A phase Ib multi-center, open-label, 4-arm dose-escalation study of oral BEZ235 and BKM120 in combination with weekly paclitaxel in patients with advanced solid tumors and weekly paclitaxel/trastuzumab in patients with HER2+ metastatic breast cancer.

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Primary:Dual-agent dose escalation part (Part 1):• To determine the maximum tolerated dose of oral, daily (qd) BEZ235 in combination with paclitaxel, qw in patients with advanced solid tumors(MTD1, Arm 1).• To determine the maximum tolerated dose of...

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

Summary

ID

NL-OMON34229

Source
ToetsingOnline

Brief title
BEZ235 or BKM120 with paclitaxel or paclitaxel/trastuzumab (phase IB)

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified
- Breast disorders

Synonym
advanced solid tumors, HER2-positive Breast Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma

Intervention

Keyword: BEZ235, BKM120, paclitaxel/trastuzumab, Phase Ib

Outcome measures

Primary outcome

Incidence of dose-limiting toxicities (DLTs) in patients with concomitant

administration of BEZ235 or BKM120 and paclitaxel (± trastuzumab).

Secondary outcome

• Safety and tolerability: type, frequency, and severity of adverse events

(AEs), adverse drug reactions, and laboratory abnormalities per

CTCAEv4.0 (Common Toxicity Criteria for Adverse Events, version 4.0)

• Pharmacokinetics:

• Time versus plasma concentration profiles of paclitaxel as single agent and

in combination treatment

• Time versus plasma concentration profiles of BEZ235 and BKM120 in combination

treatment

• Trastuzumab trough levels

• Basic PK parameters for paclitaxel, BEZ235, and BKM120 including, but not

limited to, AUCtlast, AUCinf, AUC0-24, Cmax, tmax, terminal t1/2, and other PK

parameters if deemed appropriate

• Overall response per RECIST

Exploratory endpoints :

• Antitumor activity: standard circulating tumor markers

• Phospho-S6 ribosomal protein (p-S6) in skin

• Increase in tumor apoptotic markers (circulating markers)

• PI3K pathway analysis (PIK3CA mutation, PTEN alteration in tumors)

• New biomarkers will be integrated if developed during this trial and

considered appropriate for judgment of efficacy and safety

• Basic PK parameters for the paclitaxel metabolites including, but not limited

to, AUC0-tlast, AUC0-inf, AUC0-24, Cmax, tmax, terminal t1/2, and other PK

parameters if deemed appropriate

Study description

Background summary

Although the inclusion of paclitaxel and trastuzumab in the armamentarium of cancer treatments has significantly improved the treatment outcome for many patients, a considerable number of tumors are insensitive to treatment with paclitaxel and/or trastuzumab a priori or eventually develop treatment resistance during the course of the treatment. While the exact mechanisms underlying the development of treatment resistance remain obscure, it is of note that activation of the PI3K pathway is believed to play an important role. In addition, it has been shown that concomitant inhibition of the PI3K pathway enhances the efficacy of paclitaxel and reverts resistance towards HER2-targeted treatments.

BKM120 is a potent and highly specific oral pan-class I phosphatidylinositol-3-kinase (PI3K) inhibitor, currently under investigation in a first-in-man study in patients with advanced solid tumors (wild type and PIK3CA-mutated).

Consistent, dose-dependent pharmacodynamic activity has been demonstrated and clear signs of anti-tumor activity have been seen with BKM120.

BEZ235 is a pan-class I PI3K and mTORC1/C2 inhibitor under investigation in a first-in-man study. Clinical data shows that BEZ235 treatment is well tolerated, induces dose-dependent pathway inhibition in tissues, and results in anti-tumor activity, particularly in patients with PI3K pathway deregulated cancers.

Collectively, the available data suggests that BKM120 and BEZ235 may not only enhance the antitumor activity of the paclitaxel and paclitaxel/trastuzumab regimens, but could potentially delay and/or revert treatment resistance.

Study objective

Primary:
Dual-agent dose escalation part (Part 1):
• To determine the maximum tolerated dose of oral, daily (qd) BEZ235 in combination with paclitaxel, qw in patients with advanced solid tumors (MTD1, Arm 1).
• To determine the maximum tolerated dose of oral BKM120, qd in combination with paclitaxel, qw in patients with advanced solid tumors (MTD2, Arm 2).
Triple-agent dose combination part (Part 2):
• To determine the maximum tolerated dose of oral BEZ235, qd in combination with paclitaxel/trastuzumab, qw in patients with HER2+ metastatic breast cancer (MTD3, Arm 3).
• To determine the maximum tolerated dose of oral BKM120, qd in combination with paclitaxel/trastuzumab, qw in patients with HER2+ metastatic breast cancer (MTD4, Arm 4).

Secondary:
• To assess the safety and tolerability, including acute and chronic toxicities, of the dual and triple combinations evaluated.
• To characterize the single-dose pharmacokinetics of single-agent paclitaxel on Day 1
• To characterize the multiple-dose pharmacokinetics of BEZ235/BKM120 qd and paclitaxel qw when given in combination (Day 8 and 22)
• To characterize exposure to trastuzumab (trough levels)
• To assess the preliminary anti-tumor activity of the different treatment regimens

Exploratory:
• To assess PI3K pathway inhibition in skin biopsies
• To assess treatment-related changes in circulating markers of biologic effect (antitumor effect, safety)
• To assess the mutational status of the tumor (PIK3CA, PTEN)

• To evaluate the pharmacokinetics of the 3 paclitaxel metabolites of interest: 6a-hydroxypaclitaxel (cytochrome P450 [CYP] 2C8), 3'-p-hydroxypaclitaxel (CYP3A4), and 6α and 3'-p- dihydroxypaclitaxel

Study design

This is a multi-center phase Ib, open-label, 4-arm, dose-finding study consisting of two parts:
Part 1 (dual-agent dose escalation):
• Arm 1 assesses the combination of BEZ235 with weekly paclitaxel
• Arm 2 assesses the combination of BKM120 with weekly paclitaxel

Part 2 (triple-agent dose combination):
• Arm 3 assesses the combination of BEZ235 with weekly paclitaxel/trastuzumab
• Arm 4 assesses the combination of BKM120 with weekly paclitaxel/trastuzumab

Dual-agent dose escalation part:
The first part will determine the maximum tolerated dose of the combination of weekly paclitaxel given with either daily BEZ235 (MTD1) or daily BKM120 (MTD2).
• Arm 1 : Paclitaxel qw + BEZ235 qd
• Arm 2 : Paclitaxel qw + BKM120 qd
During this dual-agent dose escalation part of the study the maximum tolerated doses in each arm will be determined based on dose-limiting toxicities (DLTs) occurring during the first cycle of treatment.

In part 1, the initial cohorts will consist of 1 patient. As soon as non-hematologic toxicities of CTCAE grade >= 2 are observed for which a relationship with the study drug cannot be ruled out, the cohort will be expanded to 3 patients (see Section 10).

It is anticipated that at least 15 patients per arm will be needed to define the MTDs in the dual-agent dose escalation part.

Triple-agent dose combination part:
The objective of the triple-agent dose combination part is to evaluate the safety and tolerability of the following combinations:
• Arm 3: BEZ235 qd, paclitaxel and trastuzumab qw
• Arm 4: BKM120 qd, paclitaxel and trastuzumab qw.

The starting doses for BEZ235, BKM120, and paclitaxel in the triple-agent dose escalation part will be determined on the basis of data from the dualagent dose escalation part.

A minimum of six patients per arm will be necessary to declare the MTDs of the triple-agent combinations.

Intervention

• BEZ235: starting dose 400 mg/day
• BKM120: starting dose 40 mg/day
• Paclitaxel: 70 mg/m2
• Trastuzumab: 2 mg/kg (if applicable starting dose of 4mg/kg)

Arm 1: Paclitaxel + BEZ235
Arm 2: Paclitaxel + BKM120
Arm 3: Paclitaxel + trastuzumab + BEZ235
Arm 4: Paclitaxel + trastuzumab + BKM120

Study burden and risks

Study assessments will be performed at prescreening, baseline, C1D1, C1D8, C1D15, C1D22, C2D1, C2D8, C2D15, C2D22 and CXD1, CXD8, CxD15, CxD22 of every consecutive cycle. Treatment duration will continue until disease progression (defined by RECIST), unacceptable toxicity, patient withdrawal, death, investigators decision or discontinuation from the study for any other reason, whereupon all patients will complete the End of Treatment visit. The final Follow up Visit should be performed at least 28 days after end of study to collect safety, further anticancer therapy and survival information.
Please refer to Protocol table 7-1, page 68.

The main side effects and observations seen in studies with BEZ235 are:
• fatigue
• skin rash
• nausea
• vomiting
• diarrhea
• thrombocytopenia
Please refer to Protocol section 1.2.4. pages 31 to 32

The main side effects and observations seen in studies with BKM120 are:
• anorexia
• nausea
• rash
• constipation
• diarrhea
• hyperglycemia
• fatigiue/asthenia
• vomiting
• anxiety
• mood disorders
• transaminase increase
• pruritus

• GI disorders
Please refer to Protocol section 1.3.4. pages 34 to 36

Anticipated risks and safety consideration of the drug combination:
Preliminary clinical data available from ongoing studies with BKM120 and BEZ235 do not suggest a major overlap in toxicities with paclitaxel. However, there is the possibility that certain toxicities may be exacerbated or seen with a greater frequency.
In the case of the combinations BEZ235/paclitaxel or BEZ235/paclitaxel/trastuzumab, special attention should be paid to the following toxicities:
• Fatigue, skin rash, thrombocytopenia, nausea/vomiting/diarrhea, disturbances of the coagulation system, disturbances of cardiac function, and disturbances of the vital signs.
In case of combination treatment with BKM120/paclitaxel and BKM120/ paclitaxel/trastuzumab, special attention should be paid to the following toxicities:
• Neuropsychiatric disorders, skin rash, hyperglycemia, nausea/vomiting/diarrhea, fatigue, disturbances of cardiac function, and disturbances of the vital signs.
The potential for clinically significant drug-drug interactions with the proposed combination of paclitaxel with BEZ235 or BKM120 is considered low.
Conversely, data from preclinical studies showed that both BEZ235 and BKM120 can induce significant myelosuppression.
Hence, combination treatment with paclitaxel and BEZ235 or BKM120 may be associated with a higher risk of bone marrow toxicity.

Toxicity due to the use of paclitaxel (refer to SMPC of paclitaxel)

Toxicity due to the use of trastuzumab (refer to SMPC of trastuzumab)

Other risks:
Taking blood and biopsies 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.
Use of contrast when making a CT-scan may cause an allergic reaction.

Contacts

Public
Novartis

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Dual-agent part:
• Patients with metastatic or locally advanced solid tumors eligible for weekly paclitaxel;Triple-agent part:
• HER2+ metastatic or locally advanced breast cancer patients eligible for weekly paclitaxel and trastuzumab;For both parts:
• WHO performance status <= 2
• Absolute neutrophil count >= 1.5 ×109/L
• Hemoglobin >= 10g/dL = 6.2 mmol/L
• Platelets >= 100 ×109/L
• Serum albumin >= 3.0 g/dL
• AST/SGOT and ALT/SGPT <= upper limit of normal (ULN) or <=2.5 × ULN if liver metastases are present
• Serum bilirubin <= ULN or <= 1.5 ×ULN if liver metastases are present
• Serum creatinine <= 1.5 × ULN or 24-hour creatinine clearance >= 50 mL/min
• Partial thromboplastin time (PTT) <= 1.5 × ULN
• Prothrombin time (PT)/international normalized ratio (INR) <=1.5 × ULN
• New York Heart Association (NYHA) grade <= 2
• Left ventricular ejection fraction (LVEF) >= 50% (MUGA scan or echocardiogram)
• QTc interval <= 460 ms on screening ECG

• Fasting plasma glucose <= 140 mg/dL (7.8 mmol/L)
• Recovery from all reversible adverse events of previous anticancer therapies to grade 1, except for alopecia and peripheral neuropathy

Exclusion criteria

• Patients with primary central nervous system (CNS) tumor or CNS tumor involvement. However, patients with a metastatic CNS lesion may participate in this trial, if the patient is > 4 weeks from therapy completion, clinically stable and not receiving enzyme-inducing antiepileptic drugs or corticosteroid therapy
• Patients who have received prior systemic anticancer therapy within the following time frames
- Chemotherapy <= 3 weeks before study treatment (6 weeks for nitrosoureas)
- Biological therapy <= 4 weeks before study treatment, except trastuzumab
- Investigational drug <= 4 weeks before study treatment
• Major surgery <= 4 weeks before study treatment
• Chronic treatment with corticosteroids or other immunosuppressive agents
• Uncontrolled diabetes mellitus
• Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug
• Treatment with agents that are metabolized solely by CYP3A and/or have a narrow therapeutic window or are strong inhibitors or inducers of CYP3A or CYP2C8.
• QT-prolonging medication known to have a risk to induce Torsades de Pointes
• Radiotherapy <= 4 weeks before starting study drug
• Prior treatment with PI3K inhibitors
• Known hypersensitivity to paclitaxel, polyethoxylated castor oil (Cremophor EL) or excipients of trastuzumab, BEZ235, or BKM120
• Patients with known human immunodeficiency virus (HIV)
• Active or history of major depressive episode, bipolar disorder, obsessive -compulsive disorder, schizophrenia, history of suicide attempt or ideation, or homicide
• Women of child-bearing potential and male patients must use adequate contraception methods throughout the study and for 12 weeks after study drug discontinuation

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-07-2011
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Herceptin
Generic name:	trastuzumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Nog niet van toepassing
Generic name:	Nog niet van toepassing
Product type:	Medicine
Brand name:	Taxol
Generic name:	paclitaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-12-2010
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-03-2011
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-06-2011
Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	28-06-2011
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	08-09-2011
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-01-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	04-06-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	06-06-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	28-09-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2010-022331-11-NL
CCMO	NL34474.031.10