An open label phase I dose finding study of BI 853520 administered orally in a continuous dosing schedule in patients with various advanced or metastatic non-hematologic malignancies

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Primary objective: to determine the safety and tolerability of BI 853520 monotherapy by defining the MTD (maximum tolerated dose) and recommending the dose for further trials in the development of this compound.Secondary objectives: A) determination...

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

Summary

ID

NL-OMON39828

Source
ToetsingOnline

Brief title
BI 853520 in solid tumours

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
cancer, solid tumours

Research involving
Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim
Source(s) of monetary or material Support: Industrie: Boehringer Ingelheim bv

Intervention

Keyword: Dose finding, Maximum tolerated dose, Phase 1, Solid tumours

Outcome measures

Primary outcome

Determination of the MTD. It will be defined by the occurrence of dose-limiting toxicities (DLT) during the first treatment cycle of each patient in the dose finding phase.

The MTD was determined as 200 mg. DLTs that occurred were fatigue (1) and proteinurea (2).

Secondary outcome

• Pharmacokinetic parameters of BI 853520 will be determined from plasma analyses after a single oral dose and after repeated dosing, at steady state: Cmax and Area Under the Curve

• Pharmacodynamic assessment: pPTK2 modulation pre- and post treatment in skin or tumor

• Exploratory evaluation of efficacy (e.g. objective response rate, disease control rate, duration of disease control, tumor shrinkage)

Study description

Background summary

Cancer is a leading cause of death globally with deaths from cancer projected

to rise. There is a substantial need for novel therapeutic strategies to improve the outcome for patients with advanced or metastatic malignancies who have failed conventional treatment, or for whom no therapy of proven efficacy exists.
In recent years, a number of novel compounds targeting specific cellular molecules have been developed based on increasing understanding of cancer biology and cell regulation. Protein tyrosine kinase-2 (PTK2), also known as focal adhesion kinase (FAK), is a nonreceptor tyrosine kinase. Several publications over the last two decades have shown that PTK2 may be over-expressed in a variety of human tumours and its over-expression is associated with an increased malignant phenotype.
There is pre-clinical evidence from both in vitro and in vivo studies demonstrating anti-tumour activity with PTK2 blockade. BI 853520 is a highly potent and exquisitely selective inhibitor of PTK2 kinase activity. The favourable pre-clinical efficacy and safety profile of BI 853520 is expected to translate into a benefit for cancer patients. Published results of a phase I study of another compound targeting PTK2 showed nausea, vomiting, diarrhea and orthostatic hypotension as dose limiting toxicities (DLTs) with several patients deriving a clinical benefit.
Biomarker studies have recently indicated that sensitivity of carcinomas to PTK2 inhibitors may be predicted based on the pattern of E-cadherin expression. Therefore, expression of E-cadherin in tumour tissue will be analyzed for all patients in this study.

Study objective

Primary objective: to determine the safety and tolerability of BI 853520 monotherapy by defining the MTD (maximum tolerated dose) and recommending the dose for further trials in the development of this compound.
Secondary objectives: A) determination of the pharmacokinetic profile; B) exploration of biomarkers; and C) collection of preliminary data on anti-tumour efficacy.

Study design

The trial is an open label, dose finding study, followed by an expansion cohort. The data obtained from this study are expected to allow the definition of the MTD of BI 853520 monotherapy in patients with advanced solid tumour.
To determine the MTD, patients will be treated at escalating dose levels, utilizing the 3+3 design. Depending on the observed adverse events, dose cohorts at escalating dose levels will be enrolled until the MTD has been defined by the occurrence of drug-related dose limiting toxicity (DLT). The MTD is defined as the dose level immediately below the dose level at which 2 or more patients out of a maximum of 6 patients experience DLT.
The observation period for DLT is the duration of the first treatment cycle only (the first 28 days). However, relevant safety information of all treatment

cycles, including any delays in start of a subsequent cycle due to drug related adverse events (AEs), will be considered for the recommendation of the dose for phase II studies.
Once the MTD has been determined, up to 50 additional patients with measurable disease will be treated in the expansion phase. This expansion phase will further evaluate the safety, pharmacokinetic and pharmacodynamic profile and preliminary data on efficacy of BI 853520 in patients..

Intervention

Once daily oral intake of BI 853520

Study burden and risks

In this study, patients with advanced or metastatic solid tumours for whom no other treatment options are available, will be treated with oral BI 853520. Preclinical studies indicate an acceptable toxicity for BI 853520 with potential adverse events being nausea, vomiting, diarrhea, and headache. Furthermore, BI 853520 may be of potential clinical benefit for these patients. Additional blood and urine samplings will be performed for safety and pharmacokinetic analyses (6 mL per sampling). Furthermore, patients will undergo recording of vital signs and repeated scans for tumour imaging. The patient will receive a financial compensation as this is an additional procedure and the patient has to stay in the hospital for 24 hours twice during the first cycle. Repeated biopsies will be taken of either tumour or skin before and after the first cycle. Blood may be drawn once for an optional pharmacogenetic test (8,5 mL) during the first cycle. The subject may refuse participation in this sampling, but can continue to participate in the main study. These procedures can lead to local pain, irritation, bruising, or an infection in rare cases.

Contacts

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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 a confirmed diagnosis of advanced, measurable or evaluable, non-resectable and/or metastatic non-hematologic malignancy, which has shown to be progressive in the last 6 months as demonstrated by serial imaging;
- Patients who have failed conventional treatment or for whom no therapy of proven efficacy exists or who are not amenable to established treatment options;
-Tumour tissue must be available for the determination of E-cadherin expression (archived tissue or fresh biopsy);
- Recovery from reversible toxicities (alopecia excluded) of prior anti-cancer therapies (CTCAE grade < 2);
- Age >= 18 years;
- Written informed consent in accordance with International Conference on Harmonisation/Good Clinical Practice (ICH/GCP) and local legislation;
- Eastern Cooperative Oncology Group (ECOG), performance score 0-1;
Additional inclusion criteria in the expansion phase:
- Patients must have measurable progressive disease within the last 6 months, according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria;
- Patients must be willing to provide paired tumour biopsies for PD determination. Refer to section 5.6.3;
- Patients should fit into one of the categories described below:;
I. Metastatic adenocarcinoma of the pancreas;
Patients should have preferably received at least one line of systemic treatment for metastatic disease and preferably not more than 2 prior regimens for metastatic disease.;
II. Platinum-resistant ovarian carcinoma, defined as recurrence within 6 months after completion of prior platinum-based chemotherapy;
Patients should have preferably received no more than 5 previous lines of systemic treatment for metastatic disease;

III. Oesophageal carcinoma;
Patients with oesophageal carcinoma of adenocarcinoma- or squamous cell histology who have received preferably not more than 2 previous lines of systemic treatment for metastatic disease;
IV. Soft tissue sarcoma;
Patients should preferably have received no more than 2 previous lines of systemic treatment for metastatic disease.;

Exclusion criteria

- Serious concomitant non-oncological disease/illness;- Pregnancy or breastfeeding;- Active/symptomatic brain metastases;- Second malignancy;- Women or men who are sexually active and unwilling to use a medically acceptable method of contraception ;- Treatment with cytotoxic anti-cancer-therapies or investigational drugs within four weeks of the first treatment with the study medication

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):	22-07-2011
Enrollment:	45
Type:	Actual

Ethics review

Approved WMO

Date:	28-04-2011
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-11-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-12-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-10-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-11-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-12-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-02-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	07-03-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-06-2013
Application type:	Amendment
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Approved WMO Date:	20-06-2013
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Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-10-2013
Application type:	Amendment
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Approved WMO Date:	17-10-2013
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Approved WMO Date:	21-10-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-11-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-12-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	24-04-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-04-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-05-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-06-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-08-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-09-2014
Application type:	Amendment
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Approved WMO Date:	13-02-2015
Application type:	Amendment
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Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-04-2015
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	EUCTR2010-024609-10-NL
ClinicalTrials.gov	NCT01335269
CCMO	NL36602.078.11