A performance evaluation study for the testing of DNA extracted from either tumor tissue biopsy samples or plasma, using the therascreen® EGFR Plus RGQ PCR Kit, from subjects with Non-Small Cell Lung Cancer, being screened for inclusion in Taiho Oncology, Inc*s Clinical Trial (Protocol No. 10073010).

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For Taiho's Study (drug study):Primary Objectives: • Phase 1 Dose Escalation: To investigate the safety and determine the recommended Phase 2 dose (RP2D) and dosing schedule of TAS3351.• Phase 1 Dose Expansion: To explore the efficacy of...

Ethical review	Approved WMO
Status	Pending
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON56744

Source
ToetsingOnline

Brief title
Testing samples using the therascreen EGFR Plus RGQ PCR Kit.

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Lung Cancer, Non Small Cell Lung Cancer

Research involving
Human

Sponsors and support

Primary sponsor: QIAGEN
Source(s) of monetary or material Support: Taiho.

Intervention

Keyword: C797 mutation, EGFR, NSCLC

Outcome measures

Primary outcome

The primary endpoint of the Phase 1 Dose Escalation part of this study is to identify the RP2D based on safety and preliminary antitumor activity observed as standard for Phase 1 first in human studies.

The primary endpoint of the Phase 1 Dose Expansion and the Phase 2 part is Overall response rate (ORR) assessed by Independent Central Review (ICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. ORR is a clinically meaningful and accepted endpoint by regulatory agencies for studies in later-line EGFRmt NSCLC patients. ORR will be assessed by ICR to avoid any potential Investigator bias and to increase the validity of the ORR results observed.

Secondary outcome

As a key secondary objective, this study will include Duration of response (DoR) as assessed by ICR to evaluate the durability of responses. Durability of

responses are considered a key factor to determine whether an observed ORR is

clinically meaningful.

Study description

Background summary

About 10%-15% of Caucasian patients with non-small cell lung cancer (NSCLC) and up to 50% of East-Asian patients with NSCLC have tumors harboring an epidermal growth factor receptor (EGFR) activating mutations (i.e., L858R or exon 19 deletion mutations) . The current standard of care for these patients with locally advanced or metastatic NSCLC is treatment with an EGFR tyrosine kinase inhibitor (TKI). Several Phase 3 clinical trials have established the role of first-generation (gefitinib and erlotinib) and second-generation (afatinib and dacomitinib) EGFR TKIs as first-line treatment with similar median response rates of 70%-75% and progression-free survival (PFS) ranging from 10-14 months, which was a significant improvement compared to platinum-based chemotherapy. The most frequent resistance mechanism to first-and second-generation EGFR TKIs is the emergence of T790M EGFR kinase domain mutations. More recently, the third generation EGFR TKI osimertinib active against T790M EGFRmt showed superior efficacy when compared against erlotinib, with improved PFS (18.9 versus 10.2 months) and overall survival (OS) (38.6 versus 31.8 months).

Despite third-generation EGFR TKIs being highly effective in advanced EGFRmt NSCLC, resistance to EGFR TKIs inevitably occurs leading to disease progression. The current treatment options for EGFRmt NSCLC patients progressing on treatment with third-generation EGFR TKIs are limited. Chemotherapy with pemetrexed alone or in combination with cisplatin is currently considered standard of care. However, the reported clinical outcome is poor with approximately 25% ORR and median PFS of approximately 3 months post osimertinib. One of the prevalent resistance mechanisms to third-generation EGFR TKIs is an acquired C797S EGFR mutation which is observed in 10%-25% of NSCLC patients progressing on osimertinib.

Study 10073010 is a first-in-human Phase 1/2 study, being conducted by Taiho Oncology Inc, that is designed to determine the RP2D and efficacy of TAS3351 in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring an acquired C797S EGFR mutation.

TAS3351 is a novel fourth-generation EGFR TKI designed to potently inhibit triple-mutant EGFR in NSCLC patients. In addition to its activity against EGFR sensitizing mutations (e.g. L858R or exon 19 deletion mutations) and the acquired T790M resistance EGFRmt, TAS3351 also inhibits C797S EGFRmt observed

in patients progressing on third generation EGFR TKIs, while sparing EGFR wild-type. In nonclinical studies, TAS3351 demonstrated dose-dependent activity in vitro and in vivo in NSCLC models with co-occurrence of sensitizing EGFRmt and T790M/C797S EGFRmt (data on file). Furthermore, TAS3351 has been shown to be brain penetrant in nonclinical models. Approximately 25%-40% of patients with NSCLC develop brain metastases and, due to limited treatment options, the prognosis of patients with brain metastases remains poor. Thus, TAS3351 might also provide a new treatment option for patients with EGFR deregulated NSCLC who have brain metastases.
Based on these results, TAS3351, is expected to have antitumor activity in NSCLC patients with tumors harboring an acquired C797S EGFRmt, a population with an unmet medical need.

Mutations in the EGFR oncogene are found in human cancers. The presence of these mutations correlates with response to certain tyrosine kinase inhibitor therapies in patients with non-small cell lung cancer. Such mutations in the EGFR oncogene are present in the general population of patients with NSCLC at a frequency of approximately 10% in patients from the USA, Europe, or Australia and up to 30% in patients from Japan and Taiwan.

The therascreen EGFR Plus RGQ PCR Kit is a real-time PCR (polymerase chain reaction) test for the detection of 42 mutations in the EGFR cancer-related gene using ARMS (Amplification Refractory Mutation System) and PCR clamp technologies for the qualitative detection and identification of mutations in the EGFR gene; exons 18, 19, 20, and 21. While both FFPE and plasma samples can be used, only plasma generates a semi-quantitation of these mutations. The kit allows the semi-quantification of G719X (X = A, S, or C; exon 18), T790M (exon 20), C797Sa and C797Sb (exon 20), S768I (exon 20), L858R (exon 21), and L861Q (exon 21) in DNA samples extracted from human plasma.

Study objective

For Taiho's Study (drug study):
Primary Objectives:
• Phase 1 Dose Escalation: To investigate the safety and determine the recommended Phase 2 dose (RP2D) and dosing schedule of TAS3351.
• Phase 1 Dose Expansion: To explore the efficacy of TAS3351.
• Phase 2: To assess the efficacy of TAS3351.

For QIAGEN's Study (Device Study)
The primary objective is to demonstrate the effectiveness of the EGFR Plus assay in identifying the population with C797S EGFRmt for the clinical study as measured through the efficacy of the device and drug in combination. Efficacy will be established based on the overall response rate (ORR) as defined in Taiho*s clinical trial 10073010.

Study design

Drug Study

Study 10073010 is a first-in-human Phase 1/2 study, being conducted by Taiho Oncology Inc, that is designed to determine the RP2D and efficacy of TAS3351 in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring an acquired C797S EGFR mutation.
The study will consist of 3 parts:

• Part A1: Phase 1 Dose Escalation

The Phase 1 Dose Escalation is designed to evaluate 6 dose levels of TAS3351 from 50 to 700 mg/day using a Bayesian Optimal Interval (BOIN) design. The BOIN design uses prespecified sample sizes and isotonic regression to pool information across doses, resulting in a more efficient statistical estimate of the MTD than a standard 3+3 design.9 The Bayesian Optimal Interval (BOIN) design has a target DLT rate of 30% and an acceptable DLT interval from 24%-36%. The decision to escalate or de-escalate the dose of TAS3351 will be based on the cumulative DLT rate at the current dose level and the predetermined DLT rate threshold for dose escalation/de-escalation boundaries as defined by the BOIN model. TAS3351 will be administered once daily (QD) on a 21-day cycle at a starting dose of 50 mg QD and escalated based on tolerability to patients who harbor any EGFR mutation, with consideration of lower increments than planned if clinically relevant toxicities are observed (intermediate dose levels). In the event of unacceptable toxicities at Dose Level 1, lower dose levels may be explored (eg, Dose Level -1). If PK, pharmacodynamic, and/or safety data indicate, twice daily (BID) dosing of TAS3351 may be explored. In order to appropriately characterize the PK profile of TAS3351, there will be a PK lead-in with a single administration of TAS3351 followed by PK sampling 3 days prior to the start of continuous daily dosing of TAS3351 for patients enrolled in the Dose Escalation Part A1 only.

• Part A2: Phase 1 Backfill Patients

When a dose level has been determined to be safe in Part A1 and preliminary antitumor activity has been observed, up to 10 further patients may be enrolled in that dose level (for a total of up to 20 backfill patients). A dose is deemed to be safe in Part A1 if there is an acceptable DLT rate in that dose level as per the BOIN design. Antitumor activity is defined as evidence of tumor shrinkage in at least one of the patients at that dose level.
If no preliminary antitumor activity is observed in Part A1, the totality of nonclinical in vitro and in vivo data as well as clinical PK data may be used to inform selection of dose level(s) for *backfill* patients. This will include IC50 values from various in vitro assays and/or the total exposure of TAS3351 and its active metabolite associated with tumor shrinkage in preclinical

xenograft mouse models to be used as thresholds for targeted efficacious Cmin and/or AUC, respectively. The exposure linked with nonclinical activity is a total TAS3351 and TAS-05-14317 Cmin of 40.3 nM. Clinical PK simulation will be applied to project dosing regimen(s) which may achieve the targeted threshold(s). The doses explored in the A2 part of the trial will be chosen in consultation between the investigators and the Sponsor based on the above safety and efficacy criteria as well as a
review of the PK data. *Backfill*patients enrolled are required to have a tumor harboring a C797S EGFRmt. The additional information from these backfill* patient cohorts will broaden the amount of safety and preliminary antitumor activity data for TAS3351 at potential active dose levels to inform the selection of the RP2D of TAS3351.

• Part B: Phase 1 Dose Expansion

The Phase 1 Dose Expansion part of the study will be initiated after an RP2D and a dosing scheme has been identified in Part A. NSCLC patients with C797S EGFRmt will be enrolled to explore the efficacy and confirm the safety of TAS3351 at the RP2D in a larger patient population. Moreover, a second dose level of TAS3351 may be evaluated in an additional cohort of patients in Part B if promising antitumor activity is observed at another lower TAS3351 dose level during Part A. In this case, patients enrolled in Part B will be randomized at a 1:1 ratio between the two treatment arms to evaluate the optimal RP2D of TAS3351 based on a comparative analysis considering the totality of efficacy and safety data observed.

The results from Part B will confirm the RP2D of TAS3351 and are expected to provide, in combination with the *Backfill* patients from Part A2, the proof of concept for the efficacy of TAS3351 in NSCLC patients with the C797S EGFRmt. Based on these results, the Phase 2 part of this study will be initiated.

Safety data will be summarized at the end of Parts A and B, and these results will be submitted to all EU member states with study sites participating in this study. The safety summaries will contain, at a minimum, the dose-finding data, the dose selected for the next study phase, and all safety data.

In addition, further cohorts may be added by an amendment to explore the activity of TAS3351 in further subgroup(s) of patients based on activity observed in the Part A dose escalation and/or emerging scientific data. This may include an additional cohort for EGFRmt NSCLC patients with brain metastases to explore the efficacy of TAS3351 against CNS metastases or against other type of EGFRmt, if promising results are observed during Part A of this study.

• Part C: Phase 2 D

The Phase 2 part of the study will be an open-label, single-arm, Phase 2 study

to assess the safety and efficacy of TAS3351 in advanced NSCLC patients with C797S EGFRmt who progressed on a prior treatment with another EGFR inhibitor. Patients will receive TAS3351 at the RP2D and dosing scheme confirmed in Part B and be evaluated for ORR based on RECIST v1.1 by Independent Central Review (ICR) as the primary endpoint. A key secondary endpoint of this part of the study will be duration of response (DoR) by ICR.

Device Study:

The therascreen EGFR Plus RGQ PCR Kit will be used to prospectively test specimens in parts A2, B and C above to select patients who do not have local results available for further screening for enrolment in the TAS3351 clinical study and to confirm the local results for patients who have these local results available. The test will also be used to retrospectively test samples from part A1 above.

Study burden and risks

All patients will have a screening visit to ensure eligibility for the study.
Phase 1:
Following the screening visit there will be a PK Lead-In period for patients in part A1 of the study where they will have a physical exam, vital signs taken, blood drawn for chemistry, hematology, and coagulation testing, give a urine sample, and have blood drawn for PK analysis and ECG*s performed.

Following this period, the study progresses in 21-day cycles. There are more visits in cycle 1 than subsequent cycles.

In cycle 1 there are 3 visits (Cycle 1 day 1, day 8, and day 15). On all of these visits patients will have their vital signs taken, and give blood for chemistry and hematology testing. On 2 of these visits, patients will undergo a physical exam, have blood drawn for chemistry and hematology, have pregnancy testing (for WOCBP), and have blood drawn for PK analysis and ECGs. On one of these visits (day 1) patients will also have blood drawn for coagulation, give a urine sample, and have blood drawn for cfDNA biomarker testing.

In cycle 2 there are 2 visits (cycle 2 day 1 and day 8). On both of these visits patients will have their vital signs taken, and give blood for chemistry and hematology testing. On one of the visits (day 1), patients will undergo a physical exam, have blood drawn for chemistry, hematology, and coagulation, have pregnancy testing (for WOCBP), give a urine sample, have ECGs performed, have blood drawn for PK testing, and have blood drawn for cfDNA biomarker testing.

In cycle 3 and after patients only need to come in on the first day of each cycle (i.e. cycle 3 day 1). At this visit patients will undergo a physical exam, have their vital signs taken, have blood drawn for chemistry, hematology,

and coagulation, they will have a pregnancy test (for WOCBP) and give a urine sample. They will also have a PK sample drawn (cycle 3 only), ECGs performed, an ECHO or MUGA scan performed, and give a blood sample for cfDNA biomarker testing.

Patients may have more visits depending on how long they remain in the study. Throughout these cycles there is an optional biopsy sample that patients can submit at any time and patients will have radiologic tumor assessments every 6 weeks after C1D1 (or after 12 months, these become every 9 weeks).

Phase 2:
Following the screening visit patients will start with cycle 1. In cycle 1 there are 2 visits (cycle 1 day 1 and day 8). On both of these visits patients will have their vital signs taken, blood drawn for hematology and chemistry. On one of the visits (day 1) patients will also have a physical exam, provide a urine sample, a pregnancy test (for WOCBP), blood drawn for hematology, chemistry, and coagulation as well as blood drawn for PK samples, ECG*s, and blood drawn for cfDNA biomarker testing.

In cycle 2 and after patients only need to come in on the first day of each cycle (i.e. cycle 2 day 1). At this visit patients will undergo a physical exam, have their vital signs taken, have blood drawn for chemistry, hematology, and coagulation, they will have a pregnancy test (for WOCBP) and give a urine sample. They will also have a PK sample drawn (cycle 2 and 3 only), ECGs performed, and give a blood sample for cfDNA biomarker testing.

Patients may have more visits depending on how long they remain in the study. Throughout these cycles there is an optional biopsy sample that patients can submit at any time and patients will have radiologic tumor assessments every 6 weeks after C1D1 (or after 12 months, these become every 9 weeks).

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. >=18 years of age (or meets the country*s regulatory definition for legal adult age,
whichever is greater)
3. Histologically or cytologically confirmed, locally advanced, non-resectable or metastatic
NSCLC
4. Has received the following prior treatment and no more than 2 lines of prior cytotoxic
chemotherapy for locally advanced or metastatic disease setting:
a. Part A1 (Phase 1 Dose Escalation): Standard of care (SOC) that is available to the
patient, unless contraindicated or intolerable to the patient
b. Part A2: Progression on third-generation EGFR TKI (eg, osimertinib, lazertinib) and having received or not eligible for platinum-based chemotherapies or other
targeted approved therapies in case of off-target alterations.
c. Parts B, and C: Progression on third-generation EGFR TKI (eg, osimertinib,
lazertinib)
5. Has the following EGFRmt status as determined by a CLIA certified (US), locally
certified (outside of the US), or the study central laboratory based on tumor tissue or
plasma cfDNA:
a. Part A1 (Phase 1 Dose Escalation): Any EGFRmt

b. Parts A2, B, and C: Any sensitizing EGFRmt and a confirmed C797S EGFRmt (Note: no T790M EGFRmt required)
6. Has tumor tissue available collected after progression on the most recent systemic EGFR
TKI treatment in a quantity sufficient to allow for analysis of EGFRmt status by the
Sponsor*s central laboratory (optional for Part A1 only). Please refer to the Laboratory
Manual for details.
7. Has measurable disease per RECIST v1.1 (optional for patients in Part A1)
8. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
9. Adequate organ function as defined by the following criteria:
a. Absolute neutrophil count (ANC) >= 1.5 × 109/L
b. Platelet count >= 100,000/mm3 (>= 100 × 109/L); last transfusion of blood products
must be >=2 weeks prior to start of study treatment.
c. Hemoglobin >= 9.0 g/dL
d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <= 3.0 × upper
limit of normal (ULN); if liver function abnormalities are due to underlying liver
metastasis, AST and ALT <= 5.0 × ULN
e. Total bilirubin <= 1.5 × ULN, or <= 3.0 × ULN for patients with Gilbert*s syndrome
f. Creatinine clearance (CrCl) (calculated or measured value): >=50 mL/min. For
calculated CrCl, use the Cockcroft-Gault formula
g. Potassium blood levels >=3.0 mmol/L
10. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test
prior to administration of the first dose of study treatment. Female patients are not
considered to be of child-bearing potential if they are post-menopausal (no menses for
12 months without an alternative medical cause) or permanently sterile (hysterectomy,
bilateral salpingectomy, or bilateral oophorectomy).
11. Both males and females of reproductive potential must agree to use highly effective birth
control throughout the study and at least for:
* 6 months after the last dose of study treatment for females
* 3 months after the last dose of study treatment for males
or longer, based on local requirements

In addition to the above, patients in France must meet the following criterion:

12. Affiliated with a social security system or be a beneficiary of an

equivalent system of
patient care as applicable by local regulations in France.

Exclusion criteria

1.Currently receiving an investigational drug in a clinical trial or participating in any other
type of medical research judged not to be scientifically or medically compatible with this
study
2. Has received prior treatment with any of the following within the specific time frame
prior to the first dose of study treatment:
a. Major surgery/surgical therapy for any cause within 4 weeks; the patient must have
recovered adequately from the toxicity and/or complications of the intervention prior
to starting study treatment
b. Chemotherapy, biologic therapy, targeted therapy, immunotherapy, or investigational
agents within 5 half-lives or within 4 weeks (whichever is shorter) prior to the first
dose of study treatment. Patient must have recovered from toxicities of the prior
therapy based on the Investigator*s judgement prior to starting study treatment
c. No prior treatment with:
(i) Part A1 (Phase 1 Dose Escalation): Systemic immunotherapy (eg, PD-1/PD-L1 antibody)
(ii) Parts A2, B, and C: Any EGFR C797S mutation-targeting agent (eg, BLU-945)
d. Radiotherapy prior to the start of study treatment within:
(i). 2 weeks for radiation therapy of non-thoracic regions (7 days for palliative
radiation of single lesions)
(ii). 3 months for radiation therapy including thoracic region.
Patients must have recovered from all radiation-related toxicities, not require
corticosteroids, and not have had radiation pneumonitis.
3. Have any unresolved clinically relevant toxicity of Grade >= 2 from previous anti-cancer
treatment, except for alopecia, skin pigmentation, and Grade 2, prior platinum-therapy
related neuropathy. Patients with chronic, but stable Grade 2 toxicities may be allowed to

enroll if the Investigator and Sponsor agree.
4. Any strong and moderate inhibitors/inducers of cytochrome P450 (CYP) 3A two weeks
prior to start of therapy. If a patient is receiving strong inhibitors/inducers
of CYP3A , these medications and substances must be discontinued >=2 weeks prior
to the first dose of study treatment.
5. Has the following CNS metastases disease status:
a. Part A1 (Phase 1 Dose Escalation): Known untreated central nervous system (CNS)
metastases, or history of uncontrolled seizures, or leptomeningeal disease. Patients
with treated brain metastases are eligible if there is no evidence of progression for at
least 4 weeks after CNS-directed treatment, as ascertained by clinical examination
and brain imaging (MRI or CT scan) during the screening period, and they are on a
stable or decreasing dose of corticosteroids for at least 2 weeks prior to the first dose
of study treatment.
b. Part A2, B, and C: Spinal cord compression, symptomatic and unstable CNS
metastases, requiring steroids over the last 4 weeks prior to enrollment
(asymptomatic and symptomatic brain metastases stable for at least 4 weeks and off
steroids are allowed). Patients with leptomeningeal disease are allowed if it is determined that
immediate CNS treatment is unlikely to be required.
6. Impaired cardiac function or clinically significant cardiac disease, including any of the
following:
a. Baseline QT interval > 470 msec corrected for heart rate using Fridericia*s formula
(QTcF, verified on repeat measurements)
b. History of QTc prolongation or predisposition for QTc prolongation (clinically
relevant electrolyte abnormalities, cardiac disorder, bradycardia, etc.), or family
history of sudden cardiac death or QT prolongation (long QT syndrome)
c. Regular use of medications known to prolong QTc interval or to be arrhythmogenic
(such as ondansetron, erythromycin, droperidol) within 2 weeks of the first dose of
TAS3351. A list of these medications can be found at:
http://crediblemeds.org.
d. History or presence of clinically important abnormalities in rhythm or conduction of
resting ECG (eg, sinus arrest, second- or third-degree atrioventricular

block (first
degree atrioventricular block not excluded), serious uncontrolled
ventricular
arrhythmias), or severe myocardial infarction within 6 months of screening.
7. General health condition of the patient is not suitable for the study
including:
a. Disease or condition that significantly affects gastrointestinal
absorption of the study
treatment
b. Clinically relevant active infection (ie, known HBC, HCV, HIV -
screening not required) or other
uncontrolled medical condition
c. History of interstitial lung disease/pneumonitis, drug-induced lung
disease/pneumonitis
d. Known additional malignancy that is progressing or requires active
treatment, with
the exception of patients with a prior or concurrent malignancy whose
natural history
or treatment does not have the potential to interfere with the safety or
antitumor assessment of
the investigational regimen. Exceptions must be discussed with the Sponsor
prior to patient
enrollment
8. Known hypersensitivity to the ingredients of TAS3351
9. Unable to swallow whole tablets
10. Pregnant female or breastfeeding female
11. Any other clinically significant acute or chronic medical or psychiatric
condition that
may increase the risk associated with study drug administration, or may
interfere with the
interpretation of study results based on Investigator discretion.
12. Vulnerable patients who are:
a. Deprived of their liberty by a judicial or administrative decision.
b. Receiving psychiatric care
c. Admitted to a health or social institution for purposes other than research.
d. Under legal protection (ie, guardianship, curatorship, and safeguard of
justice)
e. Unable to express their consent.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	14-03-2024
Enrollment:	15
Type:	Anticipated

Medical products/devices used

Generic name:	therascreen® EGFR Plus RGQ PCR Kit
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	07-05-2024
Application type:	First submission
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
Other	EU CT 2022-502595-23-00
CCMO	NL84924.000.23