A Phase 2 study of SAR245409 in patients with relapsed or refractory mantle cell lymphoma, follicular lymphoma, or chronic lymphocytic leukemia/small lymphocytic lymphoma

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Primary * To evaluate the efficacy of SAR245409 as determined by the objective response rate (ORR) in patients with 1 of the following relapsed or refractory lymphoma or leukemia subtypes: mantle cell lymphoma (MCL), follicular lymphoma (FL), or...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON36096

Source
ToetsingOnline

Brief title
ARD12130

Condition

- Leukaemias
- Lymphomas non-Hodgkin's B-cell

Synonym
chronic lymphocytic leukemia (CLL), non Hodgkin lymphoma (NHL)

Research involving
Human

Sponsors and support

Primary sponsor: Sanofi-aventis
Source(s) of monetary or material Support: sanofi-aventis

Intervention

Keyword: chronic lymphocytic leukemia, non-Hodgkin lymphoma, refractory, relapse

Outcome measures

Primary outcome

The primary endpoint will be the objective response rate (ORR) as defined as the proportion of patients who experience complete response/remission (CR) or partial response/remission (PR) as defined by the International Working Group Response Criteria for malignant lymphoma (IWRC) and modified International Workshop on Chronic Lymphocytic Leukemia guidelines (IWCLL) (1, 2). All patients with MCL, FL or SLL meeting the criteria for CR must have a confirmatory FDG-PET scan no less than 6 weeks after the CR assessment. Patients with pretreatment bone marrow involvement (determined by biopsy, flow cytometry or IHC) will be considered a PR unless CR is confirmed by bone marrow biopsy, including molecular analysis.

Secondary outcome

Main secondary endpoints will include:

* Median PFS, proportion of patients with PFS at 6 months (24 weeks), duration of response

* Safety (AEs and laboratory parameters).

* Plasma concentrations of SAR245409 will be measured in cycle 1, 3 and 6.

Study description

Background summary

The treatment of relapsed and refractory (R/R) MCL, FL, and CLL/SLL remains an important unmet medical need. Despite advances in treatment options, prognosis remains poor. There is good clinical evidence the inhibition of the PI3K/mTor/Akt pathway is an effective approach in R/R MCL, FL, and CLL/SLL as described in Section 4.1.3. SAR245409 is a novel dual PI3 kinase/mTor inhibitor which has been well tolerated in at least 10 patients with NHL.

This study uses the single-agent maximum tolerated dose of 50 mg bid. This is the maximum tolerated dose determined in the solid tumor cohort of the Phase 1 single-agent study, XL765-001. A cohort of patients with lymphoma is currently enrolling at 50 mg bid in the ongoing Phase 1 study. Ten patients with lymphoma have enrolled to date with none experiencing dose-limiting toxicities.

Study objective

Primary
* To evaluate the efficacy of SAR245409 as determined by the objective response rate (ORR) in patients with 1 of the following relapsed or refractory lymphoma or leukemia subtypes: mantle cell lymphoma (MCL), follicular lymphoma (FL), or chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
Secondary
* To assess duration of response, progression free survival (PFS), and proportion of patients with PFS at 6 months (24 weeks) in patients with either MCL, FL, or CLL/SLL treated with SAR245409
* To evaluate the safety and tolerability of SAR245409 in patients with MCL, FL, or CLL/SLL
* To further characterize the plasma pharmacokinetics (PK) of SAR245409 in patients with MCL, FL, or CLL/SLL
Exploratory
* To assess the pharmacodynamic effects of SAR245409 in patients with MCL, FL, or CLL/SLL
* To define predictive markers of response and/or resistance to SAR245409 based on molecular profiling of cancer tissue

Study design

This is a multicenter, multinational, nonrandomized, open-label, 2-stage, Phase 2 clinical trial of SAR245409 at 50 mg orally twice daily (bid) for a 28-day cycle in patients with relapsed or refractory (R/R) MCL, FL, or CLL/SLL having failed at least 2 standard treatment regimens. Patients will enroll into 1 of 3 groups based on disease:

Group 1: R/R MCL
Group 2: R/R Grade 1, 2, or 3a FL
Group 3: R/R CLL or SLL
Simon*s minimax 2-stage design will be used to determine whether the drug is potentially efficacious to warrant further study in 1 or more of the disease groups studied. Objective responses will be assessed by the Investigator according to the International Working Group for Lymphoma (IWL) and International Working Group on Chronic Lymphocytic Leukemia (IWCLL) criteria.

Intervention

A cycle is defined as 28 days of dosing with SAR245409.
Telephone safety assessments will be performed at specified intervals in between site visits. Safety assessments (AEs, vital signs, electrocardiogram [ECG], ophthalmologic examinations, laboratory tests, and concomitant medications) will be performed prior to the start of the investigational medicinal product (IMP) on Cycle1, Day1 and according to the study flowchart. Tumor assessments will be performed at the end of Cycle 2 and then every 3 cycles for a period of 2 years or until disease progression or withdrawal from study. Patients who continue on study beyond 2 years will have tumor assessments at a minimum of every 6 cycles.
SAR245409 plasma concentration analysis will be performed separately for patients with MCL, FL and CLL/SLL. Blood samples will be obtained at scheduled time points and if possible, whenever there is an IMP-related SAE.
Blood or processed blood, hair and tumor tissue samples will be obtained for analyses of a variety of established and exploratory pharmacodynamic biomarkers on a defined schedule (see Section 1.2 and Section 9.4). When possible, PD sample collection will coincide with scheduled PK time points.
Optional on study tumor biopsies maybe collected from consented patients at the time points specified in Section 1.2 of the study protocol. The maximum sampling is 3 biopsy time points, including baseline. The tumor tissues will be analyzed for biomarkers related to SAR245409 mechanism of action. Matched blood and hair sampling are required when optional biopsies are collected.
A blood sample will be obtained prior to the first dose of SAR245409 from patients who signed the optional pharmacogenetic (PGx) informed consent form. The PGx blood sample will be collected to investigate allelic variants of drug metabolizing enzyme (DME) and/or drug transporters as intrinsic factors associated with pharmacokinetic or pharmacodynamic variability of SAR245409. For CLL patients, additional buccal swabs will be obtained from consented patients for genotyping analyses. PGx blood and buccal swap may also be used for genotyping and/or tumor genome sequencing analyses.

Study burden and risks

See paragraph "Intervention" for extent of the burden.
The average expected participation period per patient is 4-12 months.

The patient may experience (any) discomfort undergoing the required procedures.
The risks of taking blood may include fainting, pain, and/or bruising.
There might only be a little discomfort, but not risk when the electrocardiogram electrodes are applied to the skin.
Having a biopsy taken may cause some pain, inflammation, bleeding, swelling, or infection at the site of the biopsy.
When having a CT scan, the patient will receive small doses of radiation. All radiation adds up over a lifetime. Some people may feel a closed-in feeling while lying in the scanner. The patient may receive intravenous contrast material to better visualize the sites of tumor. If the patient is having a CT scan of the abdomen, he/she may be asked to drink a contrast fluid that may cause nausea.

The disease of patients participating in this study is resistent or refractory.
It is possible that SAR245409 may be effective in this disease; It is hoped that the information obtained in this study may provide valuable information to assist future patients.

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

* Tissue from an archived or fresh tumor sample
* A peripheral blood buffy coat sample is required for CLL/SLL.
* Patient has mantle cell lymphoma (MCL), follicular lymphoma (FL), or chronic lymphocytic leukemia (CLL)/SLL
* Patient >< = 18 years old
* ECOG performance status < <= 2
* Adequate white blood cells and hemoglobin
* Good kidney and liver function
* Fasting glucose < 160 mg/dL
* No other malignancy
* Use of adequate birth control

Exclusion criteria

- Treatment with cytotoxic chemotherapy, biologic agents, investigational therapies within 4 weeks, or nitrosoureas or mitomycin C within 6 weeks of study enrollment
- Treatment with a small-molecule kinase inhibitor within 2 weeks, or 5 half lives of the drug or its active metabolites (whichever is longer) of study enrollment
- Prior treatment with a PI3K, mTOR, or Akt inhibitor. Prior treatment of MCL with temsirolimus is permitted in patients enrolled from countries where it is licensed for this indication.
- Radiation therapy within 2 weeks of enrollment
- Autologous stem cell transplantation within 16 weeks of enrollment
- Prior allogeneic transplantation
- Central nervous system or leptomeningeal involvement
- Positive Hepatitis B surface antigen (HBsAg) or Hepatitis C antibody (anti-HCV) serology

Study design

Design

Study phase: 2

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-11-2011
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	SAR245409
Generic name:	SAR245409

Ethics review

Approved WMO Date:	02-08-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-11-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-04-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-05-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	05-09-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-09-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-02-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2011-001616-57-NL
Other	Het onderzoek wordt vermeld op de website www.clinicaltrials.gov en www.clinicaltrialsregister.eu. Zodra de eerste goedkeuring binnen is van 1 deelnemend land; op z'n laatst bij het eerst getekend Informed Consent.
CCMO	NL36867.018.11