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Phase I/II study of S 49076, a multi-target inhibitor of c-MET, AXL, FGFR in combination with bevacizumab in patients with recurrent glioblastoma multiforme

Submission date 05/12/2014	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 13/02/2015	**Overall study status** Completed	
Last Edited 23/03/2018	**Condition category** Cancer	

Plain English summary of protocol
Not provided at time of registration and not expected to be available in the future

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
2013-003079-37

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
CL1-49076-002

Study information

Scientific Title
Phase I/II study of S 49076, a multi-target inhibitor of c-MET, AXL, FGFR in combination with bevacizumab in patients with recurrent glioblastoma multiforme

Acronym
N/A

Study objectives
To evaluate the safety and efficacy of S 49076 in combination with bevacizumab in patients with recurrent glioblastoma multiforme (GBM). This is a phase I, dose-finding study of S 49076 in combination with bevacizumab followed by a randomised efficacy phase II study.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics approval was obtained before recruitment of the first participants

Study design
International multicenter open-label dose-finding and non-comparative efficacy study with one-way cross-over

Primary study design
Interventional

Secondary study design
Dose-finding study followed by a randomised efficacy study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Glioblastoma multiforme

Interventions
Capsules containing 100 mg of S 49076 (oral use). The dose will be gradually escalated, following an algorithm-based 3+3 design, from level 1 at 400 mg/day to the MTD, with the possibility to de-escalate. A panel of four doses of S49076 (300, 400, 500 and 600 mg) could be tested.

Solution for infusion of bevacizumab; each ml of concentrate contains 25 mg of bevacizumab. Bevacizumab will be administered on day 1 and 15 of each cycle, 28-days/cycle.

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
S49076

Primary outcome measure
Phase I:
1. Dose Limiting Toxicity and recommended phase II dose in combination of bevacisumab, at end of phase I part
2. Safety profile:
2.1. Adverse Events at each visit
2.2. Coagulation: within 7 days prior to the first test drug administration, D1 of each cycle and Withdrawal Visit (WV)
2.3. Physical and clinical neurological examination, vital signs, haematology, biochemistry and urinalysis: within 7 days prior to the first test drug administration, D1 and D15 of each cycle and WV
2.4. ECG parameters: within 7 days prior to the first test drug administration, D1, D2 and D15 of cycle 1, after D1 and D15 of each cycle and WV
2.5. LVEF assessment: at inclusion, on D28 every 2 cycles from cycle 1 and WV

Phase II:
1. Progression-free survival rate according to RANO (Response Assessment in Neuro-Oncology) criteria: at 6 months (PFS-6)

Secondary outcome measures
Phase I:
1. Pharmacokinetic evaluation at D1, D2, D15 and D28 of cycle 1 and D1 of cycle 2
2. Pharmacodynamic evaluation at D1 of each cycle
3. Tumour response evaluation at within 14 days prior to the first test drug administration, D28 at each cycle and WV

Phase II:
1. ORR, CBR, OS, progression-free survival, response duration, duration of clinical benefit: within 14 days prior to the first test drug administration, D28 at each cycle and WV
2. Safety tolerance profile of the combination:
2.1. AE: at each visit
2.2. Physical and clinical neurological examinations, vital signs, ECG, Haematology, Biochemistry and Urinalysis: within 7 days prior to the first test drug administration, D1 and D15 of each visit and WV
2.3. Activity profile in subgroup with c-Met amplification or mutation: within 14 days prior to the first test drug administration, D28 at each cycle and WV
2.4. Quality of life: within 14 days prior to the first test drug administration, D28 at each cycle and WV

Overall study start date
10/03/2014

Completion date
03/11/2016

Eligibility

Key inclusion criteria
1. Male or female patient aged > or = 18 years old
2. Histologically confirmed diagnosis of glioblastoma multiforme (WHO grade IV). Patients will be eligible if original histology was low-grade glioma and a subsequent diagnosis of glioblastoma was made
3. Unequivocal evidence of first progression/recurrence after standard treatment with combined chemo-irradiation (including a possible combination of temozolomide with an investigational agent) performed by MRI within 2 weeks before the first test drug administration
4. No more than one prior line of treatment
5. Patients must have measurable tumour disease as defined by RANO
6. Ability to swallow oral capsules

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
115

Key exclusion criteria
1. Pregnant or breastfeeding women
2. Involvement in another therapeutic interventional trial at the same time or within 3 weeks prior to the first day of test drug administration
3. Major surgery (including craniotomy) within 4 weeks prior to the first day of test drug administration or minor surgical procedures (e.g., core biopsy or fine needle aspiration) within 14 days
4. Chemotherapy within 4 weeks (6 weeks for nitroso-ureas) prior to the first day of test drug administration
5. Radiotherapy within 3 months prior to the diagnosis of progression
6. Prior treatment with bevacizumab or other VEGF-receptor targeted agent
7. Prior treatment with a PI3K inhibitor, HGF or Met pathways for phase II part
8. Prior treatment with carmustine wafer
9. Impaired cardiac function

Date of first enrolment
03/10/2014

Date of final enrolment
04/06/2016

Locations

Countries of recruitment
France

Switzerland

Study participating centre
AP-HP Pitié-Salpêtrière
47-83 Boulevard de l'Hôpital
Paris
France
75013

Study participating centre
University Hospital of Lausanne (Centre Hospitalier Universitaire Vaudois)
Rue du Bugnon 46
Lausanne
Switzerland
1011

Sponsor information

Organisation
Institut de Recherches Internationales Servier (France)

Sponsor details
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Suresnes
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92284

Sponsor type
Industry

Website
http://www.servier.com/

ROR
https://ror.org/034e7c066

Funder(s)

Funder type
Industry

Funder Name
ADIR

Results and Publications

Publication and dissemination plan
Summary results and lay summary are published on www.clinicaltrials.servier.com.

Intention to publish date

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from www.clinicaltrials.servier.com if a Marketing Authorisation has been granted after 1st January 2014.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results				No	No
Basic results				No	No