Phase 3 Trial of Dovitinib (TKI258) Versus Sorafenib in Patients With Metastatic Renal Cell Carcinoma After Failure of Antiangiogenic (VEGF-Targeted and mTOR Inhibitor) Therapies

Robert Motzer,[1] Camillo Porta,[2] Georg A. Bjarnason,[3] Cezary Szczylik,[4] Sun Young Rha,[5] Emilio Esteban,[6] Ugo De Giorgi,[7] Mary MacKenzie,[8] Paul Mainwaring,[9] Scott North,[10] Roberto Sabbatini,[11] Istvan Bodrogi,[12] Fairooz Kabbinavar,[13] Giacomo Cartenì,[14] Cora N. Sternberg,[15] Nicholas Vogelzang,[16] Michael Shi,[17] Gladys Urbanowitz,[17] Bernard Escudier[18]

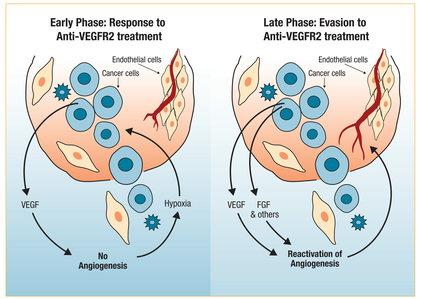
[1]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [2]Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy; [3]Sunnybrook Odette Cancer Centre, Toronto, Ontario, Canada; [4]Wojskowy Instytut Medyczny, Warsaw, Poland; [5]Yonsei Cancer Center, Seoul, Korea; [6]Hospital General de Asturias, Oviedo, Spain; [7]IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (I.R.S.T.), Meldola, Italy; [8]London Regional Cancer Centre, London, Ontario, Canada; [9]Haematology & Oncology Clinics of Australia, Brisbane, Australia; [10]Cross Cancer Institute, Edmonton, Alberta, Canada; [11]Azienda Ospedaliero Universitaria, Policlinico di Modena, Modena, Italy; [12]Országos Onkológiai Intézet, Budapest, Hungary; [13]University of California Los Angeles, Los Angeles, CA, USA; [14]Azienda Ospedaliera di Rilievo Nazionale A. Cardarelli, Naples, Italy; [15]San Camillo Forlanini Hospital, Department of Medical Oncology, Rome, Italy; [16]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [17]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [18]Institut Gustave-Roussy, Villejuif, France

BACKGROUND

FGFR Signaling and Tumor Escape From Targeted Therapies

- Therapies targeting vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) signaling have become standard first- and second-line treatments in metastatic renal cell carcinoma (mRCC)[1-3]
  - VEGF-targeted therapies include sunitinib, sorafenib, pazopanib, and bevacizumab
  - mTOR-targeted therapies include temsirolimus and everolimus
- Tumor escape from VEGF- and mTOR-targeted therapies in mRCC may involve signaling through other pathways, including the fibroblast growth factor receptor (FGFR) pathway (**Figure 1**)[4]
  - Fibroblast growth factor 2 (FGF2) was upregulated during antiangiogenic escape in an RCC tumor model[5]
  - FGF2 suppressed the antiangiogenic effects of sunitinib on cultured endothelial cells[6]
- Inhibition of FGFR signaling may have clinical effects in patients who have previously progressed following treatment with VEGF- and mTOR-targeted therapies

Figure 1. Adaptive Rescue From VEGF Blockade via the FGFR Axis

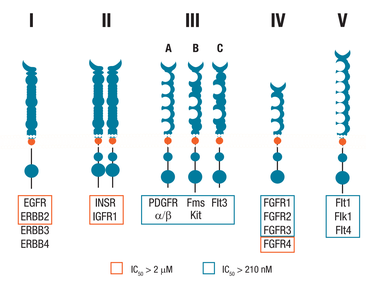


Adapted from Casanovas O, Hicklin DJ, Bergers G, et al.[4]

Dovitinib in mRCC

- Dovitinib (TKI258) is an oral tyrosine kinase inhibitor of FGFR, as well as VEGF receptor (VEGFR), C-kit and platelet-derived growth factor receptor (PDGFR), with half maximal inhibitory concentration values (IC_{50}) of ≈ 10 nM (**Figure 2**)[7,8]
- Dovitinib administered at 500 mg/day on a 5-days-on/2-days-off schedule demonstrated promising antitumor effects and was well tolerated in a phase 2 study of 59 patients with mRCC, many of whom had failed prior VEGF-targeted and mTOR inhibitor therapies[9]
  - Best clinical response (by Response Evaluation Criteria In Solid Tumors [RECIST] version 1.0) was partial response in 3% of patients and stable disease ≥ 2 months in 49% of patients
  - The most frequent grade 3/4 adverse events (AEs) were asthenia (13.6%), fatigue (13.6%), hypertriglyceridemia (11.9%), diarrhea (10.2%), and hypertension (10.2%)
- The current study is designed to evaluate the efficacy and safety of dovitinib as third-line therapy in patients with mRCC

Figure 2. Dovitinib Inhibits FGFRs and Other Class III, IV, and V Receptor Tyrosine Kinases



Cellular Autophosphorylation Assays				
Target	FGFR1	FGFR2	FGFR3	VEGFR2
Dovitinib IC_{50} nM	166	78	55	40

Enzymatic Assay	
Target	Dovitinib IC_{50} (nM)
FGFR1	8
FGFR2	40
FGFR3	9
FLT3	1
c-KIT	2
VEGFR1	10
VEGFR2	13
VEGFR3	8
PDGFRβ	12
CSFR1	15

CSFR1, colony stimulating factor receptor 1; **EGFR**, epidermal growth factor receptor; **IGFR1**, insulin-like growth factor receptor 1. Adapted from Lee SH, Lopes de Menezes D, Vora J, et al[7] and Grassot J, Mouchiroud G, Perrière G.[8] Red and blue boxes indicate kinases that have been tested.

STUDY DESIGN

Overview

- This is a multicenter, open-label, randomized, parallel-group phase 3 trial comparing the efficacy and safety of dovitinib vs sorafenib (**Figure 3**)
  - ClinicalTrials.gov NCT01223027
- Patients who have failed treatment with 1 prior VEGF-targeted therapy (excluding sorafenib) and 1 prior mTOR-targeted therapy
  - Treatment failure is defined as disease progression during treatment or intolerance to treatment with disease progression within 6 months following discontinuation of the most recent therapy

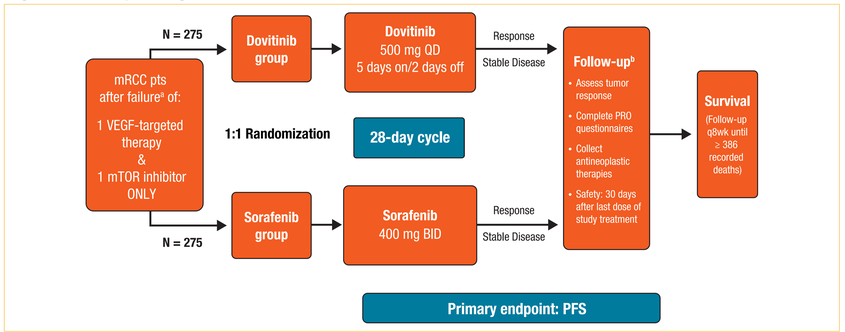
Outcome Measures

- The primary outcome measure is PFS per central radiology assessment
- The key secondary outcome measure is overall survival

Outcome Measures *(continued)*

- Other secondary outcome measures include
  - Time to definitive worsening of Karnofsky performance status
  - PFS per local review of tumor assessments
  - Overall response rate (complete or partial response) by RECIST version 1.1, per central and local radiology assessments
  - Incidence of AEs and serious AEs
  - Changes in vital signs, electrocardiogram, and laboratory results
  - PROs, including
    - Functional Assessment of Cancer Therapy Kidney Symptom Index—Disease-Related Symptoms Questionnaire (FKSI-DRS): effects on disease-related symptoms
    - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30): patient symptoms, function, and quality of life
  - Dovitinib plasma concentration
- Exploratory analysis includes evaluation of plasma and tumor biomarkers for FGFR and VEGF receptor inhibition

Figure 3. Study Design



[a] Patients must have had disease progression on or within 6 months of stopping their last therapy.
[b] Patients who discontinue the study treatment for any reason continue to have scans until disease progression is confirmed by the central radiologist.
BID, twice daily; **PFS**, progression-free survival; **PRO**, patient reported outcomes, **q8wk**, every 8 weeks; **QD**, once daily.

PATIENT POPULATION AND ELIGIBILITY

Key Inclusion Criteria

- Age ≥ 18 years
- mRCC with histologic or cytologic confirmation of clear cell carcinoma or a component of clear cell carcinoma
- Prior treatment with only 1 VEGF-targeted therapy and only 1 mTOR inhibitor in the metastatic setting
  - VEGF-targeted therapy could be sunitinib, pazopanib, axitinib, tivozanib, or bevacizumab
  - mTOR inhibitor could be everolimus, temsirolimus, or ridaforolimus
  - Adjuvant treatment with VEGF-targeted therapy or mTOR inhibitors may count as part of 1 prior VEGF or 1 prior mTOR therapy if disease progression occurred on or within 6 months of stopping the adjuvant treatment
- Prior treatment with cytokines and anticancer vaccines permitted
- Disease progression on or within 6 months of stopping the VEGF-targeted agent and/or the mTOR inhibitor therapy
- At least 1 measurable lesion at baseline (by RECIST version 1.1) assessed by computed tomography (CT) scan or magnetic resonance imaging (MRI)
- Karnofsky performance status ≥ 70%
- Laboratory values within the following parameters
  - Absolute neutrophil count ≥ 1.5 × 10^9/L
  - Platelets ≥ 100 × 10^9/L
  - Hemoglobin > 9 g/dL
  - Serum total bilirubin ≤ 1.5 × upper limit of normal (ULN)
  - Alanine aminotransferase and aspartate aminotransferase ≤ 3.0 × ULN (with or without liver metastases)
  - Serum creatinine ≤ 1.5 × ULN

Key Exclusion Criteria

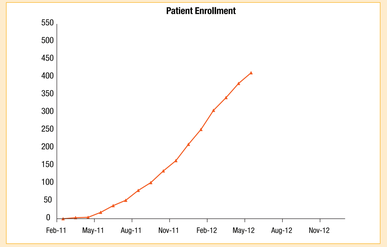
- Previous sorafenib therapy in the neoadjuvant, adjuvant, or metastatic setting
- Previous treatment with dovitinib or other FGFR inhibitors (such as brivanib) in the neoadjuvant, adjuvant, or metastatic setting
- Brain metastases or a history of brain metastases
  - Radiologic imaging (eg, CT or MRI scan) of the brain is required at screening/baseline
- Another primary malignancy within 3 years before starting study treatment (except adequately treated basal cell carcinoma, squamous cell carcinoma, or other nonmelanomatous skin cancer or in situ carcinoma of the uterine cervix)
- Administration of an anticancer-targeted small-molecule therapy ≤ 2 weeks before starting study treatment (eg, sunitinib, pazopanib, axitinib, everolimus, temsirolimus) or not recovered from the side effects of such therapy
- Treatment with any of the following anticancer therapies within the listed time frame or currently experiencing adverse effects from these treatments
  - ≤ 6 weeks before starting study treatment: nitrosourea or mitomycin C
  - ≤ 4 weeks before starting study treatment: anticancer monoclonal antibody, immunotherapy, chemotherapy (except nitrosourea and mitomycin C), or radiotherapy
    - Palliative radiotherapy for bone lesions ≤ 2 weeks before starting study treatment is allowed
- Major surgery (eg, intrathoracic, intra-abdominal, or intrapelvic) ≤ 4 weeks before starting study treatment or not recovered from the side effects of such surgery
- History of pulmonary embolism or untreated deep venous thrombosis within the past 6 months
- Concurrent severe and/or uncontrolled medical conditions that could compromise participation in the study, including
  - Impaired cardiac function or clinically significant cardiac disease
  - Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of dovitinib (eg, 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 infection; testing is not mandatory
  - Patients who are currently receiving full-dose anticoagulation treatment with therapeutic doses of warfarin or antiplatelet therapy; treatment with locally accepted low-dose acetylsalicylic acid to prevent cardiovascular events or strokes is allowed
- Pregnant or breastfeeding women or women of childbearing potential who are biologically able to conceive and are not employing 2 forms of highly effective contraception
- Fertile males not willing to use contraception

PATIENT ASSESSMENT AND FOLLOW-UP

- Baseline phase
  - Patient screening assessments are performed within 28 days before the first dose of study medication
  - Baseline radiologic tumor assessments, brain CT or MRI, and other specified assessments are conducted within 14 days before the start of study medication
  - Memorial Sloan-Kettering Cancer Center risk factors assessed for patient stratification by risk group
    - Karnofsky performance status < 80%
    - Low serum hemoglobin (≤ 13 g/dL for men and ≤ 11.5 g/dL for women)
    - Corrected serum calcium ≥ 10 mg/dL
- Treatment phase
  - Begins with administration of the first dose of study treatment, within 7 days of randomization
  - Radiologic tumor evaluation is performed every 8 weeks during the first year of treatment and every 12 weeks at the start of the second year of treatment
  - AEs are assessed throughout the treatment phase and 30 days after the last dose of study treatment
  - Ends when disease progression (based on RECIST version 1.1), unacceptable toxicity, death, or discontinuation from the study for any other reason occurs
    - Patients are required to complete an end-of-study visit within 7 days of discontinuing study medication
- Follow-up phase
  - Radiologic tumor assessments are performed during the 4 months following discontinuation of treatment
    - Patients who discontinued the study because of unacceptable toxicity, unconfirmed disease progression by the central radiologist, or other reasons should continue tumor assessments for ≤ 4 months or until the start of any new anticancer therapy
  - AEs are monitored for 30 days after discontinuation of treatment
- Survival follow-up phase
  - Patients are followed up for survival every 8 weeks until ≥ 386 deaths are observed
    - Estimated to occur ≈ 38 months after randomization of the first patient

CURRENT ENROLLMENT

- As of 21 May 2012, 412 patients are currently enrolled at 150 centers in Australia, the European Union (Belgium, France, Germany, Greece, Austria, Czech Republic, Italy, Netherlands, Poland, Hungary, Norway, Slovakia, Spain, Sweden, UK, and Switzerland), North America (US and Canada), Republic of Korea, Thailand, Japan, South America (Argentina, Brazil, and Colombia), and Israel
- Recruitment is ongoing



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DISCLOSURES

- Dr Motzer has served as a consultant or advisor for Pfizer, and has received research funding from AVEO, GlaxoSmithKline (GSK), and Novartis
- Dr Porta has served as a consultant or advisor for and has received honoraria from Novartis, Bayer-Schering, Pfizer, Hoffmann-La Roche, and GSK, and has received research funding from Novartis and Bayer-Schering
- Drs Bjarnason and Mainwaring have served as consultants or advisors for and have received honoraria from Novartis
- Dr Szczylik has served as a consultant or advisor for Novartis
- Drs Rha, Esteban, De Giorgi, Bodrogi, Kabbinavar, and Cartenì have nothing to disclose
- Drs MacKenzie and North have received honoraria from Novartis
- Dr Sabbatini has served as a consultant or advisor for and has received honoraria from Novartis, Bayer-Schering, Pfizer, Hoffmann-La Roche, and GSK
- Dr Sternberg has received honoraria from Novartis, GSK, and Pfizer
- Dr Vogelzang has served as a consultant or advisor for Amgen, ArQule, Bayer, Eisai, Boehringer Ingelheim, Celgene, Clinical Care Options, Cougar Biotechnology, J&J/Centocor, Dendreon, Genentech, GSK, Lilly, Novartis, Pfizer, sanofi-aventis, Veridex, Wilex, and Takeda/Millennium, has received research funding from Algeta, ArQule, Cougar Biotechnology, J&J/Centocor, GSK, Novartis, Pfizer, Takeda/Millennium, Tokai, Veridex, and Wilex, and is an employee of US Oncology
- Dr Shi and Ms Urbanowitz are employees of Novartis
- Dr Escudier has served as a consultant or advisor for Novartis, Pfizer, Bayer, GSK, and AVEO

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