A Phase 2 Study of LY2157299 Monohydrate Monotherapy or LY2157299 Monohydrate plus Lomustine Therapy compared to Lomustine Monotherapy in Patients with Recurrent Glioblastoma

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Interventional

Summary

ID

NL-OMON37449

Source
ToetsingOnline

Brief title
JBAL (219/410)

Condition

- Nervous system neoplasms malignant and unspecified NEC
- Nervous system neoplasms malignant and unspecified NEC

Synonym
brain cancer

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: Eli Lilly and Company

Intervention

Keyword: Glioblastoma, Lomustine, LY2157299 monohydrate

Outcome measures

Primary outcome

To compare the overall survival (OS) distributions between LY2157299 plus lomustine therapy and lomustine plus placebo therapy (control arm) in patients who have relapsed or have progressive GB after first-line treatment with chemoradiation.

Secondary outcome

The secondary objectives of the study are:

- Pharmacokinetic (PK)

• To determine the population PK of LY2157299 monohydrate.

- Safety

• To provide additional safety information on LY2157299 monotherapy and LY2157299 plus lomustine therapy and to evaluate the safety of LY2157299 monohydrate monotherapy and LY2157299 monohydrate plus lomustine therapy relative to lomustine plus placebo therapy.

Pharmacodynamic (PD) - prognostic and predictive marker assessment

• To investigate in tumor tissue, biomarkers associated with tumor growth and the TGF-* signaling pathway (phosphorylated SMAD [pSMAD] and other TGF-β-

related biomarkers, O6-methylguanine-DNA methyltransferase [MGMT] promoter status, and other relevant tumor genetic information [eg, isocitrate dehydrogenase (IDH1) mutation]) and its association with clinical responses.

• To determine serum/plasma tumor markers and secreted proteins (eg, S100β, lactate dehydrogenase [LDH], TGF-β, and PF4) and their association with clinical responses.

• To determine T cell biomarker responses, including T regulatory cell counts (eg, CD4+CD25+FoxP3+ T cells) and their association with clinical responses.

- Efficacy

• To estimate the OS and hazard ratio (HR) between lomustine plus placebo therapy and LY2157299 monohydrate monotherapy and between LY2157299 monohydrate plus lomustine therapy and LY2157299 monohydrate monotherapy.

• To estimate progression-free survival (PFS) distributions for each treatment arm and estimate additional parameters from both the OS distributions and PFS distributions for each treatment arm (such as median OS and PFS, OS and PFS rates at 6 months).

• To estimate tumor response rate based on Response Assessment in Neuro-Oncology (RANO) criteria for each treatment arm.

- Health Outcomes

• To assess patient-reported symptoms using the MD Anderson Symptom Inventory-Brain Tumor (MDASI-BT) and assess neurocognitive function using the Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test Parts A and B,

and Controlled Oral Word Association (COWA) for each treatment arm.

Study description

Background summary

Transforming growth factor beta (TGF-β) is an important protein that regulates immune response to and metastatic spread of tumor cells. It is also an important regulator of neoangiogenesis.
LY2157299 monohydrate is a small molecule designed to selectively inhibit the serine/threonine kinase of the TGF-β receptor type I (TGF-βRI). Thus, the antitumor effect of LY2157299 monohydrate is expected to result in an increased tumor immune surveillance, reduced metastatic spread, and decreased tumor-associated neoangiogenesis.
In glioblastoma (GB), anaplastic astrocytomas, anaplastic oligoastrocytoma, or anaplastic oligodendroglioma, LY2157299 monohydrate is expected to reduce neoangiogenesis, enhance antitumor cytotoxic T cells, and reduce fibrogenic remodeling associated with tumor necrosis, radiation, and surgery.
In a recent first-human-dose study, H9H-MC-JBAH (Study JBAH), single-agent administration of LY2157299 monohydrate has been associated with 2 complete and 3 partial tumor responses in 39 patients with relapsed and recurrent GB. Combination with lomustine and LY2157299 monohydrate was safe at the 160-mg/day and 300-mg/day doses. Preliminary information indicated 2 partial responses in 26 patients who were treated with the combination of lomustine and LY2157299 monohydrate.
This clinical activity of LY2157299 monohydrate together with the scientific hypothesis that blocking the TGF-β signaling pathway in GB will have clinical benefit provide the justification to conduct a trial with LY2157299 monohydrate in patients who relapsed after first-line treatment for GB.

Study objective

The primary objective of this study is to compare the overall survival (OS) distributions between LY2157299 monohydrate plus lomustine therapy with lomustine plus placebo therapy (control arm), in patients who have relapsed or have progressive GB after first-line treatment with chemoradiation.

The secondary objectives of the study are:
- Pharmacokinetic (PK)
• To determine the population PK of LY2157299 monohydrate.

- Safety
• To provide additional safety information on LY2157299 monotherapy and LY2157299 plus lomustine therapy and to evaluate the safety of LY2157299

monohydrate monotherapy and LY2157299 monohydrate plus lomustine therapy relative to lomustine plus placebo therapy.
Pharmacodynamic (PD) - prognostic and predictive marker assessment
• To investigate in tumor tissue, biomarkers associated with tumor growth and the TGF-* signaling pathway (phosphorylated SMAD [pSMAD] and other TGF-β-related biomarkers, O6-methylguanine-DNA methyltransferase [MGMT] promoter status, and other relevant tumor genetic information [eg, isocitrate dehydrogenase (IDH1) mutation]) and its association with clinical responses.
• To determine serum/plasma tumor markers and secreted proteins (eg, S100β, lactate dehydrogenase [LDH], TGF-β, and PF4) and their association with clinical responses.
• To determine T cell biomarker responses, including T regulatory cell counts (eg, CD4+CD25+FoxP3+ T cells) and their association with clinical responses.

- Efficacy
• To estimate the OS and hazard ratio (HR) between lomustine plus placebo therapy and LY2157299 monohydrate monotherapy and between LY2157299 monohydrate plus lomustine therapy and LY2157299 monohydrate monotherapy.
• To estimate progression-free survival (PFS) distributions for each treatment arm and estimate additional parameters from both the OS distributions and PFS distributions for each treatment arm (such as median OS and PFS, OS and PFS rates at 6 months).
• To estimate tumor response rate based on Response Assessment in Neuro-Oncology (RANO) criteria for each treatment arm.

- Health Outcomes
• To assess patient-reported symptoms using the MD Anderson Symptom Inventory-Brain Tumor (MDASI-BT) and assess neurocognitive function using the Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test Parts A and B, and Controlled Oral Word Association (COWA) for each treatment arm.

Study design

This is a 3-arm, randomized (1:2:1), multicenter, global, Phase 2 study of LY2157299 monohydrate monotherapy or LY2157299 monohydrate plus lomustine therapy compared to lomustine plus placebo therapy in patients with relapsed GB. In contrast to the LY2157299 monohydrate monotherapy arm, patients and investigators will be blinded to the LY2157299 monohydrate or placebo assignment in either the LY2157299 plus lomustine or the lomustine plus placebo therapy arms.

Intervention

Patients who meet all criteria for enrollment will be randomly assigned in a 1:2:1 ratio to receive:
- LY2157299 monotherapy

- LY2157299 plus lomustine therapy
- Lomustine plus placebo therapy

LY2157299 monohydrate, 300 mg/day, given orally for 14 days followed by 14 days of rest, for a 28-day cycle.
LY2157299 monohydrate-matched placebo, given orally for 14 days, followed by 14 days of rest, for a 28-day cycle.
Lomustine will be given orally once every 6 weeks. The first lomustine dose will be 100 mg/m2, and all following doses can be escalated to a maximum of 130 mg/m2, at the investigator*s discretion.

Study burden and risks

Risks associated with LY2157299
Monohydrate:

The most common risks and discomforts reported by patients who received LY2157299 monohydrate monotherapy are weakness and nausea. Other risks and discomforts reported by people who have received LY2157299 monohydrate monotherapy include low levels of cells that prevent bleeding, inflammation at the anus, loose stool, dry mouth, cramping, bloating, stomach tenderness, incontinence, gas, gastritis, mucous in stools, tiredness, stroke, numbness in the fingers, vomiting, dizziness, shortness of breath, increased bilirubin in blood, blood clot in the lung, and protein in the urine. Of these, 4 people had effects that were serious enough to require hospitalization.

Risks associated with Lomustine:
• allergic reactions like skin rash, itching or hives, swelling of the face, lips, or tongue
• low blood counts - this medicine may decrease the number of white blood cells, red blood cells and platelets. You may be at increased risk for infections and bleeding.
• signs of infection - fever or chills, cough, sore throat, pain or difficulty passing urine
• signs of decreased platelets or bleeding - bruising, pinpoint red spots on the skin, black, tarry stools, blood in the urine
• signs of decreased red blood cells - unusually weak or tired, fainting spells, lightheadedness
• breathing problems
• changes in vision
• confusion
• dry cough
• mouth sores
• swelling of the ankles, feet, hands
• trouble passing urine or change in the amount of urine
• unusual bleeding or bruising
• yellowing of the eyes or skin

Other side effects includes the following: hair loss, loss of appetite, nausea, vomiting

Furthermore patients might experience discomforts during the study procedures: Blood sampling, providing urine,
Echocardiogram, Magnetic Resonance Imaging (MRI), CT scan, contrasts for MRI and CT
scans. Please refer to Appendix 2 of the Patient Information Sheets for more information regarding the possible discomforts of these procedures.

Contacts

Public
Eli Lilly

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IN 46285 Indianapolis
US
Scientific
Eli Lilly

Lilly Corporate Center N/A
IN 46285 Indianapolis
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Eligible male and female patients are required to: (1) have confirmed diagnosis of relapsed

intracranial or secondary blioblastoma, 2) evidence of tumor progression , 3) may have undergone prior surgical resection and will be eligible if patients have recovered from the effects of surgery and evaluable or measurable disease is present , 4) have available tumor tissue, 5)have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale, 6) Have discontinued all previous treatments for cancer excluding palliative treatments and recovered from the acute effects of therapy , 7) Have adequate organ function,8)Are males or females at least 18 years old at the time of screening: Females must be women of child-bearing potential who test negative for pregnancy (at the time of enrollment) or postmenopausal women - Males must agree to use a reliable method of birth control (during the study and for at least 12 weeks following last dose of study drug), 8) Have given written informed consent/assent prior to any study-specific procedures, 9) Are able to swallow capsules (lomustine) and tablets (LY2157299/placebo).

Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled;1) Are currently enrolled in, or discontinued within the last 30 days from a clinical trial involving an investigational product (including vascular endothelial growth factor receptor [VEGF-R] inhibitors) or non-approved use of a drug or device (other than the study drug/device used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.
2) Have previously completed or withdrawn from this study or any other study investigating LY2157299.
3) Have moderate or severe cardiac disease
4) Received prior nitrosourea (including lomustine or Gliadel®/local carmustine) therapy.
5) Received prior bevacizumab as part of a first-line treatment for GB (unless the treatment was concluded 12 months prior to enrollment)
6) Have a serious concomitant systemic disorder that, in the opinion of the investigator, would compromise the patient*s ability to adhere to the protocol.
7) Have current acute or chronic myelogenous leukemia
8) Have a second primary malignancy that, in the judgment of the investigator and sponsor, may affect the interpretation of results
9) Are pregnant or breast-feeding women
10) Are unwilling or unable to participate in the study.

Study design

Design

Study phase:	2
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-02-2013
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Belustine
Generic name:	Lomustine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	LY2157299 monohydrate
Generic name:	LY2157299 monohydrate

Ethics review

Approved WMO

Date:	16-05-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	12-06-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	18-10-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-02-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-03-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-04-2013
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	EUCTR2011-004418-40-NL
CCMO	NL39459.078.12