An open-label, randomized, multi-center, Phase III study to compare the safety and efficacy of TKI258 versus sorafenib in patients with metastatic renal cell carcinoma after failure of anti-angiogenic (VEGF-targeted and mTOR inhibitor) therapies

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* To compare TKI258 vs. sorafenib with respect to progression-free survival (PFS) determined by central radiology assessment in patients with metastatic renal cell cancer (mRCC) after failure of anti-angiogenic (VEGF-targeted and mTOR inhibitor)...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON36586

Source
ToetsingOnline

Brief title
GOLD study

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Kidney cancer, Renal cell carcinoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: metastatic RCC, phase III, prior anti-angiogenic therapy, TKI258

Outcome measures

Primary outcome

Efficacy expressed as PFS, which is defined as the time from the date of randomization to the date of the first radiologically documented disease progression or death due to any cause. PFS will be assessed via a blinded, independent central review process. Clinical deterioration will not be considered as documented disease progression.

Secondary outcome

* Time to definitive worsening of Karnofsky performance status (KPS)

* Efficacy: PFS based on investigator assessment

* Efficacy: Best overall response rate (ORR) defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR) according to RECIST 1.1

* Safety parameters; Adverse drug reactions and serious adverse drug reactions, changes in hematology and chemistry values, including those associated with hepatic and renal function, and assessment of physical examinations and vital signs. CTCAE version 4.03 will be used

* Patient reported outcomes include:

* Disease-Related Symptoms of the FKSI (FKSI-DRS, Functional assessment of

cancer therapy Kidney symptom index * Disease related symptoms)

* Physical functioning scale (PF) of the EORTC QLQ-C30

* Global health status / QoL scale (QL) scores of the EORTC QLQ-C30

* Other EORTC QLQ-C30 dimensions

* PK of TKI258: plasma concentrations of TKI258 and relevant metabolites

Exploratory endpoints:

* Plasma biomarker assessments

*Tumor biomarker assessments

*Pharmacodynamics

*Genetic plymorphisms

Study description

Background summary

Renal cell carcinoma (RCC) is expected to account for more than 57,000 new diagnoses of cancer and over 12,000 cancer deaths in the United States during 2009 (American Cancer Society 2009). In Europe, the number of new diagnoses and cancer deaths from RCC is approximately double that in the United States (Ferlay et al. 2007). The treatment of mRCC has recently evolved from being predominantly cytokine-based to being grounded in the use of drugs targeting vascular endothelial growth factor and platelet-derived growth factor pathways. (Hicklin et al. 2005). Sunitinib and sorafenib, both multiple tyrosine kinase inhibitors that target the VEGF pathways, have become the standard of care for patients with advanced kidney cancer. Subsequently, other anti-angiogenic agents including temsirolimus, bevacizumab plus interferon alpha and pazopanib have been also approved for advanced RCC. Everolimus is the only approved agent after failure of VEGF-targeted therapy. Although, all these agents represent significant progress in the treatment of advanced
kidney cancer, it is clear that these therapies offer limited therapeutic benefit to patients with advanced kidney cancer and there is still an unmet

medical need, with no approved agent after failure of everolimus therapy. Thus, the development of new therapies that could further improve PFS and OS outcomes is essential. TKI258 is an inhibitor of RTKs (FGFR, VEGFR, PDGFR*, CSF 1R, c-Kit, RET, TrkA and FLT3) that mediate tumor cell proliferation and survival. Inhibition of these growth factor receptor kinases should provide powerful and broad inhibition of the angiogenesis process and provide potent anti-tumor activities. Additional blockade of the FGF pathway can overcome resistance to VEGFR inhibitors, emphasizing the importance of FGFR and specifically the need for multi-targeted inhibitors. In previous TKI258 melanoma and mRCC trials, biomarker analyses have demonstrated FGFR pathway inhibition in patients. Patients may have benefited from TKI258 through inhibition of two major angiogenic pathways required for tumor growth. Therefore, the use of TKI258 in advanced kidney cancer patients who have progression on prior VEGF-targeted and mTOR
inhibitor therapies provides an ideal setting to test whether this drug has additional therapeutic properties over other VEGF/PDGF. Results in the current phase I study show that treatment with TKI258 is well tolerated (Section 1.2.3) and offers clinical benefit in patients who had already failed prior standard VEGF-targeted and mTOR inhibitor therapies.

Study objective

* To compare TKI258 vs. sorafenib with respect to progression-free survival (PFS) determined by central radiology assessment in patients with metastatic renal cell cancer (mRCC) after failure of anti-angiogenic (VEGF-targeted and mTOR inhibitor) therapies.

Key Secondary objective:
* To compare TKI258 vs. sorafenib with respect to overall survival (OS)

Key Secondary objective:
* To assess TKI258 vs. sorafenib with respect to:
* PFS determined by local review of tumor assessments
* Overall response rate (ORR) by central and local radiology review
* Safety
* Patient-reported outcomes (PROs), including:
1. Disease-related symptoms using the Functional assessment of cancer therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS)
2. Quality of Life (QoL) using the EORTC QLQ-C30 questionnaire
* To characterize the pharmacokinetics of TKI258 in patients with mRCC

Exploratory objective:
* To assess pharmacodynamic (PD) changes from baseline in circulating growth factors and soluble receptors
* To correlate tissue expression of biomarkers and somatic mutations related to TKI258 action pathways with clinical endpoints
* To correlate TKI258 plasma concentration with concentrations of circulating

growth factors and soluble receptors (e.g., bFGF, VEGF, PLGF, sVEFR1 and 2, FGF23), tumor markers (if available), and clinical endpoints
* To explore genetic polymorphisms that may affect TKI258 metabolism and response in blood samples

Study design

This is an open-label, randomized, multi-center, Phase III study. Patients will be stratified based on the MSKCC risk groups (favorable, intermediate, and poor). Approximately 550 patients will be randomized (1:1 ratio) into 2 treatment arms (275 patients will be randomized to TKI258 and 275 patients to sorafenib [the control arm]). Patients may continue to receive study treatment until disease progression (determined according to RECIST 1.1), unacceptable toxicity, death or discontinuation from the study for any other reason. There is no treatment crossover (either from TKI258 to sorafenib or from sorafenib to TKI258) within the study. After radiologically documented disease progression is observed on TKI258 or sorafenib, the investigator is free to prescribe any treatment he/she deems appropriate. Patients who discontinued TKI258 or sorafenib for any reason will continue to have tumor assessments. Patients who discontinue the study treatment for any reasons (except for radiological progression, death, or lost to follow up) should continue to have scans performed as defined in the schedule of procedures until radiological progression. These patients should continue to have scans performed for up to 4 months following the start of any new anticancer therapy. All scans will be centrally reviewed. After follow-up phase, all patients will be followed for survival every 8 weeks until at least 386 deaths are observed. This is estimated to occur around 38 months after the randomization of the first patient.

Intervention

Patients who are randomized to the TKI258 treatment arm will receive 500 mg of TKI258 orally on 5 days on/2 days off dosing schedule. Patients who are randomized to the sorafenib control arm will receive a total of 400 mg (2 x 200 mg tablets) orally taken twice daily. Patients may continue to receive study treatment until disease, unacceptable toxicity, death or discontinuation from the study for any other reason.

Study burden and risks

Study assessments will be performed at screening, Week (W)1D1, W2D5, W4D5, W6D5, Course (C)3D1 and CxD1 of every consecutive cycle. Patients will receive either TKI258 or sorafenib (1:1 ratio) in a 28 day cycle. Patients may continue to receive study treatment until disease, unacceptable toxicity, death or discontinuation from the study for any other reason, whereupon all patients will complete the End of Treatment visit. Patients who discontinue the study

treatment for any reasons (except for radiological progression, death, or lost to follow up) should continue to have scans performed as defined in the schedule of procedures until radiological progression. These patients should continue to have scans performed for up to 4 months following the start of any new anticancer therapy. After follow-up phase, all patients will be followed for survival every 8 weeks until at least 386 deaths are observed. Please refer to Table 7-1, page 57 till 63.

Risks:
* Toxicity due to the use of TKI258 (especially nausea, fatigue, diarrhea and vomiting)
* Toxicity due to the use of sorafenib (especially hand-foot skin reactions, fatigue, hypertension and hemorrhage)
* Reaction to the use of contrast fluid (used for CT/MUGA scans)
* Side effects of blood sampling

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

1. Written informed according to local guidelines must be obtained before any study assessments are performed. ;2. Age * 18 years old.;3. Patients with metastatic renal cell carcinoma (mRCC) with histological or cytological confirmation of clear cell carcinoma or a component of clear cell;4. Patients must have received one and only one prior VEGF-targeted therapy and one and only one prior mTOR inhibitor in the metastatic setting. One prior systemic VEGF-targeted therapy could be sunitinib, or pazopanib, or axitinib, or tivozanib or bevacizumab and one prior mTOR inhibitor could be either everolimus or temsirolimus or ridaforolimus.
Patients receiving adjuvant VEGF targeted therapy or mTOR inhibitors may have this treatment count as part of one prior VEGF or one prior mTOR therapy if disease progression occurred on or within 6 months of stopping the adjuvant treatment.;5. Prior treatment with cytokines and anti-cancer vaccines is permitted.;6. Patients must have had disease progression on or within 6 months of stopping the last therapy VEGF-targeted agent and/or the mTOR inhibitor therapy.;7. Patients must have at least one measurable lesion at baseline (according to RECIST 1.1) using Computer Tomography (CT) Scan or Magnetic Resonance Imaging (MRI). If skin lesions are selected as target lesions at baseline, follow procedure specified on Section 7.6.4. ;8. Karnofsky performance status * 70%;9. Patients must have the following laboratory values:;* Absolute Neutrophil Count (ANC) * 1.5 x 109/L;* Platelets * 100 x 109/L;* Hemoglobin (Hgb) > 9 g/dL;* Serum total bilirubin: * 1.5 x ULN;* ALT and AST * 3.0 x ULN (Patients with known liver metastases: AST and ALT * 5.0 x ULN);* Serum creatinine * 1.5 x ULN

Exclusion criteria

1. Patients who have previously received sorafenib therapy in the neoadjuvant, adjuvant or metastatic setting;2. Patients who have previously received TKI258 or other VEGFR such as brivanib in the neoadjuvant, adjuvant or metastatic setting ;3. Patients with brain metastases or any history of brain metastases. Radiological imaging (e.g. CT or MRI scan) of the brain is required at screening/baseline ;4. Patients with another primary malignancy within 3 years prior to starting study treatment, with the exception of adequately treated basal cell carcinoma, squamous cell carcinoma or other non-melanomatous skin cancer, or in-situ carcinoma of the uterine cervix;5. Patients who have received the last administration of an anticancer targeted small molecule therapy * 2 weeks prior to starting study treatment (e.g. sunitinib, pazopanib, axitinib, everolimus, temsirolimus), or who have not recovered from the side effects of such therapy;6. Patients who have received the last administration of nitrosurea or mitomycin-C * 6 weeks prior to starting study treatment, or who have not recovered from the side effects of such therapy;7. Patients who have received the last administration of an anticancer monoclonal antibody, immunotherapy, or chemotherapy (except nitrosureas and mitomycin-C) * 4 weeks prior to starting study treatment or who have not recovered from the side effects of such therapy;8. 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. ;9. 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;10. Patients with a history of pulmonary embolism (PE), or untreated deep venous thrombosis (DVT) within the past 6 months. ;11. Patients with any of the following concurrent severe and/or uncontrolled medical conditions which could compromise participation in the study:;* Impaired cardiac function or clinically significant cardiac diseases, including any of the following:;- History or presence of serious uncontrolled ventricular arrhythmias;- Clinically significant resting bradycardia;- LVEF assessed by 2-D echocardiogram (ECHO) or multiple gated acquisition scan (MUGA), < 45%;- Any of the following within 6 months prior to starting study treatment: myocardial infarction (MI), severe/unstable angina, Coronary Artery Bypass Graft (CABG), Congestive Heart Failure (CHF), Cerebrovascular Accident (CVA), Transient Ischemic Attack (TIA) ;- Uncontrolled hypertension defined by a SBP * 160 mm Hg and/or DBP * 100 mm Hg, with or without anti-hypertensive medication. Initiation or adjustment of antihypertensive medication (s) is allowed prior to study entry. ;* 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);* Cirrhosis, chronic active hepatitis or chronic persistent hepatitis;* Known diagnosis of human immunodeficiency virus (HIV) infection. HIV testing is not mandatory but it should be performed if locally required;* Patients who are currently receiving full dose anticoagulation treatment with therapeutic doses of warfarin or anti-platelet therapy (e.g., Plavix® [clopidogrel bisulfate]). Treatment with locally accepted low dose of acetylsalicyclic acid (81 mg or 100mg daily) to prevent cardiovascular events or strokes is allowed.;* Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. active or uncontrolled infection, uncontrolled diabetes) that could cause unacceptable safety risks or compromise compliance with the protocol;12. Pregnant or breast-feeding women;13. Women of child-bearing potential not employing an effective method of birth control. Highly effective contraception (e.g. condom with spermicidal jelly, foam suppository or film, diaphragm with spermicide, male condom and diaphragm with spermicide) must be used by both sexes during the study and must be continued for 8 weeks after the end of study treatment. Oral, implantable, or injectable contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study. Women of child-bearing potential, defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (e.g., who has had menses any time in the preceding 12 consecutive months), must have a negative serum pregnancy test * 14 days prior to starting study treatment.;14. Fertile males not willing to use contraception, as stated above;15. Patients unwilling or unable to comply with the protocol

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-06-2011
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nexavar
Generic name:	Sorafenib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	TKI258
Generic name:	onbekend

Ethics review

Approved WMO Date:	24-11-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-03-2011

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-04-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-05-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-06-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-07-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-09-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-09-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-11-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	06-12-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-04-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-04-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-05-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-07-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-09-2012
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)
Approved WMO Date:	18-02-2013
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-02-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-06-2013
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	EUCTR2009-015459-25-NL
ClinicalTrials.gov	NCT01223027
CCMO	NL33564.078.10