A multi-center, open-label study to assess pharmacokinetics of TKI258 in adult cancer patients with normal and impaired hepatic function

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To evaluate the effects of mild, moderate or severe hepatic impairment versus normal hepatic function on the pharmacokinetics of TKI258 in patients with advanced solid tumor

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON39786

Source
ToetsingOnline

Brief title
TKI258 hepatic impairment trial

Condition

- Hepatic and hepatobiliary disorders
- Miscellaneous and site unspecified neoplasms benign

Synonym
hepatic impairment

Research involving
Human

Sponsors and support

Primary sponsor: Novartis

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

Intervention

Keyword: hepatic, pharmacokinetic, TKI258

Outcome measures

Primary outcome

Pharmacokinetic parameters of TKI258 including AUCinf following a single dose

and Cmax, Tmax, and AUClast following a single dose and at the steady state

Secondary outcome

Incidence of dose limiting toxicity (DLT) and other adverse events (AEs),

serious adverse events (SAE), and laboratory results (hematology, blood

chemistry) as assessed by the Common Terminology Criteria for Adverse Events

(CTCAE) v4.03

PK parameters and hepatic functional abnormalities (i.e. bilirubin, ALT/AST,

and Child-Pugh classification)

Best overall response (RECIST 1.1)

Study description

Background summary

TKI258 is a new investigational drug available as an oral formulation. In clinical studies, TKI258 has been investigated as a single agent in sefveral solid tumor studies. As of September 10, 2010, a total of 420 patients have received TKI258 treatment.

Hepatic impairment is one of the common co-morbidities in cancer patients.

Patients with hepatic impairment are at a higher risk to have a decreased ability to eliminate TKI258. Decreased drug clearance as a result of impaired organ function may lead to an increased systemic exposure and possibly toxicity.

Study objective

To evaluate the effects of mild, moderate or severe hepatic impairment versus normal hepatic function on the pharmacokinetics of TKI258 in patients with advanced solid tumor

Study design

Treatment period consists of a single-dose PK period and multiple dosing period on a 5 days on / 2 days off dosing schedule.
The purpose of this single-dose PK analysis is to obtain pharmacokinetics (PK) for a single dose of TKI258. A 2-day rest period was selected, based on the 28 hour half-life of a single dose of TKI258.

The multiple dosing period with TKI258 (on a 5 days on/2 days off dosing regimen) will start on Day 4 of Week 1 (Figure 6-1) and continue until disease progression, unacceptable toxicity, death or discontinuation from the study treatment for any other reason

Approximately 18-48 patients are expected to be enrolled in the study. Individual patients will be allocated to one of the three treatments groups based on their total bilirubin and ALT/AST levels on Day 1 (pre-dose). The enrollment to the individual treatment groups are in parallel, with at least 6 evaluable patients per treatment group. The mild hepatic impairment group may require 6-12 evaluable patients, whereas, moderate hepatic impairment group 6-18 evaluable patients. To the extent possible, the enrollment of the control group (Treatment Group 1, normal hepatic function) should be similar to the enrollment to Treatment Groups 2 (mild hepatic impairment) and 3 (moderate hepatic impairment in HCC patients only) with respect to age (±10 years) and body weight (±10 Kg). Therefore, enrollment in Treatment Group 1 will remain open until the enrollment in the two impairment groups (mild and moderate) is complete and a sufficient number of matching controls has been achieved for comparison, with a minimum of 6 evaluable patients in this treatment group. For Treatment Groups 2 and 3, patient enrollment will be done in a staggered fashion, one patient in every two weeks, which allows ongoing monitoring of safety data collected from the first two weeks before the next patient is treated. After the first 3 evaluable patients complete a 4-week treatment and study assessment as per protocol, the sponsor and investigators will review safety and PK data from the current treatment dose level and determine the next dose level for further evaluation.

Patients with severe hepatic impairment will start once an acceptable dose has been identified in the previous groups.

Intervention

Patients will receive, depending on the treatment group they are allocated to, 400 or 500 mg TKI258 orally administrated according a scheme of 5 days treatment, 2 days rest. During the trial, based on interim analysis of safety and pharmacokinetics, the dosing can be adjusted in favour of the patient.

Depending on the tolerance of the other group, patients in the severe hepatic impairment group will start on 100 of 200 mg TKI258

Study burden and risks

Adverse events of TKI258 as known to date from animal experiments and previous clinical trials. The main adverse events are
Diarrhea, Nausea, Vomiting, Fatigue, Decreased appetite , Headache, Dyspnea, Constipation, Dysgeusia , Abdominal pain, Rash, Hypertension , Weight decreased, Cough, Anemia, Dry skin, Edema peripheral, Dizziness, Dry mouth, Pyrexia, Stomatitis, Myalgia

Besides these the discomforts and risks during blood drawing: pain, fainting, bruising

More frequent visits to the hospital, more test than usual like blooddraws, ECG and ECHO

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 histologically or cytologically confirmed solid tumor, excluding breast cancer and lymphoma, that is either refractory to the standard therapy or has no available therapies. HCC patients with a diagnosis of advanced HCC according to the AASLD guidelines (Bruix and Sherman 2010)
2. Male or female patients * 18 years old
3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0, 1 or 2
4. Patients must meet the following criteria for laboratory values:
a. Absolute neutrophile count (ANC) * 1.5 x 109/L
b. Platelets * 75 x 109/L
c. Hemoglobin * 9 g/dL
d. Total bilirubin and ALT/AST levels as described in Table 5-1
e. Serum creatinine * 1.5 x ULN
f. Urine dipstick reading: Negative for proteinuria or, if documentation of +1 results for protein on dipstick reading, then total urinary protein * 500 mg and measured creatinine clearance * 50 mL/min/1.73m3 from a 24 hour urine collection
5. Patients must have measurable and/or non-measurable lesion(s) as assessed by Computer Tomography (CT) Scan or Magnetic Resonance Imaging (MRI) per RECIST 1.1
6. Patients who give a written informed consent obtained according to local guidelines

Exclusion criteria

1. Patients with known brain metastases or who have signs/symptoms attributable to brain metastases and have not been assessed by radiologic imaging (e.g. CT or MRI scan) to rule out the presence of metastases.
2. Patients who have received the last administration of chemotherapy or immunotherapy or hormone therapy the timeframe defined below after the end of the last treatment Cycle (prior to starting study drug), or who have not recovered from the side effects of such therapy:

a. Last administration of chemotherapy/immunotherapy/hormone therapy in a daily schedule * 7 days prior to starting study treatment
b. Last administration of chemotherapy/immunotherapy/hormone therapy in a weekly schedule * 2 weeks prior to starting study treatment
c. Last administration of chemotherapy/immunotherapy/hormone therapy in a 2-weekly schedule * 3 weeks prior to starting study treatment
d. Last administration of chemotherapy/immunotherapy/hormone therapy in a 3-weekly schedule * 4 weeks prior to starting study treatment
e. Last administration of chemotherapy/ immunotherapy/hormone therapy in a 4-weekly schedule * 5 weeks prior to starting study treatment
f. Last administration of nitrosourea, mitomycin-C * 6 weeks prior to starting study treatment
3. Patients who received small molecule targeted agents * 2 weeks prior to starting study treatment
4. Patients who have received radiotherapy * 4 weeks prior to starting the study treatment or who have not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions * 2 weeks prior to starting study treatment is allowed
5. Patients who have undergone major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) * 4 weeks prior to starting study treatment or who have not recovered from side effects of such therapy
6. Patients with another primary malignancy within 3 years prior to starting study drug, with the exception of adequately treated in-situ carcinoma of the uterine cervix, basal or squamous cell carcinoma or non-melanomatous skin cancer
7. Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
a. History or presence of serious uncontrolled ventricular arrhythmias
b. Clinically significant resting bradycardia (< 50 beats/minute)
c. LVEF assessed by 2-D echocardiogram (ECHO) < 50% or lower limit of normal (which ever is higher) or multiple gated acquisition scan (MUGA) < 45 % or lower limit of normal (which ever is higher)
d. Any of the following within 6 months prior to study entry: myocardial infarction (MI), severe/unstable angina, coronary artery bypass graft (CABG), congestive heart failure (CHF), cerebrovascular accident (CVA), transient ischemic attack (TIA)
e. Uncontrolled hypertension defined by a systolic blood pressure (SBP) * 160 mm Hg and/or diastolic blood pressure (DBP) * 100 mm Hg, with or without anti-hypertensive medication
8. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of TKI258 (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
9. Known history of human immunodeficiency virus (HIV) seropositivity (HIV testing is not mandatory)
10. Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. active or uncontrolled infection, with the exception of Hepatitis B or Hepatitis C in patients who have Hepatocellular Carcinoma (HCC), uncontrolled diabetes) that could cause unacceptable safety risks or compromise compliance with the protocol
11. Patients with known active bleeding (including bleeding from GI ulcers or esophageal varices) within 8 weeks (2 months) prior to baseline/screening visit or who have signs/symptoms attributable to portal hypertension and have not been assessed with upper GI endoscopy to rule out high-risk of GI bleeding

12. Patients with a history of pulmonary embolism (PE), or untreated deep venous thrombosis (DVT) within the past 6 months
13. Evidence of biliary sepsis in patients with biliary obstruction
14. Clinically significant third space fluid accumulation (i.e., ascites requiring tapping (despite use of diuretics) or pleural effusion that either requires tapping or is associated with shortness of breath)
15. HCC patients who have received liver transplant or who are listed for high urgent transplantationawaiting for immediate transplant
16. Patients who are currently receiving full dose anticoagulation treatment with therapeutic doses of warfarin or anti-platelet therapy (e.g., Plavix® [clopidogrel bisulfate]). However, treatment with low doses of warfarin (e.g., < 2 mg/day) or locally accepted low doses of acetylsalicyclic acid (up to 81 mg 100 mg daily) to prevent cardiovascular events or strokes is allowed.
17. Patients with known active alcohol abuse
18. Pregnant or breast-feeding women
19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using two forms of highly effective contraception during dosing and 30 days after the end of study treatment. Highly effective contraception methods include:
* Total abstinence, or
* Male or female sterilization or
* Combination of the following
a. Placement of an interuterine device (IUD) or intrauterine system (IUS)
b. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
* Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
* Use of oral, injected or implanted hormonal methods of contraception may be affected by cytochrome P450 interactions, and are therefore NOT considered effective for this study.
25. Patients with concurrent portal vein tumor thrombus, inferior vena cava tumor thrombus, or vascular invasion.
26. Patients who developed liver toxicities attributed to VEGF inhibitors or other treatments used during prior anti-cancer therapy.

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):	27-02-2012
Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nvt
Generic name:	Dovitinib

Ethics review

Approved WMO Date:	12-09-2011
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-11-2011
Application type:	First submission
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	21-12-2011
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	22-12-2011
Application type:	Amendment

Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	06-01-2012
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	12-07-2012
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	08-08-2012
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	20-08-2012
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	17-09-2012
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	19-09-2012
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	08-02-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO	

Date:	01-03-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-05-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-06-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-11-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-11-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-07-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

	Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-08-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2011-000103-41-NL
ClinicalTrials.gov	NCT01443481
CCMO	NL37661.068.11