A Phase 3 Study of Erdafitinib Compared with Vinflunine or Docetaxel or Pembrolizumab in Subjects with Advanced Urothelial Cancer and Selected FGFR Gene Aberrations

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The primary objective of this study is to evaluate efficacy of erdafitinib versus chemotherapy orpembrolizumab in subjects with advanced urothelial cancer harboring selected FGFR aberrations whohave progressed after 1 or 2 prior treatments, at least...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bladder and bladder neck disorders (excl calculi)
Study type	Interventional

Summary

ID

NL-OMON55515

Source
ToetsingOnline

Brief title
THOR (42756493BLC3001)

Condition

- Bladder and bladder neck disorders (excl calculi)

Synonym
Advanced Urothelial Cancer, bladder cancer

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: de sponsor van het onderzoek.

Intervention

Keyword: Advanced Urothelial Cancer, Erdafitinib, FGFR Gene Aberrations, Phase 3 study

Outcome measures

Primary outcome

Primary Endpoint:

The primary endpoint is overall survival (OS). Overall survival is measured from the date of randomization to the date of the subject*s death. If the subject is alive or the vital status is unknown, the subject will be censored at the date the subject was last known to be alive.

Secondary outcome

Secondary Endpoints:

• PFS: duration in days from the date of randomization to the date of disease progression (assessed per RECIST v1.1 by the investigator) or relapse from CR or death, whichever is reported first. For subjects who do not have disease progression and are alive, as well as for subjects with unknown disease progression or unknown survival status as of the clinical cutoff date, PFS will be censored at the date of the last adequate disease assessment. If there is no postbaseline tumor assessment for a subject, PFS will be censored on the date of randomization. Refer to the Statistical Analysis Plan (SAP) for further details regarding censoring rules. Adequate disease assessment is defined as having sufficient evidence to indicate correctly that progression has or has

not occurred.

• ORR: the proportion of subjects who achieve complete response or partial response, as assessed per RECIST v1.1 by the investigator.

• Change from baseline in patient-reported health status and physical functioning scales of the Functional Assessment of Cancer Therapy - Bladder Cancer (FACT-Bl), Patient-Global Impression of Severity (PGIS), and utility and visual analog scale of the European Quality of Life-5 Dimensions-5 Levels Questionnaire (EQ-5D-5L).

• DOR: for responders, duration in days from the date of initial documentation of a response to the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death. The censoring is similar to PFS.

• Safety: collection of adverse event, clinical laboratory values, electrocardiograms, vital signs, ophthalmologic evaluations, physical examinations

• Oral clearance, area under the plasma concentration-time curve (and other parameters, as needed and as data permits) will be estimated using a population approach.

Study description

Background summary

Introduction:
Erdafitinib (JNJ-42756493) is a selective and potent pan fibroblast growth factor receptor (FGFR) inhibitor with demonstrated clinical activity in subjects with solid tumors identified to have alterations in the FGFR pathway,

including urothelial carcinoma.
This Phase 3 study will evaluate single agent erdafitinib versus established chemotherapy agents (docetaxel and vinflunine) and emerging (pembrolizumab) standard of care options in relapsed/refractory subjects with selected FGFR gene aberrations.

Bladder Cancer:
The worldwide age-standardized incidence rate of bladder cancer (per 100,000 person/years) is 9.0 for men and 2.2 for women.11 Worldwide, the bladder cancer age-standardized mortality rate (per 100,000 person/years) was 3.2 for men versus 0.9 for women in 2012.11 Bladder cancer incidence and mortality rates vary across countries due to differences in risk factors, detection and diagnostic practices, and availability of treatments.
Half of the patients with muscle-invasive urothelial cancer relapse after radical cystectomy, depending on the pathological stage of the primary tumor and the nodal status. Local recurrence accounts for 30% of relapses, whereas distant metastases are more common. Ten to 15 percent of patients are already metastatic at diagnosis. Prognostic factors are crucial for assessing results and stratifying phase 3 studies. In a multivariate analysis, Karnofsky performance status of < 80% and presence of visceral metastases are independent predictors of poor survival.1

Second-line Chemotherapy:
Results of second-line treatment with chemotherapy from phase 2 studies are highly variable and depend on patient selection.3 Several agents have been tested in this setting as monotherapy or in combination. Response rates with monotherapy are lower than with combinations, but progression-free survival (PFS) has been short with both options. The only valid randomized phase 3 study in this patient population tested vinflunine and best supportive care (BSC) versus BSC alone.3 Based on the available evidence, taxanes and vinflunine are commonly recommended chemotherapy agents.

Study objective

The primary objective of this study is to evaluate efficacy of erdafitinib versus chemotherapy or
pembrolizumab in subjects with advanced urothelial cancer harboring selected FGFR aberrations who
have progressed after 1 or 2 prior treatments, at least 1 of which includes an anti-PD-(L)1 agent
(cohort 1), or 1 prior treatment not containing an anti-PD-(L)1 agent (cohort 2).
The primary endpoint of overall survival (OS) will be evaluated in 2 cohorts:
Cohort 1: erdafitinib versus chemotherapy (docetaxel or vinflunine) [subjects who have received prior
anti-PD-(L)1 agent]
Cohort 2: erdafitinib versus pembrolizumab [subjects who have not received

prior anti-PD-(L)1 agent]

Secondary Objectives:
• To evaluate progression-free survival (PFS) of subjects treated with erdafitinib versus chemotherapy or pembrolizumab
• To evaluate the objective response rate (ORR) of subjects treated with erdafitinib versus chemotherapy or pembrolizumab
• To evaluate the health-related quality of life of subjects treated with erdafitinib versus chemotherapy or pembrolizumab
• To evaluate the duration of response (DOR) for subjects treated with erdafitinib versus chemotherapy or pembrolizumab
• To characterize the safety profile of subjects treated with erdafitinib versus chemotherapy or pembrolizumab
• To evaluate the population pharmacokinetics of erdafitinib

Exploratory Objectives:
• To evaluate DNA, RNA, or protein biomarkers in tissue and blood samples which potentially predict tumor response or resistance to erdafitinib, chemotherapy, or pembrolizumab
• To assess the expression of immune markers (eg, PD-L1) and determine molecular subtype in tumor samples
• To evaluate changes in peripheral blood immune cell types, levels, and activation status in response to erdafitinib, chemotherapy, or pembrolizumab
• To assess changes in tumor immune cell infiltrate and gene expression related to bladder cancer subtype, in response to erdafitinib in paired tumor biopsies
• To evaluate the relationship between erdafitinib exposure and efficacy and safety endpoints

Study design

This is a randomized, open label, multicenter, global phase 3 study of erdafitinib versus standard of care,
consisting of chemotherapy (docetaxel or vinflunine) or anti-PD1 agent pembrolizumab, in subjects with
advanced urothelial cancer and selected FGFR aberrations who have progressed on or after 1 or 2 prior
treatments (cohort 1) or 1 prior treatment (cohort 2). Subjects will be assigned to Cohort 1 or Cohort 2
based upon prior treatment with an anti-PD-(L)1 agent. In Cohort 1, subjects who have received prior
anti-PD-(L)1 will be randomized to erdafitinib versus chemotherapy (approximately 280 subjects). In
Cohort 2, subjects who have not received prior anti-PD-(L)1 will be randomized to erdafitinib versus
pembrolizumab (approximately 350 subjects). Cohort 1 and Cohort 2 will be assessed independently.
For each cohort, a review of the safety data will be performed by an

Independent Data Monitoring
Committee (IDMC) after at least 60 subjects have been enrolled in that cohort and every 6 months
afterwards.
The Screening Phase will start with molecular screening, which will be performed by a central laboratory.
Full study screening will occur after the completion of prior treatment and documentation of disease
progression for subjects who meet the molecular screening criteria. The Treatment Phase will extend from
randomization until disease progression, intolerable toxicity, withdrawal of consent or decision by the
investigator to discontinue treatment. The post-treatment Follow-up Phase will extend from the
End-of-Treatment Visit until the subject has died, withdraws consent, is lost to follow-up, or the end of
study, whichever comes first.

Intervention

Study drug:
The study drug will be provided in either a tablet form or be given to the subject through an intravenous (IV) infusion like normal chemotherapy.

Erdafitinib:
Subject will take Erdafitinib tablets once per day with a glass of water (about 240mL). Study doctor may increase or decrease the dose depending on how the body reacts to the drug. The dose of study drug may be changed or stopped if subject has a side effect.
The tablets can be taken with or without food but they should be swallowed whole and must not be dissolved in water. Each dose should be taken at about the same time each day. If a dose is missed it can be taken up to 6 hours after the time it is usually taken and the normal dosing time resumed the following day. If it has been more than 6 hours since the dose was missed, that dose should be skipped and treatment continued as normal the next day. If vomiting occurs when the dose is taken, no replacement dose should be taken. Subject should not eat grapefruit or Seville oranges during the study treatment period as it could interfere with the study drug in the body.
On Day 14 of Cycle 1 and Day 1 of Cycle 2 the subject will need to come into clinic to have blood samples taken to find out the level of erdafitinib in their blood. On these days, subject may need to take their usual dose of erdafitinib at the clinic; the study staff will let subject know if this is the case.

Pembrolizumab or chemotherapy:
The subject will have an IV infusion once every cycle. Depending on the study drug subject is receiving, the duration of the infusion may be 20 minutes

(vinflunine), 30 minutes (pembrolizumab), or an hour (docetaxel). The study drug is put into a vein in the arm through a small tube attached to a needle.

Study burden and risks

Blood draws: 60 times.
Urine or blood pregnancy test: 1 time at screening and during treatment phase as clinically indicated or required.
IV infusions: 12 times.
Tumor biopsy: at pre-screening (the molecular eligibility testing), an archival tumor biopsy will be tested. If samples of the tumor tissue have not been previously collected or are insufficient to determine subject's eligibility in the study, a sample of subject's tumor tissue will need to be collected through a fresh biopsy.
Tumor biopsies: 3 times, for the optional part of the study.
CT-scan (or MRI-scan): 7 times.
ECG: 3 times.
The number of visits to the study clinic: 38 visits.
Physical examination: 1 time at screening, 1 time on day 1 of cycle 1, 2 and 3. One time on day 1 of cycle 4+ and one time at end of treatment.
Ophthalmologic exam: 1 time.
Amsler Grid Test (vision test): 5 times, but can be more depending on the total number of cycles.
Questionnaires:
-FACT-BI, PGIS: 1 time at Day 1 of cycle 1, 2 and 3. 1 time at Day 14 for cycle 1 only. 1 time at Day 1 of cycle 4+, and 1 time at End of Treatment.
-EQ-5D-5L: 1 time at Day 1 of cycle 1, 2 and 3. 1 time at Day 14 for cycle 1 only. 1 time at Day 1 of cycle 4+, and 1 time at End of Treatment, and during the follow-up phase (every 12 weeks +/- 7 days).

The subject may experience physical or psychological discomfort form the above tests and procedures and questionnaires.
The subject may experience side effects from the study medications.

Contacts

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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. >=18 years of age (or the legal age of consent in the jurisdiction in which the study is
taking place)
2. Histologic demonstration of transitional cell carcinoma of the urothelium. Minor components (<50% overall) of variant histology such as glandular or squamous differentiation, or evolution to more aggressive phenotypes such as sarcomatoid or micropapillary change are acceptable
3. Criterion amended per Amendment 2:
3.1 Metastatic or surgically unresectable urothelial cancer
4. Documented progression of disease, defined as any progression that requires a change in
treatment, prior to randomization
5. Criterion modified per Amendment 5:
5.3 Cohort 1: Prior treatment with an anti-PD-(L)1 agent as monotherapy or as combination therapy; no more than 2 prior lines of systemic treatment. Prior treatment with an anti-PD-(L)1 agent could have been given as neo-adjuvant, adjuvant, or in metastatic line of treatment as frontline or maintenance therapy, as follows:
* together with chemotherapy or as maintenance therapy
* together with chemotherapy in metastatic setting
* for superficial cancer (early disease/non-muscle invasive bladder cancer), OR in neo-adjuvant OR adjuvant setting. If these subjects did not relapse within a year of their last dose of anti-PD-(L)1, this will not be counted as a prior line of systemic treatment. These subjects will however still be eligible

only for Cohort 1.
Cohort 2: No prior treatment with an anti-PD-(L)1 agent; only 1 line of prior systemic
treatment.
Note: Subjects who received neoadjuvant or adjuvant chemotherapy or immunotherapy and showed disease progression within 12 months of the last dose are considered to have received systemic therapy in the metastatic setting.
6. Subjects must meet appropriate molecular eligibility criteria (as determined by central laboratory screening or local or by local historical test results (from tissue or blood) performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified or regional equivalent laboratory using the following methods: local next-generation sequencing (NGS), direct digital counting methods, or the Qiagen Therascreen FGFR Rotor-Gene Q (RGQ) reverse transcription polymerase chain reaction (RT-PCR) test.
Tumors must have at least 1 of the following translocations: FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3, FGFR3-BAIAP2L1; or 1 of the following FGFR3 gene mutations: R248C, S249C, G370C, Y373C.
7. ECOG performance status Grade 0, 1, or 2 (Attachment 1)
8. Criterion amended per Amendment 2:
8.1 Criterion modified per Amendment 3:
8.2.Criterion modified per Amendment 4:
8.3 Criterion modified per Amendment 5:
8.4 Adequate bone marrow, liver, and renal function:
a. Bone marrow function (without the support of cytokines or erythropoiesis-stimulating
agent in preceding 2 weeks):
* Absolute neutrophil count (ANC) >1,500/mm3
* Platelet count >75,000/mm3 (>=100,000/mm3 for Cohort 1 subjects at sites choosing vinflunine chemotherapy)
* Hemoglobin >8.0 g/dL (without transfusion or demonstrate stability, ie; no significant decline in hemoglobin, for 2 weeks after transfusion)
b. Liver function:
* Total bilirubin <=1.5 x institutional upper limit of normal (ULN) OR direct bilirubin <=ULN for subjects with total bilirubin levels >1.5xULN [<=1xULN for Cohort 1 subjects at sites choosing docetaxel chemotherapy]
* Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <=2.5x institutional ULN or <=5x institutional ULN for subjects with liver metastases (For subjects in cohort 1 at sites choosing docetaxel chemotherapy, both the ALT and AST values must be <=1.5xULN concomitant with alkaline phosphatase of <=2.5xULN)
c. Renal function: Creatinine clearance (CrCl) >30 mL/min either directly measured via 24-hour urine collection or calculated using the Cockcroft-Gault formula (Attachment 2).
d. Criterion deleted per amendment 3.
e. Phosphate: (medical
management allowed)
9. Criterion amended per Amendment 3:

9.1 Must sign an informed consent form (ICF) (or their legally acceptable representative must sign) indicating that he or she understands the nature, significance, purpose of, procedures for, and consequences of the study and is willing to participate in the study.
10. A woman of childbearing potential who is sexually active must have a negative pregnancy test (*-human chorionic gonadotropin [bhCG]) at Screening (urine or serum).
11. Criterion amended per Amendment 2:
11.1 Criterion amended per Amendment 3:
11.2 Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subject participating in clinical studies.
For women of childbearing potential (defined as: fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods
include hysterectomy, bilateral salpingectomy and bilateral oophorectomy):
* practicing a highly effective method of contraception (failure rate of <1% per year
when used consistently and correctly)
Examples of highly effective contraceptives include
* user-independent methods: implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence: true abstinence when this is in line with the preferred and usual lifestyle of the subject (Note: periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.)
* user-dependent methods: combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable
* agrees to remain on a highly effective method of contraception during the study and
for at least 6 months after the last dose of study drug
* agrees to not donate eggs (ova, oocytes) for the purposes of assisted reproduction
during the study and for at least 6 months after the last dose of study drug
* not breastfeeding and not planning to become pregnant during the study and for at
least 6 months after the last dose of study drug
For men who are sexually active with women of childbearing potential:
* agrees to use a condom with spermicidal foam/gel/film/cream/suppository
* agrees to not donate sperm during the study and for at least 6 months after the last
dose of study drug
* not planning to father a child during the study or within 6 months after the

last dose of study drug

Exclusion criteria

1. Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 30 days prior to randomization.
2. Criterion amended per Amendment 2:
2.1 Criterion modified per Amendment 3:
2.2 Active malignancies (ie, requiring treatment change in the last 24 months). The
only allowed exceptions are:
* urothelial cancer.
* skin cancer treated within the last 24 months that is considered completely cured.
* localized prostate cancer with a Gleason score of 6 (treated within the last 24 months or untreated and under surveillance).
* localized prostate cancer with a Gleason score of 3+4 that has been treated more
than 6 months prior to full study screening and considered to have a very low risk
of recurrence.
3. Symptomatic central nervous system metastases.
4. Received prior FGFR inhibitor treatment.
5. Known allergies, hypersensitivity, or intolerance to erdafitinib or its excipients
6. Criterion amended per Amendment 2:
6.1 Criterion modified per Amendment 3.
6.2 Current central serous retinopathy (CSR) or retinal pigment epithelial detachment
of any grade.
7. History of uncontrolled cardiovascular disease including:
a. unstable angina, myocardial infarction, ventricular fibrillation, Torsades de Pointes, cardiac arrest, or known congestive heart failure Class III-V (Attachment 3) within the preceding 3 months; cerebrovascular accident or transient ischemic attack within the preceding 3 months.
b. QTc prolongation as confirmed by triplicate assessment at screening (Fridericia;
QTc >480 milliseconds).
c. Pulmonary embolism or other venous thromboembolism (VTE) within the preceding 2 months.
8. Known active AIDS (human immunodeficiency virus (HIV) infection), unless the subject has been on a stable anti-retroviral therapy regimen for the last 6 months or
more, has had no opportunistic infections in the last 6 months, and has CD4 count

>350.
9. Criterion amended per Amendment 3: 9.1 Known active hepatitis B or C infection (unless polymerase chain reaction
[(PCR]-negative [according to local laboratory range] on all available tests for the past
6 months).
10. Criterion amended per Amendment 3:
10.1 Not recovered from reversible toxicity of prior anticancer therapy (except toxicities which are not clinically significant such as alopecia, skin discoloration,
neuropathy, hearing loss).
11. Impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers,
known gastric ulcers, or unhealed incisions.
12. Major surgery within 4 weeks before randomization.
13. Criterion amended per Amendment 2: 13.1 Criterion modified per Amendment 3:
13.2 Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. Examples include ongoing active infection requiring systemic therapy and uncontrolled ongoing medical conditions.

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):	22-11-2019
Enrollment:	40

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Erdafitinib
Generic name:	Erdafitinib
Product type:	Medicine
Brand name:	Javlor®
Generic name:	Vinflunine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Keytruda®
Generic name:	Pembrolizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Taxotere®
Generic name:	Docetaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	28-02-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-01-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-02-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-03-2019

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-04-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-05-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-08-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-08-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-06-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-06-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-07-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
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Approved WMO Date:	08-07-2021
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Approved WMO Date:	08-03-2022
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Approved WMO Date:	25-08-2022
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Application type:	Amendment
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Approved WMO Date:	22-05-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2017-002932-18-NL
ClinicalTrials.gov	NCTnumber:NCT03390504andEudraCTNUMBER:2017-002932-18
CCMO	NL64531.091.18

Study results

Date completed:	21-07-2023
Actual enrolment:	5