A Phase II multi-center, non-randomized, open-label study of TKI258 in patients with either FGFR3 mutated or FGFR3 wild type advanced urothelial carcinoma.

Published: 19-03-2010
Last updated: 03-05-2024

Primary objectives* To determine the Overall Response Rate (ORR) in patients with (FGFR3MUT) advanced urothelial carcinoma treated with TKI258* To determine the Overall Response Rate (ORR) in patients with (FGFR3WT) advanced urothelial carcinoma...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON36264

Source
ToetsingOnline

Brief title
TKI258 in advanced urothelial carcinoma

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
advanced bladdercarcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Novartis

Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: FGFR3 mutation, TKI258, urothelial carcinoma

Outcome measures

Primary outcome

Overall Response (Complete responses (CR) or partial responses (PR)) Rate. CR and PR will be defined according to RECIST as per local assessment.

Secondary outcome

Overall Response (Complete responses (CR) or partial responses (PR)) Rate. CR and PR will be defined according to RECIST as per central assessment

* PFS as defined as the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

* OS as defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last contact.

* DCR (Complete responses (CR) or partial responses (PR), Stable disease (SD)) defined according to RECIST

* Safety will be measured in terms of type, frequency and severity of adverse events, laboratory values and ECGs reported according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Study description

Background summary

Bladder Cancer is ranked ninth in cancer incidence worldwide (> 5000 new patients/year. in the Netherlands). Approximately 80% of urothelial carcinoma (UC) bladder cancers present as noninvasive. 70% of which will recur and 20 - 30% of which will progress and invade the bladder muscle. 50% of the patients initially presenting with muscle-invasive UC will relapse with metastatic disease. Prognosis of bladder tumors that are identified as muscle invasive at diagnosis is poor. Chemotherapy has an established role in the treatment of locally advanced and metastatic urothelial carcinoma. The standard of care in first line is largely uniform in North America and Europe, consisting of gemcitabine/platinum doublet. Cisplatin alone as first line treatment of patients with advanced disease showed a Progression Free Survival (PFS) of 4.3 months. PFS for gemcitabine/cisplatin as first line treatment in patients with locally advanced and metastatic bladder cancer was 7.7 months and Overall Survival (OS) was 14 months. There is currently no standard for second line chemotherapy for relapsed/refractory patients with advanced UC. Taxanes are widely used as second-line agents in patients with cisplatin-refractory UC.
As a single agent or in combination with agents such as cisplatin/methotrexate, ifosfamide or gemcitabine, paclitaxel can induce overall response rates that range from 10% to 40% with overall survival duration of 6.6 to 9 months. However, toxicity remains the major limiting aspects of these regimens. Therefore there is consequently an unmet medical need in an effective second-line treatment for advanced UC.

Study objective

Primary objectives
* To determine the Overall Response Rate (ORR) in patients with (FGFR3MUT) advanced urothelial carcinoma treated with TKI258
* To determine the Overall Response Rate (ORR) in patients with (FGFR3WT) advanced urothelial carcinoma treated with TKI258

Secondary objectives
* Overall Response Rate (ORR) as per central assessment in both groups
* Progression Free Survival (PFS) and overall survival (OS) in both groups
* To assess Disease Control Rate (DCR - CR, PR, and Stable Disease (SD) *16 weeks after start of TKI258 treatment) in both groups
* To characterize the safety and tolerability of TKI258

Study design

Open-label, multi-center, phase II study of TKI258 administered orally on a 5

days on/2 days off dosing schedule. The study is sub-divided into 4 periods: screening, treatment,follow-up and survival follow-up.
Patients will be stratified in two groups:
* Group 1: FGFR3 mutated advanced urothelial carcinoma
* Group 2: FGFR3 Wild type advanced urothelial carcinoma
A two-stage design (Simon) will be used in both groups.
Patients will continue on study treatment until disease progression occurs or unacceptable toxicity develops. Patients will be discontinued from the study if they withdrew consent, or if the treating physician judges that further therapy is no longer in the patient*s best interest. All patients, regardless of whether or not they discontinued prior to or subsequent to disease progression, must be followed every 2 months for updates of initiation of next-line therapy and overall survival until the date of data cut-off for the final analysis.
Details of the first subsequent chemotherapy received after disease progression must be collected for all patients.

Intervention

TKI258, oral, 500mg/day,
Schedule: 5 days on * 2 days off

Study burden and risks

Possible risks and side effects of TKI258.
Risks and inconveniences due to blood draw.
The risks of a tumorbiopsy are related of the site where the tumor biopsy is taken.
Additional radiation load due to CT-scans, Bone-scans and MUGA-scan. The additional radiotion load 3.5 mSv (MUGA scan) en 8 mSv (CTscan). Radiation load for bonescan is depending per patient.

Contacts

Public
Novartis

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6824 DPArnhem
NL
Scientific
Novartis

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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1.Histological confirmation of transitional cell carcinoma of the bladder, urethra, ureter, or renal pelvis
* Locally advanced or metastatic disease
2. Archival tumor tissue available FGFR3 mutational status analysis
3. Documented progressive disease at baseline
4. At least one measurable site of disease as defined by RECIST
5. Previously treated with at least 1 but not more than 3 systemic cytotoxic regimens, at least one of the following: cisplatin, carboplatin,gemcitabine or taxane
6. WHO Performance Status * 2
7. Required baseline laboratory values:
* Absolute neutrophil count (ANC) * 1.5 x 109/L
* Platelets * 100 x 109/L
* Hemoglobin * 9.0 g/dL [5,58 mmol/L]
* AST/SGOT and ALT/SGPT * 3.0 x Upper Limit of Normal [ULN] (or AST/SGOT and ALT/SGPT * 5 x ULN if abnormal liver function is due to tumor involvement of the liver)
* Bilirubin * 1.5 x ULN
* Serum creatinine * 1.5 x ULN

Exclusion criteria

1.Patients with known brain metastases or who have signs/symptoms attributable to brain metastases.
2. History of another malignancy < three years prior to study entry, with the exception of adequate treated basal cell carcinoma, squamous cell carcinoma or non-melanomatous skin cancer, excised carcinoma in situ of the cervix, or adenocarcinoma of the prostate.

3. Anti-cancer therapy and radiation for palliation * 14 days prior to starting study drug.
4. Nitrosourea or mitomycin-C * 6 weeks prior to starting study drug.
5. Anti-cancer monoclonal antibody * 6 weeks prior to starting study drug.
6. Wide field radiotherapy * 4 weeks to starting study drug.
7. Major surgery * 2 weeks prior to starting study drug.
8. Any of the following concurrent severe and/or uncontrolled medical conditions:
a) Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
* History or presence of serious ventricular arrhythmias or serious atrial fibrillation
* Clinically significant bradycardia
* LVEF < 45 %
* myocardial infarction, severe/unstable angina, Coronary Artery Bypass Graft, Congestive Heart Failure, Cerebrovascular Accident (CVA), Transient Ischemic Attack (TIA), Pulmonary Embolism within 6 months prior to study entry:
* Uncontrolled hypertension (Systolic BP * 160 mm Hg and/or Diastolic BP * 100 mm Hg), with or without anti-hypertensive medication. Initiation or adjustment
of antihypertensive medication(s) is allowed prior to study entry.
b) Previous pericarditis; clinically significant pleural effusion in the previous 12 months or current ascites requiring two or more interventions/month
c) Impairment of gastrointestinal function that may alter the absorption of TKI258.
d) Known diagnosis of HIV infection.
e) History of alcoholism, drug addiction, or any psychiatric or psychological condition
f) Therapeutic doses of warfarin
g) Uncontrolled diarrhea * CTCAE grade 2
h) Pregnant or breast-feeding women.
i) Male or female not willing to use adequate contraceptive protection (when applicable)

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Will not start

Start date (anticipated):	15-06-2010
Enrollment:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	nog niet bekend
Generic name:	dovitinib

Ethics review

Approved WMO Date:	19-03-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-10-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-11-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-12-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-02-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	03-03-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-07-2011
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	EUCTR2008-005870-11-NL
ClinicalTrials.gov	NCT00790426
CCMO	NL31823.078.10