A Phase 1, Open-Label, Non-Randomized, Dose-Escalating Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study of TAS-119 in Patients with Advanced Solid Tumours

Published: 13-06-2014
Last updated: 21-04-2024

Primary Objectives:* Identify the Maximum Tolerated Dose (MTD) and the Recommended Phase 2 Dose (RP2D, 200mg BID) of TAS-119.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON47320

Source
ToetsingOnline

Brief title
TO-TAS-119-102

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
oncology, 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: Dose escalation, Oncology, Phase 1, Selective Aurora A kinase inhibitor

Outcome measures

Primary outcome

Primary Outcome:

Identify the maximum tolerated dose (MTD) and the RP2D (200 mg BID) of TAS-119.

Secondary outcome

Safety:

* Evaluate the feasibility and tolerability of TAS-119 in the treatment of

advanced solid tumours;

Efficacy outcomes (Radiological assessments of solid tumours will be performed

throughout the study period and analysed using Response Evaluation Criteria

inSolid Tumours (RECIST):

* Evaluate the preliminary antitumour activity of the RP2D for TAS-119 in the

treatment of advanced solid tumours;

PK criteria:

* Assess the pharmacokinetic (PK) characteristics of TAS-119;

Exploratory:

* Assess Phospho-HH3 (Ser 10) and mRNA expression of BORA, SGOL2, KIF20A and DEPDC-1 as potential pharmacodynamic biomarkers for TAS-119;

* Investigate the myc oncogene as well as beta catenin mutation as a predictive biomarker for TAS 119.

* Investigate the relationship between genetic polymorphisms of SLCO1B1 and PK of TAS-119.

* Optionally, investigate the presence or absence of circulating tumour cells in peripheral blood as a biomarker to evaluate the response to TAS- 119 treatment (prior to treatment, during treatment, and at progression).

Study description

Background summary

TAS-119 is a member of the pharmacological class of Aurora A kinase inhibitors. Aurora A kinase (AurA), a key regulator in mitotic cell division, is associated with spindle assembly checkpoint and regulation of the transition from G2 to M phase1. AurA gene amplification and/or overexpression are reported in various tumour types. Overexpression of the AurA gene is also associated with poor disease progression and survival in various cancers. TAS 119 is a novel, selective, and orally active small molecular inhibitor of AurA. TAS-119 demonstrated antitumor activities in preclinical models as monotherapy and in combination with taxanes.

Indication Under Study:
The vast majority of advanced (nonresectable or metastatic) cancer remains incurable and ultimately becomes resistant to currently available therapies, including taxanes. Therefore, there is a substantial unmet medical need for novel therapies against advanced cancers.
For monotherapy, gene abnormalities in MYC amplification as well as a beta catenin mutation have the potential to act as genomic markers of drug sensitivity to TAS-119. Notably, gene amplifications of myc have been reported in various cancers including prostate, breast, small cell lung carcinoma, ovarian and neuroblastoma.
However, myc gene amplification and b-catenin mutation are not the only markers that determine TAS-119 sensitivity. There are several breast cancer cell lines

highly sensitive to TAS-119 with neither myc nor b-catenin abnormalities. Moreover, among a panel of 240 cancer cells, cell lines derived from small cell lung cancer showed highest sensitivity to TAS-119 (based on a concentration producing 50% inhibition of activity average) compared with those of cells derived from other organs/indications.

Study objective

Primary Objectives:
* Identify the Maximum Tolerated Dose (MTD) and the Recommended Phase 2 Dose (RP2D, 200mg BID) of TAS-119.

Study design

This is a Phase 1, open-label, non-randomized, dose escalation study of TAS-119, evaluating the safety, tolerability, PK, pharmacogenomics, pharmacodynamics, and preliminary antitumour activity in patients with advanced and unresectable solid tumours. The study will be consisting of two sequential phases.

A) Dose Escalation Phase performed in approximately 5 dose levels (3 to 12 patients per dose level) to determine the MTD for TAS-119 given orally (PO), twice-daily (BID) in a 28-day treatment cycle. In addition, the RP2D (200 mg BID) will be evaluated in a 4 week continuous dosing regimen (see below).
B) Expansion Phase in which approximately 40 patients will be enrolled to further evaluate safety and preliminary efficacy at the RP2D. Approximately 80 (20 patients x 4 indications) additional patients will be enrolled in an Extension of the Expansion Phase to further explore the efficacy of the RP2D.

Intervention

TAS-119 Dose Escalation:
TAS-119 will be given PO, BID, without food (ie, for at least 1 hour before or 2 hours after the morning and evening meal) during Days 1-4, Days 8-11, and Days 15-18) of each 28-day treatment cycle.
Planned monotherapy dose levels are (total daily dose (mg): 140mg, 300mg, 400, 500 and 600 mg. This dosing scheduled is altered in comparison to Amendment 2 dosing schedule.

It is required to have at least 3 evaluable patients to assess each dose level; for each dose level, the second and third patients will be enrolled * 7 days after the 1st patient started dosing. Once patients have received treatment at any given dose level, escalation to subsequent dose levels will occur only after the current dose level is considered tolerable and escalation to the next dose level is approved according to the protocol criteria. Each dose level will enrol a new set of patients; no transition of patients between assigned dose

levels will be allowed.
The TAS-119 MTD will be defined as the highest dose level at which < 33% of the patients in the dose level experience a doselimiting toxicity (DLT) during Cycle 1. At least 6 evaluable patients will be required at the Monotherapy MTD level.
The RP2D (200 mg BID) will be used for the Expansion Phase. The RP2D is defined as a dose below or equal to the
MTD based on the evaluation of all available information (eg, tolerability in cycles after Cycle 1, PK and pharmacodynamic characteristics, or other safety/efficacy information) at the initiation of the Expansion Phase.

In addition, the RP2D (200 mg BID) will be evaluated in an additional cohort of 6-12 patients (4-week continuous dosing cohort) in the Dose Escalation Phase who will receive 4-week continuous treatment (Days 1-4, Days 8-11, Days 15-18 and Days 22-25) with TAS-119 for 28 days to assess the safety and tolerability of TAS-119.

TAS-119 Expansion Phase:
The RP2D has been established at 200 mg BID, and therefore, the Expansion Phase will be initiated at that dose level.) TAS-119 will initially be administered using the same 28-day treatment cycle as in the Dose Escalation Phase (Days 1-4, Days 8-11, and Days 15 18). If the 4-week continuous dosing regimen (Days 1-4, Days 8-11, Days 15 18, and 22-25) demonstrates an acceptable safety profile in the Dose Escalation Phase, it will become the dosing regimen used in Expansion Phase of the study.
The initial 10 patients enrolled (for each indication) in the Expansion Phase will be monitored for efficacy and safety. An additional 20 patients (for that specific subgroup of patients) will be enrolled in the Extension of the Expansion Phase to further explore the efficacy of TAS-119. If the 4-week continuous dosing regimen (Days 1-4, 8-11, 15-18 and 22-25) continues to have an acceptable safety profile in the Expansion Phase, patients will receive 4-week continuous dosing.

Study burden and risks

Monotherapy toxicology studies, carried out in rat and dog species, reported toxicities that would be considered consistent and/or acceptable for developing anti-cancer agents and appeared to be largely reversible. The first-in-human dose was based on the results observed in the rat which showed that the STD10was 63mg/kg bid and provides a more conservative starting dose in humans than the HNSTD derived from the dog model. Generally, toxicity profiles were the same or improved by intermittent dosing over continuous dosing, which support the rationale for the intermittent dosing schedule.
The most common adverse events (possibly) related to TAS-119 seen during pre-clinical trials are neutropenia, thrombocytopenia and anaemia. Also gastro-intestinal problems like nausea, vomiting and diarrhoea are known.

In this study, two cases of ocular adverse events have been observed in patients treated with TAS-119. Both patients developed symptoms of blurred vision following the first week of treatment. One patient took TAS-119 overdoses for total of 6 days for the first week. Both were diagnosed with corneal epithelial microcysts. Their symptoms and signs are improving or have already resolved upon the study drug discontinuation. Additional ophthalmologic examination will be performed for all the patients to be treated with TAS-119 as a safety preventive measure.
Patients participating in the study will be asked to come to the hospital for screening, followed by day 1, 4, 8, 15, 18 and 22. During subsequent cycles (till progressive disease) patient will visit the hospital on day 1, 8 and 15.

During these visits blood samples for Clinical Chemistry and Haematology are collected, as well as for Pharmacogenomic research. Possible side effects of venapunction are infections, haematoma and mild bleeding. Since these are done by trained study staff, these risks are decreased.
ECGs are made and at the end of each 2nd cycle a tumour assessment is performed. During a CT scan, patients are exposed to radiation. The dose of the radiation is comparable to natural background radiation during approximately 3 years.
Patient participating will also be asked to provide a tumor biopsy and non-tumour tissue sample. Related risks are pain at injection site for a few days. Sampling of non-tumour tissue can result in a painful spot were skin is removed.

Contacts

Public
Taiho Oncology Inc.

101 Carnegie Center, suite 101 0
Princeton NJ 08540
US
Scientific
Taiho Oncology Inc.

101 Carnegie Center, suite 101 0
Princeton NJ 08540
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

The Subject:
1. Is a male or female, * 18 years of age, who has provided written informed consent.
2. Has histologically or cytologically confirmed advanced, unresectable and/or metastatic solid tumour(s) for which the patient has no available therapy likely to provide clinical benefit;
3. Has Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 on Cycle 1, Day 1.
4. Must have an archival formalin-fixed, paraffin-embedded (FFPE) tumour sample available, to be provided to the Sponsor upon request.
5. In the Expansion Phase: patients should be willing to undergo core tumour biopsy procedure (on or before Day 1, Cycle 1) and on Day 4, Cycle 1 (6 hours ± 2 hours postdose) if, in the judgment of the investigator, it is considered clinically safe and appropriate to do so. This requirement is optional but preferred for patients in Dose Escalation.
6. Should be willing to undergo pretreatment sampling of non-tumour surrogate tissue for pharmacodynamic assessments (ie, a 3 mm punch biopsy of skin from either the arm or the back of the scalp) if, in the judgment of the investigator, it is considered clinically safe and appropriate to do so.
7. Is able to take medications orally (eg, no feeding tube).
8. Has adequate organ function as defined by the following criteria:
i. Aspartate aminotransferase (AST/serum glutamic oxaloacetic transaminase [SGOT]) and alanine aminotransferase (ALT/serum glutamic pyruvic transaminase [SGPT]) * 3.0 × upper limit of normal (ULN).
ii. Total serum bilirubin within normal limits. Patients with Gilbert's Syndrome could be considered eligible if bilirubin is * 1 × ULN, but serum bilirubin ratio of unconjugated/conjugated is greater than 1 or most of serum bilirubin fraction should be unconjugated.
iii. Absolute neutrophil count of * 1,500/mm3 (ie, * 1.5 × 109/L by International Units [IU]).
iv. Platelet count * 100,000/mm3 (IU: * 100 × 109/L). Transfusion of whole blood, platelets, or red blood cells (RBCs) is prohibited within 1 month prior to initiation of study treatment.
v. Hemoglobin value of * 9.0 g/dL.
vi. Total serum creatinine of * 1.5 × ULN.
vii. Serum albumin * 2.5 g/dL.

9. Women of childbearing potential must have a negative pregnancy test (urine or serum) within 7 days prior to starting the study drug. Both males and females and must agree to use effective birth control during the study [prior to the first dose and for 6 months after the last dose if conception is possible during this interval] if conception is possible during this interval. Female patients are considered to not be of childbearing potential if they have a history of tubal ligation or hysterectomy or are post-menopausal with a minimum of 1 year without menses.
10. Is willing and able to comply with scheduled visits and study procedures.

Exclusion criteria

The Subject:
1. Has received prior treatment with TAS-119.
2. Has received treatment with any of the following within the specified time frame prior to study drug administration:
a) Major surgery within prior 4 weeks (the surgical incision should be fully healed prior to study drug administration).
b) Radiotherapy for extended field within 4 weeks prior to study drug administration or limited field radiotherapy within 2 weeks prior to study drug administration.
c) Previous cytotoxic chemotherapy for advanced or metastatic solid tumors consisting of more than 5 different regimens in total.
d) Any anticancer therapy within 3 weeks prior to study drug administration (mitomycin within prior 5 weeks). Patients with metastatic prostate cancer receiving luteinizing hormone-releasing (LHRH) analogs will be eligible.
e) Any investigational agent received either concurrently or within the last 30 days.
f) Transfusion of whole blood, platelets, or packed red blood cells is prohibited within 1 month prior to study treatment.
3. Has a serious illness or medical condition(s) including, but not limited to, the following:
a) Known brain metastasis unless the lesions have been previously treated with surgery or radiotherapy, and have been stable off steroids for * 2 months.
b) Known leptomeningeal metastasis.
c) Known acute systemic infection.
d) Myocardial infarction, severe/unstable angina, symptomatic
congestive heart failure (New York Heart Association [NYHA] class III or IV within the previous 6 months (if > 6 months cardiac function must be within normal limits [ie, known ejection fraction * 50%] and the patient must be free of cardiac-related symptoms).
e) Chronic nausea, vomiting, or diarrhoea, considered to be clinically significant in the opinion of the Investigator.
f) Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or a history of serum positivity to hepatitis B or C.
g) Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the Investigator would make the patient inappropriate for entry into this study.
4. Has known hypersensitivity to TAS-119 or any of its components;

5. Is pregnant or lactating female.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-10-2014
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Not applicable
Generic name:	Not applicable

Ethics review

Approved WMO Date:	13-06-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	11-09-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-04-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-05-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-06-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-09-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-10-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-01-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-03-2017
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-05-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2014-001272-63-NL
CCMO	NL49246.078.14

Study results

First publication
01-01-1900

URL result
Type
ext
Naam
ascopubs.org
URL