Phase I dose-escalation study of S 81694 administered intravenously in adult patients with advanced/metastatic solid tumours

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Primary Objective: to determine the maximum tolerated dose (MTD) and the associated dose-limiting toxicities (DLTs) of S 81694.Secondary Objectives:- To define the safety and tolerability profile of S 81694;- To define the recommended phase II dose…

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

Summary

ID

NL-OMON47049

Source
ToetsingOnline

Brief title
CL1-81694-001: study of S 81694 in patients with solid tumors

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Advanced/metastatic Solid Tumor, Malignant solid tumor

Research involving
Human

Sponsors and support

Primary sponsor: Institut de Recherches Internationales Servier I.R.I.S
Source(s) of monetary or material Support: INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

Intervention

Keyword: Metastatic, Phase I, S 81694, Tumours

Outcome measures

Primary outcome

DLT(s) occurring during the first cycle

Secondary outcome

Safety and tolerability profile characterized by type, frequency, severity,

intensity, timing and relationship of adverse events and laboratory

abnormalities;

PK parameters of S 81694 and its metabolite(s);

Objective tumour response (unconfirmed), as defined by the Response Evaluation

Criteria in Solid Tumours (RECIST version 1.1);

Biomarkers associated with outcome to S 81694.

Study description

Background summary

S 81694 is an inhibitor of MPS1 kinase activity.
Monopolar Spindle 1 (MPS1) kinase, also known as TTK, is a dual

tyrosine/threonine kinase expressed only in proliferating cells; upon activation by phosphorylation, MPS1 plays a critical role in the control of mitosis regulating the Spindle Assembly Checkpoint (SAC) through proper kinetochore recruitment of other essential SAC proteins. The SAC complex regulates a mitotic mechanism required for proper chromosome alignment, influencing the stability of the kinetochore-microtubule interaction and ensuring that cells do not divide until all sister chromatids correctly align to the metaphase plate. Aneuploidy is a common feature of cancer cells: approximately 90% of solid tumours and 70% of haematological cancers are aneuploid, with the majority (> 70%) having a gain rather than a loss of chromosomes. MPS1 has been found highly expressed in a number of tumours of different origins including melanoma, bladder, anaplastic thyroid, breast, lung, oesophageal, colon, pancreas, glioblastoma and prostate cancer.
S 81694 was characterized in repeated toxicity studies after IV administration in rats and monkeys.

Study objective

Primary Objective: to determine the maximum tolerated dose (MTD) and the associated dose-limiting toxicities (DLTs) of S 81694.

Secondary Objectives:
- To define the safety and tolerability profile of S 81694;

- To define the recommended phase II dose (RP2D);

-To determine the pharmacokinetics (PK) profile of S 81694 and its metabolite(s);

- To explore the relationship between PK and selected adverse events;

- To explore any potential exposure-response relationship for safety, efficacy and pharmacodynamics;

- To explore early signs of antitumor efficacy;

- To identify potential predictive biomarkers of efficacy.

Study design

This is a phase I, first-in-human, open-label, non-randomized, multicentre, multinational, non-comparative, dose-escalation trial in sequential cohorts of adult patients with advanced/ metastatic solid tumours who have exhausted standard treatment options or for whom no standard treatment is available.
At the beginning of the study the dose escalation followed a 3+3 design; once the 4th amendment is applicable, a Bayesian Logistic Regression Model (BLRM)

will guide the dose escalation to determine the MTD. Increments of no more than 100% of the dose of previous cohort will be allowed, providing the proposed dose satisfies the Escalation With Overdose Control (EWOC) criterion.

Intervention

S 81694, administered as intravenous infusion, will be dosed based on the patient's body surface area. Dose will be escalated according to the study design. Dose Modification during a cycle of therapy are foressen.

Study burden and risks

According to the toxicity studies, the S 81694 safety profile appears to be manageable, with target organ toxicity appearing related to its pharmacological mechanism of action and observed principally in the haemolymphopoietic system and marginally in the gastrointestinal (GI) tract.

Patients will undergo a full clinical examination, and electrocardiogram evaluations (ECGs).
Blood and urine samples will be frequently taken. The total amount of blood withdrawn for study assessments during induction period, first cycle of treatment and end of treatment period is around 348 ml.
The extent of the tumor will be assessed by CT or MRI.
Pregnancy tests for women of childbearing potential will be performed.
Only in patients enrolled in the expansion part of the study, a fresh tumour tissue biopsy will be collected.

Risks associated with partcipation to the study:
-The risks of having blood sample taken from the vein include pain, bruising and infection, moreover puncuteres may induce vertigo and fainting.
- The risks of biopsies include pain at the site of biopsy, soreness, bruising, bleeding and infection.

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

- Male or female patients with age * 18 years;
- Histologically or cytologically confirmed diagnosis of advanced/metastatic solid tumour in patients for whom no effective standard therapy is available or suitable;
- For patients participating to the expansion cohort at RP2D , acceptance of pre- and post-treatment biopsies;
- Elapsed time of 4 weeks or, in absence of toxicity, of 5 half-lives between the completion of the prior antineoplastic therapy including biologic, immunologic or targeted anticancer therapy and S 81694 first administration. Elapsed time of 6 weeks for nitrosoureas or mitomycin C;
- Prior radiotherapy is allowed provided that no more than 25% of bone marrow reserve has been irradiated;
- Controlled CNS involvement is accepted as long as therapy with corticosteroids and/or anticonvulsant is not required;
- Resolution (return to baseline) or return to NCI CTCAE Grade * 1 of all acute toxicities due to prior anticancer therapy except alopecia, grade 2 paraesthesia, grade 2 hyper- or hypothyroidism and other non-clinically significant adverse events;
- ECOG (WHO) performance status 0-1 ;
- Effective contraception both for female patients of childbearing potential and male patients with partners of childbearing potential;
- Adequate haematological and blood chemistry measurements

Exclusion criteria

- Pregnancy, breastfeeding or possibility of becoming pregnant or fathering during the study;
- Blood transfusion * 3 weeks before treatment start;
- Episode(s) of clinically relevant active bleeding in the past 3 weeks;
- Known history of haemolytic anaemia (including G6PD deficiency), thrombotic thrombocytopenic purpura (TTP), microangiopathic haemolytic anaemia (MAHA), haemolytic uremic syndrome(HUS);
- Major surgery within 4 weeks before the first day of investigational drug administration without recovery of ECOG 0-1.
- Any of the following in the past 6 months: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, pulmonary embolism, deep vein thrombosis or thrombolysis;
- Clinically significant respiratory or metabolic diseases uncontrolled by medication;
- Patients with uncontrolled high blood pressure;
- Presence of risk factors for torsade de pointes (e.g. heart failure, hypokalaemia, family history of long QT syndrome);
- Patients who have undergone treatment with high-dose chemotherapy requiring progenitor cell transplantation;
- Known active or uncontrolled infections (bacterial, fungal, viral including HBV and HCV infections); patients who are seropositive following HBV vaccine are eligible as well as patients HBV and HCV seropositive, but negative for viral DNA by RT-PCR.
- Known HIV seropositive patients;
- Any known organ dysfunction, serious illness, medical condition, or other medical history, including laboratory abnormalities, which, in the Investigator's opinion, would be likely to interfere with the patient's participation in the study or with the interpretation of the results;
- Any condition (e.g., known or suspected poor compliance, psychological instability, geographical location, etc.) that, in the judgment of the Investigator, may affect the patient's ability to
understand and sign the informed consent and fully comply with all study procedures.
Patients who, within 7 days prior to the first S 81694 intake, are receiving or received strong inducers of FMO1 and FMO3;
Patients who are receiving sensitive CYP3A4 substrates, CYP3A4 and BCRP substrates with narrow therapeutic index (NTI)

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):	01-12-2015
Enrollment:	24
Type:	Actual

Ethics review

Approved WMO Date:	11-08-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-10-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-02-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	02-11-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-11-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-03-2019
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	EUCTR2014-002023-10-NL
CCMO	NL51604.078.15

Study results

Results posted: 15-04-2020

First publication
17-03-2020