A randomized, double-blind, controlled phase III study of Stimuvax® (L-BLP25 or BLP25 liposome vaccine) in combination with hormonal treatment versus hormonal treatment alone for first-line therapy of post-menopausal women with estrogen receptor (ER)-positive and/or progesterone receptor (PgR)-positive, inoperable locally advanced, recurrent, or metastatic breast cancer

Published: 31-07-2009
Last updated: 05-05-2024

PrimaryDemonstration of superior efficacy (as measured by PFS time) of L-BLP25 in combination with hormonal treatment (HT) over placebo plus HT, when used for first-line therapy of hormone receptor-positive (ER+ and/or PgR+), inoperable locally...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Reproductive tract and breast disorders congenital
Study type	Interventional

Summary

ID

NL-OMON33179

Source
ToetsingOnline

Brief title
STRIDE

Condition

- Reproductive tract and breast disorders congenital
- Breast disorders

Synonym
breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Merck
Source(s) of monetary or material Support: Farmaceutisch bedrijf: Merck KGaA

Intervention

Keyword: breast cancer, first-line therapy, hormonal treatment, vaccine

Outcome measures

Primary outcome

Progression-free survival (PFS) time (assessment of Progressive Disease as

determined by an independent radiology reading)

Secondary outcome

• Overall Survival Time

• Objective Tumor Response

• Duration of Response

• Clinical Benefit

• Time to Progression

• Time to Chemotherapy

• Quality of Life

• Healthcare Resource Utilization

• Serum CA 15-3

Tolerability / safety variables

• Drug exposure

• Incidence and type of AEs

• Vital signs

• Safety laboratory tests

• Incidence and reasons for deaths

Study description

Background summary

Stimuvax® is a registered trademark of Merck KGaA. Merck KGaA has licensed Stimuvax® (L-BLP25 or BLP25 liposome vaccine) from Biomira Inc. of Edmonton, Alberta, Canada (now Oncothyreon Inc., Bellevue, Washington, USA).
L-BLP25 is an investigational therapeutic cancer vaccine developed for use as an active specific immunotherapy against MUC1-expressing malignant tumors. Details of the physical, chemical, and pharmaceutical properties; the nonclinical studies, and efficacy and safety in humans are summarized in the Investigator*s Brochure (IB) [1].

3.1 Introduction
3.1.1 Epidemiology of Breast Cancer
Breast cancer (BRCA) is the most common form of cancer in women worldwide, accounting for 32% of all female cancers [2], and represents a major public health problem due mainly to its high incidence, excess mortality, and multiple therapeutic challenges. To date, more than 1.2 million women are diagnosed with BRCA each year worldwide, and more than 320,000 will succumb to this disease. The incidence rates of BRCA are exceedingly high, especially in the European Union, Australia, and the United States of America (USA) with respective rates of 67.4, 71.7, and 86.3 per 100,000 [2, 3].
It is estimated that more than 182,460 women will be diagnosed with BRCA and that
40,480 will die from it in the USA alone this year [2]. In Europe, an estimated 429,000 breast cancer-specific deaths occurred in 2006 [3]. Approximately 75% to 80% of newly diagnosed patients are women with early stage BRCA. Despite the

use of chemotherapy or hormonal therapy (HT), many of these patients will die as a result of local recurrence that is not amenable to surgery, or of metastatic disease. The outlook for metastatic BRCA is bleak, with five-year survival rates averaging 25% to 26% [4]. These alarming facts call for the development of more effective therapeutic strategies for BRCA.

3.1.2 Management of Breast Cancer

Management of BRCA has been difficult. Treatment of early BRCA has established a gold standard (combined modality therapy with surgery plus radiotherapy, followed by adjuvant chemotherapy, HT, or biologic therapy) for most women, with reasonable gains in terms of reduction of risk of recurrence (i.e., five-year recurrence rates of 15.1% and 26.5% for tamoxifen-treated and control, respectively), and overall reduction of risk of mortality (five-year mortality rates of 8.3% and 11.9% for tamoxifen-treated and control, respectively) [5].

Unlike early BRCA, there is no standard of care for women who present with inoperable locally advanced, recurrent, or metastatic disease (herein referred to as advanced BRCA). Because advanced BRCA is an incurable disease, treatment is largely palliative in nature and is aimed at improving quality of life (QOL), and prolonging survival. Endocrine therapy is now widely accepted as treatment modality of choice for women with hormonesensitive estrogen receptor-positive (ER+) and/or progesterone receptor-positive (PgR+) disease (approximately 70% of patients) [6]. Such treatment is aimed at blocking estrogen from binding to its ligand in the tumors or at reducing estrogen biosynthesis.

For more than two decades, the anti-estrogen drug tamoxifen has been the drug of choice for women with ER+ or "ER-unknown" advanced BRCA. By blocking the binding of estrogen to its receptor, tamoxifen prevents estrogen-signaling through the ER and, consequently, induces tumor shrinkage and reduces tumor growth, resulting in response rates of 21% to 40% and time to progression (TTP) of approximately six to eight months [7, 8, 9]. However, a significant number of women have a disease that is tamoxifen-refractory, or will become tamoxifen-resistant during therapy. Furthermore, long-term use of tamoxifen is associated with the risk of developing endometrial cancer [7, 8, 9]. These observations have fueled the search for alternative approaches to inhibit the estrogen stimulus to hormone-sensitive tumors.

Aromatase inhibitors (AIs) have emerged as attractive pharmacological agents and effective alternatives to tamoxifen for front-line or second-line endocrine therapy of advanced BRCA. These drugs cause tumor shrinkage by reducing systemic levels of estrogen via inhibition of aromatase, a cytochrome P450-dependent enzyme. A new generation of AIs, anastrozole and letrozole, have been used with great success in frontline endocrine therapy for hormone-sensitive advanced BRCA. Several randomized studies have demonstrated the superior efficacy of these agents over tamoxifen in women with ER+, PgR+, or "hormone receptor unknown" advanced BRCA.

Two large randomized studies supported the superior efficacy of anastrozole for front-line therapy of post-menopausal women with hormone receptor-positive or

"hormone receptor unknown" advanced BRCA [7, 8]. In the first study, Nabholtz et al. observed anastrozole to be as effective as tamoxifen in terms of response rate (21% and 17%, respectively) an TTP (medians 11.1 and 5.6 months, respectively; p = 0.09, with a hazard ratio (HR) of tamoxifen:anastrozole of 1.44) [7]. Treatment was generally well tolerated, with subjects in the tamoxifen arm developing more thromboembolic events (8.2%) and vaginal bleeding (3.8%). In the second study, Bonneterre et al. found anastrozole to be as effective as tamoxifen (median TTP of approximately eight months for both arms, generally similar response rates of 32.9% and 32.6%, respectively) [8]. Again, tamoxifen induced more thromboembolic events and vaginal bleeding.

The efficacy and tolerability of letrozole was evaluated in one large multicenter, doubleblind study that randomized women with hormone receptor-positive or "hormone receptor unknown" advanced BRCA to either letrozole or tamoxifen. Letrozole demonstrated significantly superior efficacy over tamoxifen in terms of response rate (32% vs. 21%, respectively) and TTP (median 9.4 months and 6.0 months, respectively) [9]. Additionally, letrozole demonstrated a slight survival advantage by extending median survival by 4 months over that of tamoxifen (34 months vs. 30 months, respectively). Treatment was generally well tolerated in both groups, with tamoxifen patients having the same incidence of thromboembolic events as those administered letrozole.

Overall, the two AIs showed superior efficacy relative to tamoxifen, and thus, they have become a standard of care for women with ER+ and PgR+ advanced BRCA. As can be seen from these results of HT studies in advanced BRCA, the main goal of extending survival in this disease remains largely unfulfilled. Furthermore, combined modality therapies that include potent anti-neoplastic drugs (e.g., vinca alkaloids, antimicrotubule agents, and DNA intercalating agents) and rationally designed targeted novel agents (herceptin, lapatinib) have all proven to be effective anticancer drugs when used alone or in combination with HT [10]. However, their limited effect on survival and increased toxicity highlight the urgent need for novel therapeutic strategies, such as cancer immunotherapy, that aim to improve the clinical outcome of BRCA patients treated with vaccines, antibodies, or immunomodulatory agents.

One of the most important advances in the field of cancer immunotherapy is the identification of tumor antigens that could be successfully used to target tumor cells. The mucin MUC1 is one of the most studied antigens expressed by BRCA cells. Its characterization and the identification of the core repeat peptide (20-mer repeated peptide) as a major T-cell immunogen has allowed the development of several vaccines that are under intensive investigation for therapy of BRCA [11, 12]. L-BLP25 is a MUC1-based vaccine consisting of a 25-mer synthetic peptide (encompasses the core repeated peptide) into a liposomal formulation. Previous phase I and II studies have established its immunogenicity in patients with refractory non-small cell lung cancer (NSCLC) and hormone-naïve prostate cancer [13].

One of the recent advances with L-BLP25 is the observation of a strong survival trend in favor of L-BLP25 in a subgroup of NSCLC patients with locoregional stage IIIB disease [14]. These results are encouraging and have served as the

impetus for the current study. This phase III study proposes to use L-BLP25 as an add-on therapy to either tamoxifen or either of the two AIs (anastrozole, letrozole) to assess the treatment effect, focusing primarily on the ability of L-BLP25 to improve survival (measured asprogression-free survival [PFS]) afforded by HT alone.

Study objective

Primary
Demonstration of superior efficacy (as measured by PFS time) of L-BLP25 in combination with hormonal treatment (HT) over placebo plus HT, when used for first-line therapy of hormone receptor-positive (ER+ and/or PgR+), inoperable locally advanced, recurrent, or metastatic breast cancer (BRCA).

Secondary
• Safety and Tolerability;
• Overall Survival (OS) Time;
• Objective Tumor Response;
• Duration of Response;
• Clinical Benefit;
• Time to Progression (TTP);
• Time to Chemotherapy;
• Quality of Life (QOL);
• Healthcare Resource Utilization (HRU);
• Serum CA 15-3.

Study design

Randomized (2:1), double-blind, controlled, multicenter, multinational, safety and eff

Intervention

Randomized (2:1), double-blind, controlled, multicenter, multinational, safety and efficacy study of HT with or without L BLP25.

Investigational product:
• A single I.V. infusion of 300 mg/m2 (to a maximum of 600 mg) of cyclophosphamide will be administered 3 days prior to the first L-BLP25 vaccination.
• Subjects will then receive eight consecutive subcutaneous vaccinations with 1,000 mg L-BLP25 at weeks 1, 2, 3, 4, 5, 6, 7 and 8, followed by maintenance vaccinations (1,000 mg L-BLP25) at six-week intervals, beginning at week 14, and continuing until PD is documented or the subject discontinues for any other reason.

Study burden and risks

Participation in this study has the risk on the following side effects:

The pre-treatment dose of cyclophosphamide or saline can cause nausea. Your doctor can give you drugs to help overcome any nausea you may feel. In previous clinical trials with cyclophosphamide given prior to Stimuvax injections, about half of the patients said they felt mild nausea, and the other half did not experience any side effects. Because the pre-treatment is given through a vein, some discomfort or bruising might occur at the site of the needle insertion.
The injection of Stimuvax or the placebo can cause some discomfort. In addition, you may notice some temporary itching, swelling or redness at the sites of injections. In some cases, you may feel a lump at the injection sites. You may also experience some mild flu-like symptoms like fatigue, nausea, headache, fever and muscle pain for a few days after the injections.
As with any drug, it is possible that an allergic reaction to a study treatment drug could occur. This may result in a rash, a drop in blood pressure, or difficulty in breathing.
This is unlikely to happen, and when it occurs, it often starts within an hour of the injection. This is the reason why you must wait at the clinic for one hour after the injection so that a doctor is available in case emergency treatment is required.
As Stimuvax is similar to a substance made naturally by your cancer cells, there is a possibility you may develop an *autoimmune disorder* like rheumatoid arthritis or lupus, although this has never, thus far, been reported.
There is also a risk of discomfort, bruising, and possible infection as the result of drawing blood for laboratory testing.
Stimuvax contains a so-called adjuvant, a component that enhances the activity of Stimuvax. Cases of brain and spinal cord inflammation and autoimmune diseases have been reported with products containing a component of the adjuvant along with a component of this vaccine. The relationship of the product under study or its components to these events is unknown. Evaluation of these and similar events continues.
The side effects listed above may be temporary, long-lasting or permanent. However, most of these side effects are reversible, that is, they will stop once the drug is discontinued.
Treatment with these drugs and procedures performed may have also other risks that have not yet been identified. If you have any side effects, either those mentioned above or others, or if you want more information on how the drug(s) may affect you, you should talk with the doctor or study nurse in charge of the study. Their contact telephone numbers are on the last page of this Subject Information Sheet.

CT-Scans
You will have extra CT (Computer Tomography)/Isotope scans (modern techniques that allow more detailed assessment of the size of your cancer) during the

study that would not be part of normal care. This will mean you are exposed to very slightly more radiation than normal, and there is a tiny theoretical risk to your future health.

In addition to the risks listed above, there may be risks or side effects that are unexpected or unknown at this time.

Contacts

Public
Merck

Frankfurterstrasse 250
64293 Darmstadt
Germany
Scientific
Merck

Frankfurterstrasse 250
64293 Darmstadt
Germany

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Female, inpatient or outpatient, 18 years of age or older, who are post-menopausal as defined by at least one of the following:
- No spontaneous menses for at least five years
- Spontaneous menses within the past five years but amenorrheic for at least 12 months and

luteinizing hormone (LH) and follicle-stimulating hormone (FSH) within the post-menopausal normal range. (Subjects who are amenorrheic following a hysterectomy but who have not had bilateral salpingo-oophorectomy are not eligible unless they have additional biochemical evidence of menopause as reflected by ovarian suppression and FSH and plasma estradiol levels in the postmenopausal range.)
- Prior bilateral oophorectomy
- Prior bilateral ovarian irradiation and castration, amenorrheic for at least three months, and FSH levels > 40 IU/L
- No menstrual period for 12 months or longer and a serum estradiol level in the post-menopausal range (<= 22 pg/mL)
• ER- and/or PgR-positive, histologically or cytologically confirmed primary carcinoma of the breast (institutional pathological diagnosis of BRCA is acceptable).
• Expressing at least one of the following five human leukocyte antigen (HLA) haplotypes as centrally assessed by HLA-genotyping: HLA-A2, -A3, -A11, -B7, or -B35.
• Locally advanced, recurrent, or metastatic BRCA. (Subject must have at least one lesion not located in bone.)
• Measurable disease by RECIST, and inoperable (not eligible for breast-conserving surgery or mastectomy) with no reasonable expectation of surgery for cure now or in the future.
• ECOG performance status of 0 or 1.
• Adequate hematologic, hepatic, and renal function within two weeks prior to initiation of therapy as defined by the following:
- White blood cells >= 2,500/mm3, absolute neutrophils >= 1,500/mm3 and platelets >= 100,000/mm3
- Hemoglobin >= 9 g/dl
- Bilirubin <= 1.5 x ULN, or <= 5 x ULN in case of hepatic metastasis
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <= 2.5 x ULN, or <= 5 x ULN in case of hepatic metastasis
- Creatinine <= 1.5 x ULN
- International Normalized Ratio (INR), prothrombin time (PT), and partial thromboplastin time (PTT) in the normal range
• Life expectancy of at least 12 weeks.
• Written informed consent given before any study-related activities are carried out.
• Willingness to comply with study protocol requirements.

Exclusion criteria

• Progressive disease either during HT for early BRCA (adjuvant therapy) or within 12 months of completing such therapy.
• HER2 receptor-positive BRCA defined as follows: Immunohistochemistry (IHC) staining of 3+ (uniform, intense membrane staining of > 30% of invasive tumor cells), or a fluorescent in situ hybridization (FISH) result of > 6 HER2 gene copies per nucleus, or a FISH ratio (HER2 gene signals to chromosome 17 signals) > 2.2.
• Autoimmune disease that, in the opinion of the investigator, could compromise the safety of the subject. (Exception will be granted for well-controlled Type I diabetes mellitus.)
• Recognized immunodeficiency disease, including cellular immunodeficiencies,

hypogammaglobulinemia, or dysgammaglobulinemia; hereditary or congenital immunodeficiencies.
• Known active Hepatitis B infection or carrier state and/or Hepatitis C infection, known Human Immunodeficiency Virus infection, or any other infectious process that in the opinion of the investigator could compromise the subject*s ability to mount an immune response or could expose her to the likelihood of more and/or severe side effects.
• Past or current history of malignant neoplasm other than BRCA, 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 five years.
• Receipt of immunotherapy (e.g., interferons, tumor necrosis factor, interleukins, or growth factors [GM-CSF, G-CSF, M-CSF], or monoclonal antibodies) or chemotherapy within four weeks (28 days) prior to randomization. Note: subjects who have received monoclonal antibodies for imaging are eligible.
• Prior receipt of investigational systemic drugs (including off-label use of approved products) or any kind of systemic treatment (chemotherapy, HT, or immunotherapy) for inoperable, locally advanced, recurrent, or metastatic BRCA.
• Prior radiotherapy to the site of cancer, if only one site will be used for evaluation of tumor response.
• Central nervous system disease or brain metastases, as documented by CT or MRI scan.
• Medical or psychiatric conditions that would interfere with ability to provide informed consent, communicate side effects, or comply with protocol requirements.
• Clinically significant cardiac disease, e.g. cardiac failure of NYHA classes III-IV; uncontrolled angina pectoris, uncontrolled arrhythmia, uncontrolled hypertension, or myocardial infarction in the previous six months as confirmed by an ECG.
• Splenectomy.
• Need for concurrent treatment with a non-permitted therapy (e.g., concurrent chemotherapy, radiotherapy, systemic immunosuppressive drugs, use of herbal medicines or botanical formulations intended to treat cancer) while on protocol therapy. Palliative radiation to painful bone lesions is allowed.
• Participation in another clinical study within 30 days prior to randomization.
• Known hypersensitivity to the study drugs.
• Known alcohol or drug abuse.
• Legal incapacity or limited legal capacity.
• Signs and symptoms suggestive of transmissible spongiform encephalopathy, or family members who suffer(ed) from such.
• Subject who could be regarded as "vulnerable" according to ICH GCP guidelines (e.g., the subject*s willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate, plus persons kept in detention; persons in nursing homes; patients in emergency situations; homeless persons; and nomads).
• Any other reason that, in the opinion of the investigator, precludes the subject from participating in this 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):	29-07-2010
Enrollment:	25
Type:	Actual

Ethics review

Approved WMO Date:	31-07-2009
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-01-2010
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-04-2010
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	EUCTR2008-005544-17-NL
ClinicalTrials.gov	NCT00925548
CCMO	NL27089.000.09