PHASE 1/2 STUDY OF TAS-120 IN PATIENTS WITH ADVANCED SOLID TUMORS HARBORING FGF/FGFR ABERRATIONS

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Phase 1 Dose Escalation:Phase 1 Dose Escalation has been completed as of Amendment 6Phase 1 Expansion Primary• To evaluate ORR in cholangiocarcinoma (intra-hepatic [iCCA] or extra-hepatic [eCCA]) patients with tumors harboring FGFR2 gene fusions or…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON48846

Source
ToetsingOnline

Brief title
TPU-TAS-120-101

Condition

- Other condition
- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Advanced solid tumors

Health condition

Advanced solid tumors

Research involving
Human

Sponsors and support

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

Intervention

Keyword: advanced solid tumors, FGF / FGFR, TAS-120

Outcome measures

Primary outcome

Standard safety monitoring and grading using National Cancer Institute (NCI)

Common Terminology Criteria for Adverse Events (CTCAE) will be used.

Efficacy Criteria for Evaluation:

For patients who discontinued treatment for reasons other than disease

progression, tumor assessments should be continued until radiologic disease

progression or initiation of new anticancer therapy (whichever occurs first).

Solid Tumors

Measurements of solid tumors will be performed throughout study treatment using

Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1,

2009). Radiographic tumor assessments (computed tomography [CT] scan with

contrast will be performed at baseline and at the end of every 2 cycles (up to

+ 2 weeks) up to Cycle 4 (or as clinically indicated). Following Cycle 4, CT

scans will be performed after every 3 cycles (± 7 days) or as clinically

indicated, and at study completion.

Brain Tumors

Patients with brain tumors will be assessed using Response Assessment in Neuro-Oncology (RANO) criteria (2010). Patients with brain tumors will be evaluated for response by contrast magnetic resonance imaging (MRI) (gadolinium-based magnetic resonance imaging [Gd-MRI]). All MRIs should be performed when the patient is on a stable dose of steroids. Gd MRI will be performed at baseline and at the end of every 2 cycles (up to + 2 weeks) up to Cycle 4 (or as clinically indicated). Following Cycle 4, Gd MRI scans will be performed after every 3 cycles (± 7 days) or as clinically indicated, and at study completion.

Neurological examination for patients with brain tumors must always be performed within one week of the date of the Gd-MRI as part of the response assessment.

Endpoints

Phase 1 Expansion: the primary endpoint is ORR in each treatment group (and EPR for primary CNS tumors) and the secondary endpoints of DOR, DCR, PFS, and OS in each treatment group.

Phase 2: the primary endpoint is ORR and the secondary endpoints of DOR, DCR, PFS, PROs and OS.

Primary endpoints will be based on the independent review of images by the Core Imaging Laboratory. In addition, for the Phase 2 part of the study, sensitivity analyses for some key efficacy endpoints (e.g., ORR, and PFS) will be performed

based on investigators or local radiologist assessments.

Secondary outcome

For phase 1 Expansion the secondary endpoints is DOR, DCR, PFS, and OS.

For phase 2, the secondary endpoints is DOR, DCR, PFS, Patient-Reported

Outcomes (PROs) and OS.

Study description

Background summary

Activating fibroblast growth factor receptor (FGFR) gene abnormalities are reported in various cancers including non-small cell lung cancer (NSCLC) (FGFR1 amplification), breast (FGFR1 and 2 amplification), gastric (FGFR2 amplification), bladder (FGFR3 activating mutation or gene translocation), endometrial (FGFR2 activating mutation), multiple myeloma (FGFR3 gene translocation), and rhabdomyosarcoma (FGFR4 activating mutation).

TAS-120 is a novel selective small molecule FGFR inhibitor.

TAS 120 equally inhibited all 4 subtypes of FGFR and showed high selectivity for FGFR when tested against a panel of 296 kinases. Half maximal inhibitory concentration (IC50) values (nmol/L) were 3.9 for FGFR1, 1.3 for FGFR2, 1.6 for FGFR3, and 8.3 for FGFR4. TAS 120 was highly active against cancer cell lines with FGFR gene abnormalities including cancer cell lines that acquired resistance to other (adenosine triphosphate (ATP) competitive FGFR tyrosine kinase inhibitors (TKIs). In vitro studies have shown that TAS 120 selectively inhibits cell growth of human cancer cell lines that have FGFR gene abnormalities. In vivo studies showed that TAS-120 had strong antitumor efficacy in nude mouse or nude rat xenograft models bearing tumors with various FGFR gene abnormalities (FGFR1 or FGFR2 amplification and FGFR3 translocation).

In addition, TAS-120 retained inhibitory potency against mutant FGFR2 including the V565I gatekeeper mutation with a similar potency compared to wild type FGFR2. N550H and E566G mutations in the FGFR2 hinge region, which were reported to cause resistance to dovitinib (another FGFR inhibitor), were also sensitive to TAS 120. Furthermore, TAS 120 showed inhibitory potency against mutant FGFR2 including a K660M activation loop mutation. IC50 values for

pFGFR2 inhibition (nmol/L) were 0.9 for WT, 1.3 for V565I, 3.6 for N550H, 2.3 for E566G, and 5.2 for K660M. In contrast, when several ATP competitive inhibitors of FGFR were tested against these FGFR2 mutants, their inhibitory potencies were reduced compared to their potency against the wild type.

Cholangiocarcinoma (CCA), a bile duct cancer, is a rare tumor that arises from the malignant transformation of epithelial cells of the bile ducts. It is typically classified as either intrahepatic (iCCA) or extrahepatic (eCCA). Intrahepatic cholangiocarcinoma develops in the smaller bile ducts inside the liver and is the least common form of the disease (approximately 10%), whereas eCCA includes cancers in the peri-hilar (also known as Klatskin tumor) and distal bile duct area and is most common (approximately 90%).

Although CCA is known to have the histological and molecular features of an adenocarcinoma of epithelial cells lining the biliary tract, the actual cell of origin is unknown. Fibroblast growth factor/fibroblast growth factor receptor aberrations are a reported genetic modification in CCA. In iCCA, FGFR2 gene rearrangement including fusions has been identified as an early driver of oncogenic events. These gene rearrangement / fusions are present in an estimated 10% to 20% of patients. Therefore, inhibiting the FGFR pathway in patients with iCCA is a plausible therapeutic strategy for appropriately selected patients with this disease.

For disease that is localized at diagnosis, surgical resection offers the only chance of cure for patients with CCA. Unfortunately, symptoms are not usually apparent until CCA is at an advanced stage, and thus, most patients (>65%) have disease which is unresectable at diagnosis. Unresectable locally advanced (stage III) and metastatic (stage IV) disease has a poor prognosis with 5-year overall survival (OS) of 10% and 0%, respectively. For such patients, chemotherapy and supportive care are usually offered. Although there are no approved treatments for CCA, gemcitabine/cisplatin is the standard 1st line chemotherapy regimen for patients with advanced, metastatic, unresectable CCA. There is no standard regimen beyond first line treatment.14 In the second line treatment setting, a retrospective evaluation of 761 patients with advanced biliary tract cancers, including CCA has shown a median overall response rate of 7.7% (95% confidence interval (CI): 5% to 11%) and a median progression-free survival (PFS) of 3.2 months (95% CI: 2.7 - 3.7 months).These poor results confirm a substantial unmet medical need for new therapies in patients with advanced CCA who have failed initial chemotherapy.

The FGFR signaling axis has been well characterized for its role in proliferation, differentiation, migration, and survival, and it is fundamental to embryonic development, regulation of angiogenesis, and wound healing in adults. Dysregulation of the FGFR signaling pathway has been associated with many developmental disorders and with cancer. An extensive amount of literature indicates that FGFR is one of the receptor tyrosine kinases most frequently mutated or otherwise abnormally activated in late-stage human cancer.

Therefore, FGFR has been shown to be a valid target, and TAS-120 is a selective inhibitor of FGFR. TAS-120 exhibits convincing antitumor activity in several xenograft models. Importantly, it delivers antitumor efficacy in xenograft models with a large safety window.

This Phase 1/2 clinical trial was planned to investigate the pharmacokinetics (PK), pharmacodynamics, efficacy, safety, and tolerability of TAS 120 in patients with advanced solid tumors, with or without FGFR abnormalities who have failed all standard therapies or for whom standard therapy does not exist.

During the Phase 1 Dose Escalation part of the study, dose levels of 4, 8, 16, 20 and 24 mg once daily (QD) were evaluated. At 24 mg, 3 of 9 evaluable patients experienced a dose-limiting toxicity (DLT) during Cycle 1, thus, 24 mg was determined as the DLT dose level. At 20 mg QD, no DLT was reported in the 5 evaluable patients during Cycle 1, and thus, 20 mg QD was determined as the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D).

The original design of the Phase 2 portion of the study (enrolling patients with iCCA harboring FGFR2 gene fusions) was based on preliminary anti-tumor activity observed in this population in the Phase 1 portions of the study. Specifically, at the time the Phase 2 portion was designed (data cut off 17 September 2017), a total of 3 confirmed partial responses had been observed among 14 response-evaluable patients with iCCA harboring FGFR2 gene fusions. Additional findings from the ongoing Phase 1 portion of the study have shown 4 confirmed PR in 13 patients with iCCA harboring other FGFR2 rearrangements and treated at 16 and 20 mg QD.
Accordingly, as of Amendment 7 to this protocol, the study population for the Phase 2 portion of the study will include approximately 100 patients with iCCA harboring confirmed FGFR2 gene fusions or other FGFR2 rearrangements.

Study objective

Phase 1 Dose Escalation:
Phase 1 Dose Escalation has been completed as of Amendment 6

Phase 1 Expansion

Primary
• To evaluate ORR in cholangiocarcinoma (intra-hepatic [iCCA] or extra-hepatic [eCCA]) patients with tumors harboring FGFR2 gene fusions or other FGFR abnormalities.
• To evaluate ORR and EPR (defined as progression-free rate at the end of Cycle 2) in patients with primary CNS tumors harboring FGFR gene fusions or FGFR1 activating mutations.
• To evaluate ORR in a basket of tumor types with tumors harboring FGFR2 amplifications.

• To evaluate ORR in a basket of tumor types with tumors harboring any FGFR gene fusions or activating mutations.

Secondary
• To investigate the safety of TAS-120.
• To evaluate disease control rate (DCR), DOR, PFS and OS in each treatment group.

Exploratory
• To investigate the concentration ratio of TAS-120 in cerebral spinal fluid (CSF) vs. plasma in patients with primary CNS tumors.
• To assess FGF/FGFR aberrations and concurrent molecular alterations in circulating tumor DNA (ctDNA) (if data is available), and its association with tumor resistance to TAS-120
• To investigate the PK and to explore the relationship between PK and efficacy or toxicity of TAS-120

Phase 2:

Primary
• To confirm ORR in iCCA patients with FGFR2 gene fusions or other FGFR2 rearrangements based on independent central radiology review.

Key secondary
• To evaluate DOR

Other secondary
• To evaluate the safety and tolerability of TAS-120
• To evaluate DCR, PFS, and OS
• To evaluate Patient-Reported Outcomes (PROs)

Exploratory
•To investigate the PK and to explore the relationship between PK and efficacy or toxicity of TAS-120.

Study design

This is an open-label, nonrandomized, dose-escalation and dose-expansion, phase 1/2 study of TAS-120, evaluating the safety, tolerability, PK, pharmacodynamic, and antitumor activity of TAS 120 in patients with advanced solid tumors with FGF/FGFR-related abnormalities who have failed all standard therapies or for

whom standard therapy does not exist or is not tolerated.

The study will be conducted in 3 parts:
• phase 1 Dose Escalation: to determine the MTD and/or RP2D of TAS-120
• phase 1 Expansion: to further evaluate the efficacy and safety of the MTD and/or RP2D of TAS-120 in patients with tumors harboring specific FGF/FGFR aberrations;
• phase 2: to confirm the ORR of TAS-120 in iCCA patients with tumors harboring FGFR2 gene fusions or other FGFR2 rearrangements.

As of amendment 6, the phase 1 dose escalation phase is completed and the MTD/RP2D of 20 mg QD was established. Details of the phase 1 dose escalation study design can be found in previous versions of the study protocol.

Study burden and risks

TAS-120 may help with the cancer regression, but it is not certain. Patient participation may provide new information which may benefit cancer patients in the future. It is hoped that information gained in this study will aid in the understanding of cancer and help in the development of new approaches to its treatment.

Disadvantages of participation in the study may be:
• possible side effects/complications of the cancer;
• possible adverse effects and/or discomforts of the evaluations in the study.

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 (or according the country's regulatory definition for legal adult age)., 3. Has histologically or cytologically confirmed, locally advanced, metastatic cancer meeting the following criteria:
a.Phase 1 Expansion , i.Patient has failed ((or in the case of Group 2, failed or refused) all standard therapies or standard therapy does not exist or is not tolerated. , ii. Patient is eligible for 1 of the following enrollment groups, based on diagnosis, prior therapy, and FGF/FGFR aberrations as shown:
a. Group 1 (Enrollment Suspended as of Amendment 7): Patient has intrahepatic or extrahepatic cholangiocarcinoma harboring FGFR2 gene fusions.
b. Group 2: Patient has intrahepatic or extrahepatic cholangiocarcinoma withharboring FGFR2 gene fusions or other FGFR2 , and has not received or received less than 1 cycle of prior chemotherapy (due to intolerance or patient refusal).
c. Group 3 (Enrollment Suspended as of Amendment 7): Patient has intrahepatic or extrahepatic cholangiocarcinoma harboring FGFR2 gene fusions and has received prior treatment with FGFR inhibitors.
d. Group 4 (Enrollment suspended as of Amendment 7): Patient has intrahepatic or extrahepatic cholangiocarcinoma harboring FGFR abnormalities, other than FGFR2 gene fusions (for example, mutations, rearrangements, or amplifications).
e. Group 5: Patient has a primary CNS tumor harboring FGFR gene fusion or FGFR1 activating mutation and fulfills the following criteria (i and ii):,
i. Patients who are presenting in recurrence or relapse must have at least one measurable enhancing mass lesion with 2 perpendicular diameters of at least 10 mm documented on baseline contrast magnetic resonance imaging (MRI) (gadolinium-based MRI).
ii. Patients should be on a stable dose of steroids for at least

7 days prior to obtaining the baseline contrast MRI of the brain and at least 7 days prior to starting study drug. , f. Group 6 (Enrollment Suspended as of Amendment 7): Patient has advanced urothelial carcinoma harboring FGFR3 fusions or FGFR3 activating mutations.
g. Group 7: Patient has any tumor type not included in one of the prior groups, harboring FGFR2 amplification (no minimum number of copies).
h. Group 8 (Enrollment Suspended as of Amendment 7): Patient has any tumor type not included in one of the prior groups, harboring FGFR gene fusions or activating mutations.
, b. Phase 2, i. Patient has histologically or cytologically confirmed, locally advanced, metastatic, unresectable iCCA harboring FGFR2 gene fusions or other FGFR2 rearrangements based on results from either of the following:
a. Testing by Foundation Medicine:
i. As part of study pre-screening; or
ii. Previously tested by Foundation Medicine; in this case, it is requested that tumor tissue be provided to Foundation Medicine if available.
b. Local laboratory testing using next generation sequencing [NGS], fluorescence in situ hybridization [FISH], or other assays that can determine FGFR2 gene fusions or other FGFR2 rearrangements on tumor tissues or from ctDNA. It is requested that patients enrolled on this basis provide tumor tissues to Foundation Medicine, if available from either archival samples or fresh tumor biopsy.
ii. Patient has been treated with at least one prior systemic gemcitabine and platinum-based chemotherapy. Patients with prior adjuvant gemcitabine-platinum chemotherapy are eligible if the patient had recurrence within 6 months of the last dose of the regimen.
iii. Patient has documentation of radiographic disease progression on the most recent prior therapy, 4. Patient has measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1, 2009) for advanced solid tumors or RANO criteria (2010) for brain tumors., 5. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 on Day 1 of Cycle 1 (ECOG Performance Status)., 6. Able to take medications orally (e.g., no feeding tube)., 7. Adequate organ function as defined by the following criteria:
a. 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.
b. Total bilirubin <= 1.5 × ULN, or <= 3.0 mg/dL for patients with Gilbert*s syndrome.
c. International normalized ratio (INR) <1.3 (or < 3.0 on anticoagulants)
d. Absolute neutrophil count >= 1000/mm3 (i.e., >= 1.0 × 109/L by International Units [IU])
e. Platelet count >= 75,000/mm3 (IU: >= 75 × 109/L)

f. Hemoglobin >= 9.0 g/dL, 8. Creatinine clearance (calculated* or measured value**): >= 40 mL/min
* For a calculated creatinine clearance (Ccr) value, the eligibility should be determined using the Cockcroft-Gault formula:
a. Male Ccr (mL/min) = Body weight (kg) × (140 - age)/[72 × creatinine (mg/dL)]
b. Female Ccr (mL/min) = male Ccr × 0.85
**A measured Ccr value (i.e., not calculated) should meet this criterion., 9. Women of child-bearing potential (WOCBP) must have a negative pregnancy test (urine or serum) within 7 days prior to administration of the first dose of TAS 120. 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 6 months after the last dose. , 10. Willing and able to comply with scheduled visits and study procedures.

Exclusion criteria

1. History and/or current evidence of clinically significant non-tumor related alteration of calcium-phosphorus homeostasis., 2. History and/or current evidence of clinically significant ectopic mineralization/calcification. , 3. History and/or current evidence of clinically significant retinal disorder confirmed by retinal examination. , 4. History or current evidence of serious uncontrolled ventricular arrhythmias.

5. Fridericia*s corrected QT interval (QTcF) > 470 ms on ECG conducted during Screening.

6. Treatment with any of the following within the specified time frame prior to the first dose of TAS-120:, a. Major surgery within the previous 4 weeks (the surgical incision should be fully healed prior to the first dose of TAS 120)., b. Radiotherapy for extended field within 4 weeks or limited field radiotherapy within 2 weeks. , c. Patients with locoregional therapy, e.g., transarterial chemoembolization (TACE), selective internal radiotherapy (SIRT) or ablation within 4 weeks. , d. Any noninvestigational anticancer therapy within 3 weeks or have not recovered from side effects of such therapy prior to TAS 120 administration (mitomycin within prior 5 weeks). , • Targeted therapy or immunotherapy within 3 weeks or within 5 half-lives (whichever is shorter) , e. Any investigational agent received within 5 half-lives of the drug or 4 weeks, whichever is shorter. Concurrent participation in an observational study may be allowed after review by the Sponsor*s Medical Monitor.
f. Patients with prior FGFR-directed therapy., 7. A serious illness or medical condition(s) including, but not limited to, the following:, a. Known brain metastasis (not including primary brain tumors) unless patient is

clinically stable for >= 1 month., b. Known acute systemic infection., c. Myocardial infarction, severe/unstable angina, symptomatic congestive heart failure (New York Heart Association [NYHA] Class III or IV (see Appendix D, New York Heart Association [NYHA] Classification) within the previous 2 months; if > 2 months, cardiac function must be within normal limits and the patient must be free of cardiac-related symptoms., d. Chronic nausea, vomiting, or diarrhea considered to be clinically significant in the opinion of the investigator., e. Congenital long QT syndrome, or any known history of torsade de pointes, or family history of unexplained sudden death. , f. 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 that is currently clinically significant, and has potential for metastases or currently requires active intervention (except for gonadotropin-releasing hormone (GnRH) or luteinizing hormone-releasing hormone (LH-RH) agonists in prostate cancer or adjuvant hormonal therapy in breast cancer)., 9. Pregnant or lactating female.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-07-2019
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	TAS-120
Generic name:	TAS-120

Ethics review

Approved WMO Date:	28-12-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-06-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-12-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	01-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2013-004810-16-NL
ClinicalTrials.gov	NCT02052778
CCMO	NL64142.056.17