START * Stimulating Targeted Antigenic Responses To NSCLC A multi-center phase III randomized, double-blind placebo-controlled study of the cancer vaccine Stimuvax® (L-BLP25 or BLP25 liposome vaccine) in non-small cell lung cancer (NSCLC) subjects with unresectable stage III disease

Published: 14-05-2007
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Primary objective:* To compare survival duration of all randomized subjects by treatment arm.Secondary objectives of this trial are to compare all randomized subjects by treatment arm for:* Time to symptom progression (TTSP) as measured by the Lung...

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

Summary

ID

NL-OMON40067

Source
ToetsingOnline

Brief title
START

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
non-small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Merck
Source(s) of monetary or material Support: Merck KgaA

Intervention

Keyword: cancer vaccine, non-small cell lung cancer

Outcome measures

Primary outcome

The primary variable of this study is the survival duration. Survival will be

measured as the number of months between the date of randomization and the date

of death.

Survival will be analyzed in the intention-to-treat (ITT) population (primary

analysis) and in the per protocol (PP) population.

Secondary outcome

* TTSP as measured by the LCSS.

* TTP as determined by the investigator.

* One-, two- and three-year survival.

Reactions on the injection site, side effects, vital functions and clinical

laboratorium testing:

* Progression free survival (PFS).

* QoL index (EQ-5D).

* Healthcare resource utilization and work status.

* Additional QoL analyses utilizing the LCSS.

* Time to treatment failure (TTF).

* HLA-typing.

* Molecular markers.

Study description

Background summary

Lung cancer continues to be the most common cancer in the world, both in terms of
incidence (1.2 million new cases or 12.3% of the world total) and mortality (1.1 million deaths or 17.8% of the world total) (2, 3, 4). Worldwide, lung cancer is by far the most common cancer among men (17% of all new cancers in 2000) with the highest rates observed in North America, Europe (especially eastern Europe), South America, and Australia/New Zealand. Moderately high rates are also seen in parts of eastern Asia. In less developed regions the highest rates are seen in the Middle East, China, the Caribbean, South Africa, Zimbabwe, and the Pacific. In 2000, lung cancer was reported to be the number one cancer among men in southern and eastern Europe, Western and southeastern Asia, as well as Micronesia/Polynesia. In females, the incidence rates are much lower
worldwide (the rate is 11.1 per 100,000 in women compared with 34.9 per 100,000 in men). The highest estimated rates are in northwestern Europe and North America, where in the year 2000 lung cancer was the fourth most frequent cancer of women. Moderately high rates are also seen in Australia, New Zealand and China (2, 3, 4). In North America, lung cancer remains the leading cause of cancer death for both men and women in 2004. Although breast cancer and prostate cancer have the highest incidence rate, lung cancer remains the most frequent cause of death from cancer. In 2004, an estimated 21,700 new cases of lung cancer will be diagnosed in Canada and 173,770 new cases in the United States (US). In the same year, an estimated 18,900 deaths are anticipated from lung cancer in Canada and 160,440 deaths in the US (5, 6).
Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for about 80% of all cases (7). The majority of NSCLC subjects present with advanced disease at diagnosis and a large number of those diagnosed with early stage disease eventually experience recurrent disease (8).

Chemotherapy and radical radiotherapy have become the standard of care for unresectable stage III NSCLC, but even with this aggressive approach the median survival is often less than two years with only 15% surviving five years (8). Analyses of phase III trials of chemotherapy for advanced NSCLC demonstrate improvements in survival and quality of life, although the absolute gains have been small (9, 10, 11). Given the considerable toxicity and modest benefit of chemotherapy for NSCLC, it is apparent that additional therapies
A variety of treatment strategies have been evaluated in recent years in an effort to improve outcomes for patients with advanced NSCLC. Studies evaluating the addition of gefitinib (12, 13), erlotinib (14, 15), or trastuzumab (16) to standard platinum based chemotherapy regimens as well as studies on maintenance therapy with vinorelbine (17) for patients with stable disease or an objective response following first line chemotherapy, have shown limited success. Even with combined modality treatment, median survival rates, ranging from approximately 13 to 27 months for unresectable stage III disease, indicate much room for improvement (18, 19, 20). While immunologic approaches have not yielded important advances in disease control to date, there is a growing body of
literature describing the potential of immunotherapy. Much of the focus on cancer
immunotherapy has been in the area of cancer vaccine development, particularly with the identification of specific antigens associated with cancer (21).
L-BLP25 is a cancer vaccine that targets the exposed core peptide of the MUC1 tumorassociated antigen. Recent studies have identified that MUC1 is associated with cellular transformation as demonstrated by tumorigenicity (22) and can confer resistance to genotoxic agents (23). High level cell surface expression (24, 25), reported immunosuppressive activities of its released ectodomain (26), and anti-adhesive properties (27, 28) all contribute to this mucin's ability to protect and promote tumor cell growth and survival and make MUC1 an attractive target for cancer immunotherapy.
Currently, there are no recommended treatment options for unresectable stage III NSCLC patients who are stable or responding following primary chemo-radiotherapy. Preliminary survival results from a previous L-BLP25 study (B25-LG-304) performed in stage IIIB and IV NSCLC patients show the greatest treatment effect in survival to be in stage IIIB locoregional (LR) patients (see Section 3.5.3). Based on these results, L-BLP25 may have potential as a maintenance therapy for unresectable stage III NSCLC patients.

Study objective

Primary objective:
* To compare survival duration of all randomized subjects by treatment arm.
Secondary objectives of this trial are to compare all randomized subjects by treatment arm for:
* Time to symptom progression (TTSP) as measured by the Lung Cancer Symptom Scale (LCSS).
* Time to progression (TTP) as determined by the investigator.

* One-, two- and three-year survival.
* Safety.

Study design

A multi-center phase III randomized, double-blind placebo-controlled study in subjects with unresectable stage III NSCLC who have demonstrated either stable disease or objective response following primary chemo-radiotherapy (concomitant or sequential). Subjects will be randomized 2:1 either to L-BLP25 drug product (hereinafter "LBLP25") (investigational arm) or to L-BLP25 placebo (hereinafter "placebo")respectively.
Subjects will be stratified by:
* Disease stage (IIIA versus IIIB).
* Response to primary chemo-radiotherapy (stable disease versus objective response).
* Type of primary chemo-radiotherapy (concomitant versus sequential).
* Region (1: North America [Canada, United States] and Australia, 2: Western Europe, or 3: Rest of World [Mexico, Central and South America, Eastern Europe and Asia]).
Periodic evaluations of the trial data will be conducted by an independent Data Monitoring Committee (DMC) to ensure subject safety and the validity and scientific merit of the study.

Intervention

Hiervoor verwijzen wij graag naar de flowchart in het protocol (pagina 108-109) en pagina 56 (6. Treatments)

Study burden and risks

In the 2 weeks preceding the study, the doctor will record the medical history of the patient and will do a physical examination, including vital functions. A blood sample will be taken to determine the general condition and to confimr that the patient can start the study. Part of this sample will be kept to do additional testing. Possibly, an x-ray, CT-scan, bone scan or other medical imaging tests can be done to determine the tumor size. A brain (CT- or MRI-scan) scan must be performed to exclude metastases to the brain. With the help of an ECG, the condition of the heart will be determined. The doctor will inform the patient about the x-rays or scans that are required. the patient will be asked to fill out 2 questionnaires about the quality of life. During the study, information will be collected regarding the working condition (currently employed or not), the use of health resources (e.g. hospitalisations, visit to the doctor and medication) for patients who are participating to this study.

Before an injection (Stimuvax or placebo) is administered, the patient will get

a single dose of another drug, either cyclophosfamide or a saline solution, depending on the treatment group to which the patient is assigned.

Is has been shown that the effects of Stimuvax of letting the immune system work against the cancer, is increased if a low dosis of cyclophosfamide is administered before Stimuvax is administered. The saline solution will not have an effect on the body. The cyclofosphfamide or saline solution will be administered once through an infusion with a needle in the arm. The patient will get this treatment during a visit to the day clinic.
3 days after the pre-treatment, the patient will get 7 additional treatments with Stimuvax or the placebo: 1, 2, 3, 4, 5, 6 and 7 weeks after the first treatment. Each treatment consists of 4 small injections with either Stimuvax or placebo, under the skin of the upper arm of abdomen. Each visit will take about 2 hours and an inspection of the injection site will be done, together with the monitoring of the vital functions, during maximum 1 hour after the injections.
during the visit in week 4 an additional blood sample will be taken, to determine the general health. The patient will also undergo a physical examination.
During the visits in week 2, 5 and 8 and during the 6-weekly visits, the patient will complete 2 questionnaires about the quality of life.
1 week after the eight treatment with Stimuvax or placebo, a physical examination will be done to determine the effect of the treatments on the patient. A new blood sample will be drawn to determine the general condition and to do additonal testing afterwards.
Of the doctor feels that the patient will continue to benefit from the treatments, the injections will be continued. the maintenance injections will be given every 6 weeks, beginning at week 13. Each 2nd treatment visit a new blood sample will be
drawn.
The dose cyclophosfamide or saline during the pre-treatment can cause nausea. The doctor can prescribe medication to take away this nausea. Because the pre-treatment is administered through a vein, some discomfort or bruising is possible at the injection site.
The injection with Stimuvax or placebo can cause some discomfort. Itching, swelling or redness can temporarily cause some discomfort. In some cases, a lump is felt on the injection sites. You could also have flue-like symptoms during a couple of days after the injections.
As with all drugs, an allergic reaction can happen. This can lead to rash, blood pressure drop, difficulty breathing.

Contacts

Public

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Both inpatient and outpatient, male and female subjects are eligible for randomization.
* Subject has given written informed consent before any study-related activities are carried out.
* Histologically or cytologically documented unresectable stage III NSCLC. All histological subtypes are acceptable, including bronchioalveolar carcinomas. Cancer stage must be confirmed and documented by computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET) scan.
* Documented stable disease or objective response, according to RECIST, after primary chemo-radiotherapy (either sequential or concomitant) for unresectable stage III disease, within 4 weeks (28 days) prior to randomization*.
* Receipt of concomitant or sequential chemo-radiotherapy, consisting of a minimum of two cycles of platinum-based chemotherapy and a minimum radiation dose of * 50 Gy. Subjects must have completed the primary thoracic chemo-radiotherapy at least four weeks (28 days) and no later than 12 weeks (84 days) prior to randomization. Subjects who received prophylactic brain irradiation as part of primary chemo-radiotherapy are eligible.
* Geographically accessible for ongoing follow-up, and committed to comply with the

designated visits.
* An ECOG performance status of 0-1.
* A platelet count * 140 x (1E+9)/L; WBC * 2.5 x (1E+9)/L and hemoglobin * 90 g/L.
* * 18 years of age.
* If imaging after primary chemo-radiotherapy was earlier than 4 weeks prior to randomization, it must be repeated within 4 weeks prior to randomization, and the results of the second restaging after end of primary chemo-radiotherapy must be compared with the first restaging after end of primary chemo-radiotherapy. Subjects that show progression between these two assessments are not eligible for this trial.

Exclusion criteria

Pre-Therapies:
* Undergone lung cancer specific therapy (including surgery) other than primary chemo-radiotherapy.
* Receipt of immunotherapy (e.g. interferons, tumor necrosis factor [TNF], interleukins, or biological response modifiers [granulocyte macrophage colony stimulating factor {GM-CSF}, granulocyte colony stimulating factor {G-CSF}, macrophage-colony stimulating factor {M-CSF}], monoclonal antibodies) within 4 weeks (28 days) prior to randomization. Note: Subjects who have received monoclonal antibodies for imaging are acceptable.
* Receipt of investigational systemic drugs (including off-label use of approved products) within 4 weeks (28 days) prior to randomization.
Disease Status:
* Metastatic disease.
* Malignant pleural effusion at initial diagnosis and/or at study entry.
* Past or current history of neoplasm other than lung carcinoma, except for curatively treated non-melanoma skin cancer, in situ carcinoma of the cervix or other cancer curatively treated and with no evidence of disease for at least 5 years.
* Autoimmune disease
* A recognized immunodeficiency disease including cellular immunodeficiencies, hypogammaglobulinemia or dysgammaglobulinemia; subjects who have hereditary or congenital immunodeficiencies.
* Any preexisting medical condition requiring chronic steroid or immunosuppressive therapy (steroids for the treatment of radiation pneumonitis are allowed).
* Known Hepatitis B and/or C.
Physiological Functions:
* Clinically significant hepatic dysfunction (i.e. Alanine aminotransferase [ALT] > 2.5 times normal upper limit [ULN]; or Aspartate aminotransferase [AST] > 2.5 times ULN; or bilirubin * 1.5 x ULN).
* Clinically significant renal dysfunction (i.e. serum creatinine * 1.5 x ULN).
* Clinically significant cardiac disease, e.g. New York Heart Association (NYHA) classes III-IV; uncontrolled angina, uncontrolled arrhythmia or uncontrolled hypertension, myocardial infarction in the previous 6 months as confirmed by an electrocardiogram (ECG).
* Splenectomy.
* Infectious process that in the opinion of the investigator could compromise the subject*s

ability to mount an immune response.
Standard Safety:
* Pregnant or breast-feeding women, women of childbearing potential, unless using effective contraception as determined by the investigator. Subjects whom the investigator considers may be at risk of pregnancy will have a pregnancy test performed per institutional standard.
* Known drug abuse/alcohol abuse.
* Participation in another clinical study within the past 28 days.
* Requires concurrent treatment with a non-permitted drug*.
* Known hypersensitivity to any of the study treatment ingredients.
* Legal incapacity or limited legal capacity.
* Any other reason that, in the opinion of the investigator precludes the subject from participating in the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-02-2007
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Stimuvax - L-BLP25

Ethics review

Approved WMO Date:	14-05-2007
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-07-2007
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-11-2007
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-11-2007
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-12-2007
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-03-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-11-2008
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	27-01-2009
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-03-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-05-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-06-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-04-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-06-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-11-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-03-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	20-03-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-04-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-06-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-03-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-10-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-10-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2006-000579-14-NL
CCMO	NL15526.000.07

Study results

Date completed:	16-12-2014
Actual enrolment:	25