A Phase 3, Open-Label, Randomized Study of Futibatinib Versus Gemcitabine-Cisplatin Chemotherapy as First-Line Treatment of Patients with Advanced Cholangiocarcinoma Harboring FGFR2 Gene Rearrangements

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Primary end point• Progression-free survival (PFS) per ICR central assessmentSecondary end point• Objective response rate (ORR)• Disease control rate (DCR)• Overall survival (OS)• PFS according to Investigator assessment of radiologic images•...

Ethical review	Approved WMO
Status	Pending
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON52381

Source
ToetsingOnline

Brief title
FOENIX-CCA3

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Bile duct cancer, cholangiocarcinoma

Research involving

Human

Sponsors and support

Primary sponsor: Taiho Oncology Inc.
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Cholangiocarcinoma, Futibatinib, Open-label, Phase 3

Outcome measures

Primary outcome

PFS per central assessment (primary): defined as the time from date of randomization to the date of documentation of disease progression by ICR, or date of death, whichever occurs first.

Secondary outcome

• ORR: defined as the proportion of patients experiencing a best overall response of partial response (PR) or complete response (CR) (per RECIST 1.1), based on ICR.

• DCR: defined as the proportion of patients experiencing a best overall response of stable disease (SD), PR, or CR (per RECIST 1.1), based on central assessment of radiologic images.

• OS: measured from the date of randomization until the date of death due to any cause.

• PFS per Investigator assessment: defined as the time from date of randomization to the date of disease progression based on Investigator assessment of radiographic images or death, whichever occurs first.

Study description

Background summary

Aberrations in fibroblast growth factor (FGF) or the FGF receptor (FGFR) are a reported genetic modification in cholangiocarcinoma (CCA); in particular, FGFR2 gene rearrangements, including gene fusions, have been identified as an early driver of oncogenic events in approximately 15% of CCA patients. Futibatinib (TAS-120), an oral, highly selective, irreversible tyrosine kinase inhibitor (TKI) that inhibits both mutant and wild-type FGFR1-4 isoforms, has shown promising antitumor activity in preclinical studies against a variety of tumor cell lines or tumor models harboring FGFR aberrations. In an ongoing Phase 1/2 clinical study (Study TAS-120-101), treatment with futibatinib resulted in further evidence of efficacy.
The Phase 3 study described in this protocol will evaluate the efficacy and safety of futibatinib against that of the current standard of care (gemcitabine-cisplatin chemotherapy) in the first-line treatment of patients with locally advanced, metastatic, or recurrent unresectable intrahepatic CCA (iCCA) harboring FGFR2 gene rearrangements.

Study objective

Primary end point
• Progression-free survival (PFS) per ICR central assessment

Secondary end point
• Objective response rate (ORR)
• Disease control rate (DCR)
• Overall survival (OS)
• PFS according to Investigator assessment of radiologic images
• Treatment-emergent adverse events (TEAEs), including serious adverse events (SAE's), clinical laboratory tests, vital signs, ophthalmological exams and 12-lead electrocardiogram (ECG)

Exploratory
• PFS on next-line therapy (PFS2)
• Duration of response (DOR)
• Patient-reported outcomes (PRO)
• To assess the population pharmacokinetics (Pop PK) of futibatinib and to explore the relationship
between PK and efficacy or toxicity.

Study design

Study TAS-120-301 is an open-label, multinational, parallel 2-arm, randomized

Phase 3 study evaluating the efficacy and safety of futibatinib versus gemcitabine-cisplatin chemotherapy as first-line treatment of patients with advanced, metastatic, or recurrent unresectable iCCA harboring FGFR2 gene rearrangements. Eligible patients will be randomized on a 1:1 basis to the following study arms:
• Experimental Arm: Patients will receive futibatinib at an oral dose of 20 mg, administered daily (QD)
on every day of a 21-day cycle.
• Control Arm: On Days 1 and 8 of a 21-day cycle, patients will receive:
o Cisplatin 25 mg/m2 in 1000 mL 0.9% saline by intravenous (I.V.) infusion over 1 hour,
followed by 500 mL 0.9% saline over 30 minutes; and
o Gemcitabine 1000 mg/m2 in 250-500 mL 0.9% saline by I.V. infusion over 30 minutes,
beginning after completion of the cisplatin and saline infusions.
Patients in the Experimental Arm may continue to receive continuous futibatinib until documentation of progressive disease (PD) per RECIST 1.1, or until other withdrawal criteria are met, whichever comes first. However, treatment may continue following PD per RECIST 1.1 if the patient is clinically stable and is considered by the Investigator to be deriving continued clinical benefit from futibatinib. Patients in the Control Arm may receive gemcitabine-cisplatin chemotherapy for up to 8 cycles or until PD or other withdrawal criteria are met, whichever comes first. Patients who discontinue gemcitabine-cisplatin due to documented disease progression (by ICR) may receive treatment with futibatinib (*crossover*), if medically appropriate in the opinion of the Investigator and if criteria for futibatinib treatment are met.

Intervention

• Experimental Arm: Patients will receive futibatinib at an oral dose of 20 mg, administered daily (QD)
on every day of a 21-day cycle.

• Control Arm: On Days 1 and 8 of a 21-day cycle, patients will receive:
o Cisplatin 25 mg/m2 in 1000 mL 0.9% saline by intravenous (I.V.) infusion over 1 hour,
followed by 500 mL 0.9% saline over 30 minutes; and
o Gemcitabine 1000 mg/m2 in 250-500 mL 0.9% saline by I.V. infusion over 30 minutes,
beginning after completion of the cisplatin and saline infusions.

Study burden and risks

TAS-120-301 study and the procedures are designed to ensure the safety of participants. Patients with iCCA who harbor FGFR2 rearrangement as confirmed by central lab will be randomized at 1:1 ratio to either experimental arm or

control arm. Additionally, an assessment was made of the immediate necessity of patients eligible for recruitment into studies with futibatinib during the Covid-19 pandemic. There is a marked evidence of absence of curative treatments or viable alternative therapies for cancer patients overall. In particular, patients with FGFR mutations have no approved targeted treatment available in the EU and their condition is life-threatening and chronically debilitating. For these reasons, the Sponsor believes that new studies with futibatinib can be started during the Covid-19 pandemic as the benefits to patients largely outweigh the risks associated with study procedures. The Sponsor has made plans and allows minimise the risk of undue exposure to Taiho*s Trial patients including drug shipment from Study Sites to patients, remote SDVs (where feasible), protocol deviation tracking. The Sponsor performs a risk assessment of the study on an ongoing basis and prioritizes patient*s safety.

Given the information above, the Sponsor concludes that the overall benefit/risk supports the initiation of TAS-120-301 study. Taiho Oncology Inc., procedures are designed to primarily ensure the safety of participants, especially during the COVID-19 pandemic.

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. Provide written informed consent.
2. Is >18 years of age (or meets the country*s regulatory definition for legal adult age).
3. The patient has histologically confirmed, locally advanced, or metastatic, or recurrent unresectable iCCA harboring FGFR2 gene rearrangements based on testing performed by the designated central laboratory.
4. Patient has radiographically measurable disease per RECIST 1.1.
5. Patients who have received treatment for locally advanced disease (for example, trans-arterial chemoembolization, selective internal radiation therapy, external beam radiation) must have evidence of radiographic progression with measurable disease outside the previously-treated lesions.
6. Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1.
7. Adequate organ function as defined by the following criteria:
• Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <= 3.0 ×upper limit of normal (ULN); if liver function abnormalities are due to underlying liver metastasis, AST and ALT <= 5 × ULN.
• Total bilirubin <= 1.5 × ULN, or <= 3.0 × ULN for patients with Gilbert*s syndrome.
• White Blood Count (WBC) >= 2000/mm3 (>= 2.0 × 109/L)
• Absolute neutrophil count (ANC) >= 1000/mm3 (ie, >= 1.0 × 109/L by International Units [IU])
• Platelet count >= 100,000/mm3 (IU: >= 100 × 109/L)
• Hemoglobin >= 9.0 g/dL
• Phosphorus <= 1.5 × ULN
• Creatinine clearance: >= 60 mL/min
8. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test within 7 days prior to administration of the first dose of futibatinib. Female patients are not considered to be of child bearing potential if they have a history of hysterectomy or are post menopausal defined as no menses for 12 months without an alternative medical cause. Both males and females of reproductive potential must agree to use effective birth control during the study prior to the first dose and for 3 months after the last dose.
9. Willing and able to comply with scheduled visits and study procedures.

Exclusion criteria

1. Patient has received previous systemic anticancer therapy.
• Patients receiving adjuvant or neoadjuvant treatment and completed >=6 months prior to randomization are eligible.
2. Patient has mixed hepatocellular carcinoma - iCCA disease.
3. History and/or current evidence of any of the following disorders:
• Non-tumor related alteration of calcium-phosphorus homeostasis that is clinically significant in the opinion of the Investigator.
• Ectopic mineralization/calcification, including but not limited to soft tissue, kidneys, intestine, or myocardia and lung, considered clinically significant in the opinion of the Investigator.
• Retinal disorder confirmed by retinal examination and considered clinically significant in the opinion of the ophthalmologist.
4. History or current evidence of uncontrolled ventricular arrhythmias
5. Fridericia*s corrected QT interval (QTcF) > 470 ms on electrocardiogram (ECG) conducted during Screening.
6. Treatment with any of the following within the specified time frame prior to the first dose of study therapy, or failure to recover from side effects of these prior therapies:
• Major surgery within the previous 4 weeks (the surgical incision should be fully healed prior to the first dose of study therapy).
• Radiotherapy (any dose) for extended field within 4 weeks or limited field radiotherapy within 2 weeks, and/or has not recovered from acute impact of radiotherapy.
• Patients with locoregional therapy, eg, transarterial chemoembolization (TACE), selective internal radiotherapy (SIRT) or ablation within 4 weeks.
• Any history of liver transplant.
7. A serious illness or medical condition(s) including, but not limited to, the following:
• Brain metastases that are untreated or clinically or radiologically unstable (that is, have been stable for <1 month).
• Known acute systemic infection.
• Myocardial infarction, severe/unstable angina, or symptomatic congestive heart failure within the previous 6 months.
• Chronic nausea, vomiting, or diarrhea considered to be clinically significant in the opinion of the Investigator.
• Congenital long QT syndrome, or any known history of torsade de pointes, or family history of unexplained sudden death.
• Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that in the judgment of the Investigator would make the patient inappropriate for entry into this study.
8. Patients with a history of another primary malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen in the opinion of the investigator.
9. Pregnant or breast-feeding female.

10. The patient is unable to take oral medication.

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:	Pending
Start date (anticipated):	19-01-2021
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Cisplatin
Generic name:	Cisplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Futibatinib
Generic name:	N/A
Product type:	Medicine
Brand name:	Gemcitabin
Generic name:	Gemcitabin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	31-12-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-08-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-02-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-03-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-03-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-07-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-11-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-12-2022
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	EUCTR2019-004630-42-NL
ClinicalTrials.gov	NCT04093362
CCMO	NL73877.091.20