Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial of Infigratinib for the Adjuvant Treatment of Subjects with Invasive Urothelial Carcinoma with Susceptible FGFR3 Genetic Alterations (PROOF 302)

Published: 15-06-2020
Last updated: 17-01-2025

To determine if treatment with infigratinib improves centrally reviewed disease-free survival (DFS) compared with placebo treatment in subjects with invasive urothelial carcinoma with susceptible FGFR3 alterations after nephroureterectomy, distal...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON55032

Source
ToetsingOnline

Brief title
QED_PROOF 302

Condition

- Other condition
- Urethral disorders (excl calculi)

Synonym
bladder cancer, Urothelial Carcinoma

Health condition

Invasive Urothelial Carcinoma with Susceptible FGFR3 Genetic Alterations

Research involving
Human

Sponsors and support

Primary sponsor: QED Therapeutics, Inc.
Source(s) of monetary or material Support: QED Therapeutics;Inc.

Intervention

Keyword: Adjuvant Treatment, Infigratinib, Phase 3, Urothelial Carcinoma

Outcome measures

Primary outcome

Primary endpoints: Centrally reviewed DFS, from date of randomization to local/regional or contralateral invasive or metastatic recurrence, or death due to any cause, whichever occurs earlier

Secondary outcome

Secondary endpoints:

Investigator-reviewed DFS including intraluminal low risk (noninvasive, low-grade, or high-grade) recurrence, from date of randomization to any recurrence or death due to any cause, whichever occurs earlier

Investigator-reviewed MFS, from date of randomization to metastatic recurrence or death due to any cause, whichever occurs earlier

OS (from date of randomization to death)

Investigator-reviewed DFS, from date of randomization to local/regional or

contralateral invasive or metastatic recurrence, or death due to any cause,

whichever occurs earlier

Type, frequency, and severity of adverse events and serious adverse events,

laboratory abnormalities, and other safety findings

QOL as measured by the EQ-5D-5L and the EORTC QLQ C30

PK parameters (trough and maximum plasma concentration).

FGFR3 alterations detected by cfDNA and/or RNA sequencing as biomarkers of

disease recurrence

Study description

Background summary

There is a need for a treatment of urothelial cell carcinoma for patients who cannot receive standard chemotherapy. In laboratory studies, infigratinib has been shown to shrink or slow the growth of several different types of cancers or tumors in animals whose tumor cells have a genetic abnormality in the FGFR3 gene. This genetic abnormality in the FGFR3 gene can cause cells to grow abnormally and develop into cancer. It may be the case that infigratinib will inhibit the abnormal FGFR3 gene, thus preventing cells from growing without inhibition. Infigratinib may prevent or delay your tumor from coming back. However, infigratinib is an investigational (study) drug, and its actual ability to affect malignant cells remains unknown.

Study objective

To determine if treatment with infigratinib improves centrally reviewed disease-free survival (DFS) compared with placebo treatment in subjects with invasive urothelial carcinoma with susceptible FGFR3 alterations after nephroureterectomy, distal ureterectomy, or cystectomy.

Study design

This is a Phase 3 multicenter, double-blind, randomized, placebo-controlled study to evaluate the efficacy of infigratinib in approximately 218 adult subjects with invasive urothelial carcinoma with susceptible FGFR3 genetic alterations (mutations, and gene fusions or translocations [ie,

rearrangements]; hereafter referred to collectively as *FGFR3 alterations*) who are within 120 days following nephroureterectomy, distal ureterectomy, or cystectomy and ineligible for cisplatin-based (neo)adjuvant chemotherapy or with residual disease after neoadjuvant therapy. The sample size can be increased up to a total of 328 subjects based on interim analysis result using an adaptive design promising zone approach. Subjects with invasive urothelial carcinoma includes subjects with invasive upper tract urothelial carcinoma (UTUC) and urothelial carcinoma of the bladder (UBC).
Subjects will be randomly assigned (1:1) to receive oral infigratinib or placebo administered once daily for the first 3 weeks (21 days) of each 28-day cycle for a maximum of 52 weeks, until local/regional or contralateral invasive or metastatic recurrence, or until other criteria specified in Section 8.1.1 is met, whichever occurs first. Subjects will be evaluated for tumor recurrence radiographically and by urine cytology. For subjects with UTUC (ie, subjects with a bladder), cystoscopy will be performed. Radiography, urine cytology, and cystoscopy will continue until metastatic recurrence by blinded independent central review (BICR) or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred. After that time, subjects will be followed up for survival status and use of anticancer therapy for 1 year after the final DFS event goal is reached (ie, End of Study).
An interim analysis for adaptation and futility for centrally reviewed DFS will be conducted after approximately 35 centrally reviewed DFS events have been reached. Based on the results of the interim analysis on DFS, if a sample size increase is deemed necessary using the promising zone approach, the sample size/centrally reviewed DFS event goal will be increased by a maximum of 50% (328/105). If sample size is increased and event goal is adjusted, then the subsequent analyses will be adjusted accordingly time-wise when the adjusted event goal is reached. The details of the sample size adaptation method will be prespecified in the adaptation plan.
Subjects will be stratified according to lymph node involvement (yes vs no), prior neoadjuvant chemotherapy (yes vs no), AJCC Stage (pT2 vs >pT2), and disease (UTUC vs UBC).

Intervention

Subjects randomly assigned to placebo will receive placebo matching in appearance the investigational product (infigratinib), which will be provided as hard gelatin capsules for oral use and will be administered once daily on a 3 weeks on (Days 1-21) /1 week off (Days 22 28) dosing schedule.

Study burden and risks

Extract from the patient information and consent form:

All drugs may cause certain side effects and discomforts. The most common side

effects and discomforts reported for the infigratinib are:

Very Common (Frequency of 10% (1 in 10) or higher) adverse events reported:
• Temporary increases in the mineral phosphate in the blood. Change to your blood phosphate levels may not cause symptoms, or the change could lead to calcium deposits in your body, including in your skin, heart, or blood vessels. A blood test will determine if there have been changes in your blood phosphate levels. If your phosphate level is high, your doctor may decrease your study drug dose or may ask you to take medicine to lower the phosphate level.
• Temporary decreases in the mineral phosphate in your blood.
• Temporary increases in the mineral calcium in the blood. You may not have any symptoms if you have a slight increase or decrease of the calcium level in your blood. In severe cases of high levels of calcium, you might experience kidney problems, irregular heartbeat, or confusion.
• Temporary changes in measurements of your kidney function which are most frequently seen at the same time as the changes in your phosphorus blood levels.
• Muscle weakness and/or discomfort and fatigue.
• Joint pain.
• Stomatitis (inflamed and sore mouth).
• Gastrointestinal (GI) adverse effects including constipation, diarrhea, nausea, vomiting, abdominal pain, indigestion, changes in taste.
• Dry mouth.
• Decreased appetite and weight changes.
• Skin and nail changes, including blistering and peeling of the skin on the hands and feet.
• Eye related adverse effects (most frequently dry eye and blurry vision) and less frequently corneal or retinal problems, worsening cataracts, or inflammation of the eye.
• Hair loss.
• Temporary, mild changes in blood tests that monitor the ability of your liver to work. These changes will most likely go away when you stop taking infigratinib.
• Decrease in the number of red blood cells, which may cause fatigue and shortness of breath.
• Nose bleeds.
• Low sodium in the blood which can lead to weakness.
• Pain in extremity which might be at rest or with exercise.
• Headache.
Infigratinib has caused mild to moderate visual changes in some patients. While this type of visual impairment may improve again, there is a risk that it might be permanent after you stop taking infigratinib. Blurred vision and, in some cases, loss of vision have been seen with similar drugs tested in other human studies. All patients will undergo a detailed eye examination at the start of the study and this is repeated during the study. If the results of eye exams conducted at screening are abnormal, you will not be able to participate in this study and you may need to discontinue from the study if abnormal changes

are found while you are on study. It is important to tell your doctor about any pre-existing eye problems you have and visual changes that occur while taking the study drug as your doctor may decide to change or stop your treatment with the study drugs. It is important that you do not drive a car or work with machinery if you begin to experience any visual changes while on the study.
Common (Frequency of 1% up to 10%) adverse events reported:
1. Injury to the cornea, which is the transparent, dome-shaped window covering the front of the eye. These changes may be noticed as blurry vision or may only be found by an ophthalmologist (a doctor that specializes in eye care).
2. Changes to your retina (the light sensitive portion of your eye).
3. Dehydration.
4. Changes in body*s ability to produce hormones.
5. Numbness in your fingers or toes.
6. Increases in blood levels of potassium which usually does not cause any symptoms but can cause nausea, palpitations, and low energy.
7. Some changes to the function of your kidneys are temporary but some may continue after you stop taking infigratinib and may impact on the ability of your kidneys to function.
8. Increases in the digestive enzymes amylase and lipase without symptoms, which can be related to the function of your pancreas. Changes to the function of your liver that may continue after you stop taking infigratinib and may impact on the ability of your liver to work.
9. Temporary worsening of measurements of the pumping ability of your heart most often without symptoms and may go away when you stop taking infigratinib.
10. Dizziness.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Are >=18 years of age (>=20 years of age in Taiwan) of either sex.
2. Have signed informed consent.
3. Are randomized within 120 days following nephroureterectomy, distal ureterectomy, or cystectomy. Note: at the time of definitive surgery, lymph node dissection (LND) should be performed in cases of suspected lymph node invasion based on preoperative imaging or intraoperative findings. In other cases, LND is to be performed in accordance with surgeon preferences/local standard practices. Additional details on recommended standards for LND are provided in the protocol.
4. Have histologically or cytologically confirmed, invasive urothelial carcinoma with susceptible FGFR3 alterations. Variant histology is allowed provided urothelial carcinoma is predominant (>50%). Neuroendocrine (including small and large cell), sarcomatoid, and plasmacytoid variants are excluded (any component):
a. Regarding samples and documentation of FGFR3 alterations:
i. FGFR3 mutation is confirmed if: FGFR3 gene is mutated in Exon 7 (R248C, S249C), Exon 10 (G370C, A391E, Y373C), or Exon 15 (K650M/T, K650E/Q)
OR
ii. FGFR3 gene fusion or FGFR3 rearrangement is confirmed based on the following genomic criteria:
(1) Any fusion/rearrangement with a literature-derived known partner gene regardless of strand or frame.
(2) Fusion/rearrangements in the same strand that are in frame with a novel partner gene.
(3) Fusion/rearrangements with one breakpoint in the intron 17 - exon 18 hotspot region and the other breakpoint in an intergenic region or another gene. This rule excludes 3* duplications comprising only exon 18.
iii. The amino acid numbers for the FGFR3 mutations refer to the

functional FGFR3 isoform 1 (NP_000133.1) that is the NCBI Refseq ID used to report genetic alterations in FGFR3 by the FoundationOne® CDx test (F1CDx, Foundation Medicine, USA).
iv. Written documentation of central laboratory determination by F1CDx testing of FGFR3 alterations is required for study eligibility.
v. For subjects who require molecular prescreening to confirm the presence of the FGFR3 alteration to meet the inclusion criteria, a tumor sample with a pathology report must be sent to Foundation Medicine USA for F1CDx testing. (Instructions for optimal tumor specimens are provided in the protocol).
(1) The tumor sample to be used should be from the definitive surgical resection (cystectomy, nephroureterectomy, or distal ureterectomy).
(2) An archival biopsy of confirmed invasive urothelial carcinoma (>=pT2) can be used if (1) tissue from definitive surgery cannot be submitted, (2) the biopsy sample is not older than 4 months prior to surgery date and (3) the subject did not receive any type of systemic anticancer treatment since the biopsy was obtained. If more than one biopsy is available, the most recent one is to be sent.
b. If status post neoadjuvant chemotherapy, pathologic stage at surgical resection must be Stage >= ypT2 and/or yN+. Prior neoadjuvant therapy is defined as at least 3 cycles of neoadjuvant cisplatin-based chemotherapy with a planned cisplatin dose of 70 mg/m2/cycle. Subjects who received less than this or non-cisplatin-based neoadjuvant treatment are not excluded. If enrolled, they will be stratified as having received no neoadjuvant chemotherapy.
c. If not status post neoadjuvant chemotherapy, is ineligible to receive cisplatin-based adjuvant chemotherapy based on Galsky (2011):
i. Creatinine clearance <=60 mL/minute, or
ii. Common Terminology Criteria for Adverse Events (CTCAE version 5.0) Grade >=2 hearing loss, or
iii. CTCAE Grade >=2 neuropathy.
d. Subjects who refuse cisplatin-based chemotherapy or who are ineligible to receive cisplatin-based chemotherapy based on Galsky (2011), must also meet the following criteria:
i. UTUC should be Stage >=pT2 pN0-2 (post-lymphadenectomy or no lymphadenectomy [pNx]), or pN+, M0
ii. UBC should be Stage >=pT3 or pN+, M0.
e. Must have a centrally reviewed negative postoperative computed tomography (CT) (defined as lymph nodes with short axis <1.0 cm and without growth and no distant metastases according to Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) or negative biopsy within 28 days before randomization to confirm absence of disease at baseline
5. If have had adverse events (AEs) associated with prior surgery or neoadjuvant chemotherapy, they have stabilized or resolved to Grade <=2 before randomization.
6. Have Eastern Cooperative Oncology Group (ECOG) performance status

of <=2.
7. If a woman of childbearing potential, must have a negative pregnancy test within 7 days of the first dose of study drug.

For the complete list of inclusion criteria please refer to the Protocol.

Exclusion criteria

1. Presence of positive invasive surgical margins following nephroureterectomy, distal ureterectomy, or cystectomy. In subjects not eligible for further surgery, radiotherapy, or other efficacious treatment, microscopic positive noninvasive margins (eg, carcinoma in situ) without gross residual disease are allowed.
2. Have received Bacillus Calmette-Guerin (BCG) or other intravesical therapy for nonmuscle invasive bladder cancer (NMIBC) within the previous 30 days.
3. Are currently receiving or are planning to receive during participation in this study, treatment with agents that are known moderate or strong inducers or inhibitors of CYP3A4 and medications which increase serum phosphorus and/or calcium concentration. Subjects are not permitted to receive enzyme-inducing antiepileptic drugs, including carbamazepine, phenytoin, phenobarbital, and primidone. Prior anticancer or other therapies are restricted as follows:
a. Prior adjuvant treatment for urothelial cancer is not allowed.
b. Prior neoadjuvant therapy (eg, chemotherapy, immunotherapy, or investigational) is allowed if inclusion criterion #4 is met. Prior neoadjuvant chemotherapy must have been completed within a period of time that is greater than the cycle length used for that treatment before the first dose of study drug.
c. Prior biologic, immunotherapy, or investigational therapy should have been completed within a period that is >=5 half-lives or 30 days, whichever is shorter, before the first dose of study drug.
4. Are planning to receive other systemic therapies intended to treat invasive urothelial carcinoma while on this study.
5. Have previously or currently is receiving treatment with a mitogenactivated protein kinase (MEK) or selective FGFR inhibitor.
6. Have a history of primary malignancy within the past 3 years other than (1) invasive UBC or UTUC (ie, disease under study), (2) noninvasive urothelial carcinoma, (3) any adequately treated in situ carcinoma or non-melanoma carcinoma of the skin, (4) any other curatively treated malignancy that is not expected to require treatment for recurrence during participation in the study, or (5) an untreated cancer on active surveillance that may not affect the subject's survival status for >=3 years based on clinician assessment/statement and with medical monitor approval. For any other cancers that do not meet the criteria

above, and for which the natural history or treatment do not have the potential to interfere with the safety or the efficacy assessments of the study, written approval is required by the medical monitor.
7. Have current evidence of corneal keratopathy or retinal disorder including, but not limited to, bullous/band keratopathy, inflammation or ulceration, keratoconjunctivitis, macular degeneration, or diabetic retinopathy, confirmed by ophthalmic examination. Subjects with asymptomatic ophthalmic conditions assessed by the investigator to pose minimal risk for study participation may be enrolled in the study.
8. Have a history and/or current evidence of extensive tissue calcification including, but not limited to, the soft tissue, kidneys, intestine, vasculature, myocardium, and lung with the exception of calcified lymph nodes, minor pulmonary parenchymal calcifications, small renal cyst or stone calcifications, and asymptomatic coronary calcification.
9. Have impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral infigratinib (eg, active ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).
10. Have current evidence of endocrine alterations of calcium/phosphate homeostasis (eg, parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis), unless well controlled.
11. Have consumed grapefruit, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, or Seville oranges or products containing juice of these fruits within 7 days before the first dose of study drug; have taken any Chinese herbal medicine or Chinese patent medicine treatments with anticancer activity within 14 days of the first dose of study drug.
12. Have insufficient bone marrow function:
a. Absolute neutrophil count (ANC) <1,000/mm3 (1.0 × 109/L)
b. Platelets <75,000/mm3 (<75 × 109/L)
c. Hemoglobin<8.5 g/dL; transfusion support is allowed if >1 week before randomization and hemoglobin remains stable
13. Have insufficient hepatic and renal function:
a. Total bilirubin >1.5 × upper limit of normal (ULN) of the testing laboratory (for subjects with documented Gilbert syndrome, direct bilirubin must be <=1.5× ULN and enrollment requires approval by the medical monitor)
b. AST/SGOT and ALT/SGPT >2.5× ULN of the testing laboratory
c. Serum creatinine >1.5 × ULN or a calculated (using the Cockcroft-Gault [C-G] formula [Cockcroft 1976]) or measured creatinine clearance of <30 mL/min

For the complete list of exclusion criteria please refer to the Protocol.

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):	16-03-2020
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Infigratinib
Generic name:	Infigratinib

Ethics review

Approved WMO Date:	15-06-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-11-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	12-01-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-04-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-05-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-06-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-10-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-11-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-12-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-01-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-05-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	19-05-2022
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	EUCTR2019-003248-63-NL
ClinicalTrials.gov	NCT04197986
CCMO	NL73746.091.20

Study results

Date completed:	19-12-2022
Results posted:	20-09-2023

Summary results
Trial ended prematurely

First publication
02-08-2023