 weeks prior to starting study treatment.
• any other investigational agents within a period of time that is less than the cycle length used for that treatment or <= 4 weeks prior to starting study treatment.
Prior radiotherapy to > 30% of bone marrow.
Major surgery <= 4 weeks prior to starting study treatment.
History of prior significant toxicity from another MEK- or PI3K pathway inhibitor requiring discontinuation of treatment.
Prior treatment with combinations of MEK and PI3K/mTOR/ AKT inhibitors.
Impaired cardiovascular function or clinically significant cardiovascular diseases, including any of the following:
• History/evidence of acute coronary syndromes (including MI, unstable angina, CABG, coronary angioplasty, or stenting), < 6 months prior to screening.
• Symptomatic heartfailure, history or current evidence of clinically significant cardiac arrhythmia and/or conduction abnormality, e.g. congential long QT syndrome, high-grade/complete AV-blockage.
• Uncontrolled arterial hypertension defined by BP > 140/100 mmHg at rest.

Patients with diabetes mellitus.
Mood disorders as judged by the Investigator or a Psychiatrist, or meets the cut-off score of >= 10 in the PHQ-9 depression scale or a cut-off of >= 15 in the GAD-7 mood scale, respectively, or selects a positive response of *1, 2, 3* to question number 9 in the PHQ-9 depression scale (potential for suicidal thoughts) and any of the following:
• Medically documented 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 (immediate risk of doing harm to others)
• >=CTCAE grade 3 anxiety
History or current evidence of central serous retinopathy (CSR), retinal vein occlusion (RVO) or ophthalmopathy at baseline that would be considered a risk factor for CSR/RVO
Any other condition that would, in the investigator*s judgment, contraindicate patient*s participation in the clinical study due to safety concerns or compliance with clinical study procedures.

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):	21-03-2012
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Geen
Generic name:	Geen

Ethics review

Approved WMO Date:	14-06-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-10-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-10-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-11-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-12-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-01-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-02-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-03-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-07-2012

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-12-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	31-01-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-04-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-06-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-06-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-01-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-01-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2011-001083-22-NL
ClinicalTrials.gov	NCT01363232
CCMO	NL36637.041.11