A Phase 1/2 Multicenter Study of BMS-986012 in Subjects with Relapsed / Refractory Small Cell Lung Cancer (CA001-030)

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Primary ObjectiveThe primary objectives are to determine the multidose safety, tolerability, dose limiting toxicities (DLTs), and the maximally tolerated dose (MTD) of BMS-986012 administered as monotherapy in subjects with relapsed/refractory SCLC....

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON43272

Source
ToetsingOnline

Brief title
CA001-030 BMS-986012 in Relapsed / Refractory Small Cell Lung Cancer

Condition

- Other condition

Synonym
small cell lung cancer

Health condition

neoplasms in the lung

Research involving

Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: anti Fucosyl-GM1, Efficacy, Safety, Small Cell Lung Cancer

Outcome measures

Primary outcome

The primary endpoint of this phase 1/2 study is safety as measured by the rate of adverse events (AEs), serious adverse events (SAEs), discontinuations due to AEs, deaths, and clinically significant laboratory abnormalities. Safety will be evaluated once a subject signs informed consent through Clinical Follow-up.

Secondary outcome

Efficacy:

The objective response rate (ORR), duration of response, and progression free survival (PFS) will be assessed based on RECIST v1.1 criteria. In addition, PFS rates at pre-specified time points, e.g. 24, 36 weeks will be assessed.
Individual best overall response (BOR) will be a subject level endpoint. The above will be determined based on tumor measurements occurring every 6 weeks during the Treatment Period, and at approximiately the 100-day Clinical Follow-up visit, according to institutional practice. Subjects not progressing at discontinuation of study treatment will undergo tumor assessments every 3-4 months or as per institutional practice until the date of the first objective documentation of tumor progression or death due to any cause.

Pharmacokinetics: Cmax, Tmax, Ctau, AUC(0-T), AUC(TAU)

Immunogenicity: Occurrence of specific anti-drug antibodies (ADA) to BMS-986012. Samples will be collected at multiple time points.

Exploratory Biomarkers: Shed fuc-GM1, fuc-GM1 positive CTCs, NK and monocyte/macrophage counts, NK immunophenotyping, complement levels and Fc*R polymorphisms. If available, fuc-GM1 IHC of fresh biopsies and evaluation of fuc-GM1 related biomarkers of archived FFPE biopsies.

Study description

Background summary

Lung cancer has been the most common cancer in the world. It is also the most common cause of death from cancer. Approximately 57% of patients have metastatic disease at diagnosis, and in these patients the prognosis is poor; with a 5-year survival less than 4%. These statistics include small cell lung cancer (SCLC), which has an even poorer prognosis. Patients with SCLC rarely survive more than a few months without treatment. However, SCLC is highly responsive to multiple chemotherapeutic drugs, and chemotherapy dramatically prolongs survival compared to best supportive care. Management of SCLC depends on the stage of the disease at diagnosis. About 70-90% of newly-diagnosed patients will respond to first-line therapy chemotherapy. Regimens containing a platinum and etoposide are often chosen as first-line treatment in patients with good performance status. However, median survival is 9-11 months and long-term survival is rare. Fewer than 5% of patients with extensive disease live beyond 2 years, even with multi-agent, intensive treatment with multiple lines of therapy.

Few new agents with activity in SCLC have been identified, and none have been successful thus far in Phase 3 studies. Fucosyl-GM1 (fuc-GM1) offers a cell surface target known to be expressed in 70% of SCLC tumors by IHC. Fuc-GM1 has been implicated in promoting cell proliferation, angiogenesis and immune tumor cell evasion. Antibodies to fuc-GM1 have been shown to inhibit tumor growth and to induce apoptosis of antigen

positive cells. BMS-986012 is a first-in-class fully human immunoglobulin G 1 monoclonal antibody that specifically binds to the fuc-GM1. In vivo results in mice demonstrate that BMS-986012, as a single agent, is a potent inhibitor of human SCLC tumor growth and can improve outcomes when combined with chemotherapy. This first-in-human study will evaluate safety, tolerability, and preliminary efficacy of this study drug in the SCLC population.

Study objective

Primary Objective
The primary objectives are to determine the multidose safety, tolerability, dose limiting toxicities (DLTs), and the maximally tolerated dose (MTD) of BMS-986012 administered as monotherapy in subjects with relapsed/refractory SCLC.

Secondary Objectives
- To characterize the pharmacokinetics (PK) of BMS-986012.
- To investigate the preliminary antitumor activity of BMS-986012 as monotherapy as measured by objective response rate (ORR), duration of response, and progression-free survival (PFS).
- To characterize the immunogenicity of BMS-986012.
- To assess the effect of BMS-986012 on the QT interval.

Exploratory Objectives
- To explore associations between shed fucosyl-GM1 (fuc-GM1) at baseline and antitumor activity.
- To explore associations between baseline fuc-GM1 positive circulating tumor cells (CTCs) and anti-tumor activity.
- To explore associations of baseline NK-cell numbers, phenotype (by FACS) and complement levels with pharmacodynamic changes and anti-tumor activity.
- To explore fuc-GM1-related biomarkers such as, but not limited to, markers of neuroendocrine differentiation as potential prognostic markers of anti-tumor activity.
- To explore associations between Fc gamma receptor (Fc*R) polymorphisms with anti-tumor
activity.
- To explore the PK-PD relationship(s) of BMS-986012.
- To assess overall survival (OS).

Study design

This is an open-label ascending multiple dose study of BMS-986012 administered once every 21 days (one cycle) as a single agent and will be conducted in two parts. Dose escalation (Part 1) is to identify a potential MTD, (or maximum administered dose (MAAD) if no MTD is determined). In Part 2, additional

subjects with SCLC will be enrolled at two doses at or below the MTD or MAAD to confirm safety and evaluate efficacy at
these doses. The site in the Netherlands will only participate in part 2.

Subjects will complete up to 4 periods in the study: Screening (within 28 days prior to administration of study medication), Treatment (until meeting protocol-specified discontinuation criteria), Clinical Follow-up (approximately 100 days, see Table 5.1-3) and Survival Follow-up (up to approximately 3 years following end of treatment).

Intervention

The medicinal intervention includes BMS-986012 therapy. Study drug will be supplied by the sponsor.

Part 2 will evaluate toxicity and preliminary efficacy of BMS-986012 as second-line monotherapy in subjects who have relapsed following first-line chemotherapy as follows: Cohort A: <= 3m response duration (refractory) at the MTD/MAAD, Cohort B: <= 3m response duration (refractory) at a dose level below the MTD/MAAD, Cohort C: > 3m response duration (sensitive) at the MTD/MAAD, and Cohort D: > 3m response duration(sensitive) at a dose level below the MTD/MAAD. The response duration referenced above is relative to the prior first-line therapy.

Each treatment cycle consists of an IV infusion of BMS-986012 every 21 days.

Study burden and risks

As part of the trial, patients will be expected to attend multiple clinic visits, where they will undergo physical examinations, vital sign measurements (including oxygen saturation levels), blood tests for safety assessment, pregnancy testing (for females of child bearing potential), and monitoring for adverse events. In addition, every 6 weeks, patients will undergo radiographic assessment of their tumours (by CT or MRI) until disease progression or treatment discontinuation whichever occurs later.
Subjects may have pre-treatment biopsies performed or archival material, if available, will be requested. Blood will also be collected at certain visits for research purposes (PK, PD, immunogenicity and biomarker studies).
The frequency of visits and number of procedures carried out during this trial would typically be considered over and above standard of care. These procedures are conducted by medically trained professionals and every effort will be made to minimise any risks or discomfort to the patient. Treatment for cancer often has side effects, including some that are life threatening. Patients will be instructed when to contact their treating physicians if side effects occur and are given a patient card with detailed information.

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

- Signed Written Informed Consent
- Men and women at least 18 years of age with histological or cytological confirmed pulmonary SCLC
- Have relapsed after or are refractory to first line therapy and have not yet received two or more lines of anticancer treatment
- Last exposure to anticancer therapy within 4 weeks or 5 half-lives (whichever is longer) prior to study drug administration
- At least one measurable lesion per RECIST v1.1
- Adequate organ function
- Comply with visit and treatment schedule, sample collection for laboratory tests, and treatment and follow-up

Exclusion criteria

- Known or suspected brain metastasis
- Non-pulmonary small cell cancer
- Acute or chronic medical illness
- Uncontrolled or significant cardiac disease
- Infection requiring systemic treatment
- Grade 2 or higher peripheral neuropathy
- Other concomitant malignancies (except unless complete remission was achieved 3 yrs prior to study entry)
- HIV-related disease, HIV+, HepB, HepC
- Allergies or adverse drug reaction

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	20-07-2016
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BMS-986012
Generic name:	BMS-986012

Ethics review

Approved WMO Date:	15-03-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-07-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-09-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-11-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-11-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2014-002372-89-NL

Register	ID
ClinicalTrials.gov	NCT02247349
CCMO	NL56777.091.16

Study results

Date completed: 21-12-2017

Results posted: 21-12-2023

First publication
01-01-1900