A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Ramucirumab plus Docetaxel versus Placebo plus Docetaxel in Patients with Locally Advanced or Unresectable or Metastatic Urothelial Carcinoma Who Progressed on or after Platinum-Based Therapy.

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

Summary

ID

NL-OMON47462

Source
ToetsingOnline

Brief title
RANGE

Condition

- Renal and urinary tract neoplasms malignant and unspecified
- Bladder and bladder neck disorders (excl calculi)

Synonym
Advanced, unresectable or metastatic urothelial carcinoma / Bladder cancer

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: Eli Lilly and Company

Intervention

Keyword: Confirmatory Phase 3 Study, CYRAMZA (Ramucirumab), Urothelial Carcinoma in the second line, VEGF-receptor 2 antibody

Outcome measures

Primary outcome

The primary efficacy measure is progression-free survival (PFS).

Patients will be evaluated for response according to Response Evaluation

Criteria in Solid Tumors, Version 1.1 (RECIST v 1.1)

Secondary outcome

Overall survival (OS): The time from the date of randomization to the date of

death from any cause.

Objective Response Rate (ORR): The number of randomized patients who achieve a

best response of CR or PR, using the investigator response assessments, divided

by the total number of patients randomized to that study arm, based on the

achievement of measurement criteria. RECIST 1.1 will be used to make the

determination in this trial.

Disease control rate (DCR): The proportion of randomized patients achieving a

best response of CR, PR, or SD. Stable

disease definition per RECIST and must achieve a minimum duration of 5 weeks

from randomization.

Duration ofresponse (DOR): DOR is defined only for responders (patients with

CR or PR [confirmation not required]).

It is measured from the date of first evidence of CR or PR to the date of

objective progression or the date of death due to any cause, whichever is

earlier. If a responder is not known to have died or have objective progression

as of the data inclusion cutoff date, DOR will be censored at the date of the

last complete objective progression-free disease assessment.

Study description

Background summary

Efficacy data from the 75% interim analysis for the Phase 2 Study I4Y-IE-JCDC (JCDC) showed a clinically significant improvement in progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR) when ramucirumab was given with docetaxel versus docetaxel alone. Furthermore, early evaluation of overall survival (OS; 43% censoring) demonstrated survival results trending in favor of the ramucirumab arm. The combination was well tolerated. As a result, the current confirmatory Phase 3 Study I4T-MC-JVDC (JVDC) is
planned.

Study objective

The primary objective of this study is to compare the progression-free survival (PFS) of ramucirumab in combination with docetaxel with the PFS of placebo in combination with docetaxel, in patients with locally advanced or unresectable or metastatic urothelial carcinoma who have had disease progression on or after one prior first-line platinum-based chemotherapy.

The secondary objectives of this study are to compare each of the following variables between the treatment arms:
- overall survival (OS) time
- objective response rate (ORR; complete response [CR] + partial response [PR]) and disease control rate (DCR)
- duration of response (DOR)
- safety profile
- patient-reported outcome (PRO) measures (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 [EORTC QLQ-C30] and EQ-5D-5L)

Secondary objectives also include the evaluation of:
- the pharmacokinetic profile of ramucirumab
- the immunogenicity of ramucirumab (anti-ramucirumab antibodies)

The exploratory objectives of this study are to:
- assess the change in tumor size in patients with measurable disease
- examine biomarkers relevant to ramucirumab, angiogenesis, and the disease state, and to correlate these markers to clinical outcome

Study design

Phase 3, randomized, double-blind, placebo-controlled study of ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or unresectable or metastatic urothelial carcinoma who progressed on or after one prior first-line platinum-based chemotherapy. Patients will be randomized 1:1 to receive one of these study regimens on Day 1 of each 21-day cycle: ramucirumab (10 mg/kg) intravenously (I.V.) plus docetaxel (75 mg/m2) I.V. OR placebo (10 mg/kg volume equivalent) I.V. plus docetaxel (75 mg/m2) I.V. Provided no prespecified discontinuation criteria have been met (including radiographic documentation of disease progression, toxicity requiring cessation, protocol noncompliance, or withdrawal of consent), treatment with docetaxel may continue for up to six 21-day cycles (up to 4 additional cycles of docetaxel [maximum of 10 cycles total] may be administered with approval of the Lilly clinical research physician [CRP]/clinical research scientist [CRS] or designee). Treatment with ramucirumab or placebo (monotherapy) may continue on 21-day cycles until at least one discontinuation criterion is met. This is an outpatient study.

Intervention

Experimental treatment arm A: receives ramucirumab plus docetaxel
Control (placebo)- arm B: receives placebo plus docetaxel

Ramucirumab will be administered as an IV infusion at a dose of 10 mg/kg on Day 1 every 21 days.

Docetaxel will be administered as an IV infusion at a dose of 75 mg/m2 on Day 1 every 21 days.

Randomisation 1:1

Study burden and risks

There are risks associated with the use of the study drug, docetaxel and the study procedures.
You will find an overview in the risks appendix of the patient Information folder (appendix 3). In addition, the combination
of medicines and the study procedures can come with other, unknown risks.
Because the patients who participate In this study have a serious disease and the treatment options are limited, It is of
importance to develop medicines that can Increase life duration and quality of life as much as possible.
Although the drug Is tested as a potential treatment for this form of urothelial carcinoma, it is possible that the subject does not
experience any medical benefit. The results of the study could lead to information where patients benefit from in the
future.

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

1) Histologically or cytologically confirmed, locally advanced or unresectable or metastatic urothelial (transitional cell) carcinoma of the bladder, urethra, ureter, or renal pelvis. Patients with mixed pathology are eligible only if they have predominantly transitional cell tumor based on local pathology review.;2) Demonstrated disease progression while on a platinum-containing regimen in the first-line setting or within 14 months after completing the first-line platinum regimen. Patients who received treatment with one immune checkpoint inhibitor (for example PD-1, PDL1, CTLA4) regimen may have a longer interval since prior platinum-containing therapy (<=24 months), as noted in Inclusion Criterion [4].;3) A life expectancy of >=3 months, in the judgment of the investigator.;4) The patient has received no more than one prior systemic chemotherapy regimen in the relapsed or metastatic setting. Prior cytotoxic therapy in an adjuvant or neoadjuvant setting is not considered as a prior line of systemic chemotherapy in the relapsed or metastatic setting. Prior treatment with intravesicular chemotherapy, bacillus Calmette-Guérin (BCG), or platinum given as a radiation-sensitizing agent will not be considered as a systemic line of treatment. Prior treatment with no more than one prior immune checkpoint inhibitor is permitted and will not be considered as a line of systemic chemotherapy. Patients enrolling after immune checkpoint inhibitor therapy must have demonstrated disease progression while on that therapy or within 24 months after the last dose of that therapy.;5) Measurable disease or nonmeasurable but evaluable disease as defined by Response Evaluation Criteria in Solid Tumors, Version 1.1 ;6) Resolution, except where otherwise stated in the inclusion criteria, of all clinically significant toxic effects of prior chemotherapy, surgery, or radiotherapy to Grade <=1 by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.;7) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.;8) The patient has adequate hematologic function and has not received blood or blood components transfusion within 2 weeks prior to the laboratory test.;9) Adequate coagulation function as defined by international normalized ratio (INR) <=1.5 and a partial thromboplastin time (PTT) <=1.5 × upper limit of normal (ULN) if not receiving anticoagulation therapy. Patients on full-dose anticoagulation must be on a stable dose of oral anticoagulant or low molecular weight heparin. If on warfarin, the patient must have an INR <=3 and have no active bleeding (defined as within 14 days prior to randomization, excluding trace hematuria) or pathological condition that carries a high risk of bleeding.;10) Adequate hepatic function as defined by bilirubin within normal limits (WNL), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <=3.0 × ULN, and alkaline phosphatase (AP) <=2.5 × ULN.;11) The patient does not have:;• cirrhosis at a level of Child-Pugh B (or worse), or;• cirrhosis and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or

paracentesis.;12) Adequate renal function as defined by creatinine clearance >30 mL/min either as measured by 24-hour urine collection or as calculated.;13) The patient*s urinary protein is <=1+ on dipstick or routine urinalysis; if urine protein >=2+, a 24-hour urine collection must demonstrate <2 g of protein in 24 hours.;14) The patient, if female, is surgically sterile, postmenopausal, or agrees to use a highly effective method of contraception during and for 12 weeks after the treatment period. The patient, if male, is surgically sterile or agrees to use a reliable method of contraception and to not donate sperm during and for 12 weeks after the treatment period or country requirements, whichever is longer.;15) The patient is able to provide signed informed consent and is amenable to compliance with protocol schedules and testing.;16) The patient is >=18 years of age ;17) The patient is willing to provide blood, urine, and tissue samples for research purposes. Submission of blood and urine specimens is mandatory for participation in this study, unless restricted per local regulations. If prior archived tumor specimens are available, and unless restricted by local regulations, submission of archived tumor tissue is mandatory. If an archived specimen is not available, submission of a newly acquired biopsy is requested when biopsy is safe and feasible.

Exclusion criteria

18) The patient has received more than one prior systemic chemotherapy regimen for metastatic disease (except as noted in Inclusion Criterion [4]). A treatment regimen must consist of a minimum of 2 cycles to be considered as a prior regimen.;19) The patient has received prior systemic taxane therapy for TCC of the bladder, urethra, ureter, or renal pelvis in any setting (neoadjuvant, adjuvant, metastatic). Prior intravesical taxane therapy is allowed and will not be considered as a prior line of systemic therapy.;20) The patient has received more than one prior antiangiogenic agent (that is, bevacizumab, sorafenib, sunitinib) for TCC of the urothelium.;21) The patient has received radiation therapy (including full-dose pelvic radiotherapy) within 4 weeks prior to randomization or has not recovered from toxic effects of the treatment that was given >4 weeks prior to randomization. Single fraction radiotherapy for palliative bone stabilization within 4 weeks prior to randomization is allowed. If any tumor lesion is administered radiotherapy, then it cannot be considered for response assessment.;22) The patient has a history of uncontrolled hereditary or acquired bleeding or thrombotic disorders.;23) The patient has experienced a Grade >=3 bleeding event (for example, via gastric ulcers, gastric varices, rectal bleeding, or gross hematuria) within 3 months prior to randomization. Patients must have complete resolution of any prior bleeding event prior to randomization.;24) The patient has uncontrolled intercurrent illness, including, but not limited to symptomatic anemia, uncontrolled hypertension (>160 mm Hg systolic and/or >100 mm Hg diastolic, despite antihypertensive medication), symptomatic congestive heart failure, unstable angina pectoris, symptomatic or poorly controlled cardiac arrhythmia, psychiatric illness, or any other serious uncontrolled medical disorders in the opinion of the investigator.;25) The patient has experienced any arterial or venothrombotic or thromboembolic events, including, but not limited to myocardial infarction, transient ischemic attack, or cerebrovascular accident, within 6 months prior to randomization.;26) The patient has known untreated brain metastases, uncontrolled spinal cord compression, or leptomeningeal disease. (Note: A brain scan via computed tomography [CT] with contrast or

magnetic resonance imaging [MRI] is to be performed only after study eligibility is confirmed, to detect the presence of intracranial metastasis.);27) The patient has an ongoing or active infection requiring antibiotic, antifungal, or antiviral therapy.;28) The patient has known human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome-related illness.;29) The patient has received a prior autologous or allogeneic organ or tissue transplantation.;30) The patient:;• received chemotherapy within 21 days prior to randomization; and/or;• is currently enrolled in, or discontinued within 21 days prior to randomization from, a clinical trial involving an investigational product (IP) or non-approved use of a drug or device, or is concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study; and/or;• was treated with antiangiogenic therapy within 28 days prior to randomization.;31) The patient has undergone major surgery within 28 days prior to randomization or subcutaneous venous access device placement within 7 days prior to randomization.;32) The patient has had a serious nonhealing wound, ulcer, or bone fracture within 28 days prior to randomization.;33) The patient has an elective or planned major surgery to be performed during the course of the trial.;34) The patient is pregnant or lactating.;35) The patient has a concurrent malignancy or had another malignancy within 5 years of study enrollment (with the exception of adequately treated non-melanomatous skin cancer, in-situ cervical cancer, other noninvasive carcinoma or in situ neoplasm, or localized prostate cancer with no evidence of biochemical or clinical recurrence over a minimum of 6 months [>=6 months]).;36) The patient has an acute/subacute bowel obstruction or history of chronic diarrhea requiring ongoing medical intervention.;37) The patient has a history of gastrointestinal perforation and/or fistula within 6 months prior to randomization.;38) The patient has active diverticulitis.;39) The patient has a known hypersensitivity to docetaxel or other drugs formulated with polysorbate 80.;40) The patient has a known hypersensitivity to agents of similar biologic composition as ramucirumab, or other agents that specifically target VEGF.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	12-08-2015
Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CYRAMZA
Generic name:	Ramucirumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Taxotere
Generic name:	Docetaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	08-04-2015
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-06-2015
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-07-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-08-2015
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-03-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-03-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-06-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-06-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-05-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-08-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-05-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-05-2018
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-02-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-02-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2014-003655-66-NL
CCMO	NL52931.028.15