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Stimuvax®

Cancer Vaccine

L-BLP-25

Mucin-1 (MUC-1)-based cancer vaccine that incorporates a synthetic 25-amino-acid sequence of the MUC-1 cancer mucin encapsulated in a synthetic liposomal delivery system

EN: 243623

Abstract

Non-small cell lung cancer (NSCLC) accounts for approximately 75% of all lung cancers, the leading cause of cancer-related deaths in both men and women worldwide. Advances in vaccine therapy strategies, designed to stimulate an immune response against tumor cells, are becoming increasingly important for NSCLC patients. L-BLP-25 (Stimuvax®) is a new vaccine candidate for NSCLC that targets tumor-specific MUC-1 antigens, which are overexpressed and exposed due to underglycosylation in neoplastic tissues. L-BLP-25 benefits from an adjuvant that primes the immune system and facilitates uptake of the vaccine and a liposomal delivery system. Preclinical studies have demonstrated that L-BLP-25 generates a potent cytotoxic T helper type 1 (Th1) response against MUC-1-expressing tumor cells and has antitumor activity *in vivo*. Clinical studies have shown that L-BLP-25 improves median survival time in NSCLC patients and provides clinically meaningful improvements in tumor profile and quality of life in those receiving the vaccine combined with best supportive care. In these clinical trials, no patients discontinued vaccine therapy due to adverse events, with no grade 3/4 events related to treatment; however, injection-site reactions were consistently reported. Phase IIb/III trials in NSCLC are currently ongoing at Merck Serono and Oncothyreon (formerly Biomira), with additional preliminary clinical data in prostate cancer.

Background

Lung cancer is the leading cause of cancer-related deaths in both men and women worldwide, killing more people than colon, breast and prostate cancers combined. Estimated new cases and deaths from lung cancer in the United States in 2008 have been calculated as 215,020 and 161,840, respectively (1). Non-small cell lung cancer (NSCLC) accounts for approximately 75% of all lung cancers and, due to only moderate sensitivity to currently available therapeutic modalities, relies heavily on palliative care. Therefore, advances in vaccine therapy strategies are becoming increasingly important for NSCLC patients (2). Therapeutic vaccines for cancer are designed to stimulate the immune system to recognize antigens specific to tumor cells, without harming normal cells. Vaccines currently under development for NSCLC are detailed in Table I.

MUC-1 has emerged as a tumor-specific antigen and is one of 21 mucin genes encoding the protein backbone of mucin proteins, which are synthesized by cells lining the ducts and lumen of various epithelial surfaces and contribute to the protective and lubricating functions of mammalian mucus (3, 4). Abnormalities in MUC-1 expression have been documented in a variety of cancers, with overexpression in breast cancer (5-7), prostate cancer (8), NSCLC (9, 10), as well as ovarian (11, 12), colorectal (13) and pancreatic cancers (14, 15). Importantly, studies have shown that it is possible to discriminate between MUC-1 antigens specific for tumor cells and those associated with normal tissues. In neoplastic tissues, MUC-1 is underglycosylated, revealing epitopes that are normally masked (8, 16). Tumor-associated MUC-1 antigens have therefore been identified as promising targets for immunologically based therapies/vaccines.

Merck Serono and Oncothyreon (the former Biomira) are currently developing a MUC-1-based therapeutic cancer vaccine for NSCLC, L-BLP-25 (Stimuvax®). L-BLP-25 is a synthetic human MUC-1 protein consisting of a 20-amino-acid tandem repeat sequence on its extracellular domain that is highly antigenic. The vaccine also contains the immunoadjuvant monophosphoryl lipid A (MPL), a nonspecific stimulant designed to prime the immune system and facilitate uptake of the vaccine. Both are enclosed in a liposomal delivery system to induce a pref-

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Table I: Vaccines currently under active clinical development for non-small cell lung cancer (NSCLC).

Vaccine	Phase	Source
Belagenpumatucel-L (Lucanix™)	III	NovaRx
MAGE-A3 ASCI	III	GlaxoSmithKline
Stimuvax® (L-BLP-25)	III	Oncothyreon/MerckSerono
Agatolimod sodium (CpG-7909)	II	Pfizer
CADI-05	II	Cadila Pharmaceuticals
CG-201	II (pending)	CG Therapeutics
1650-G	II	University of Kentucky
HyperAcute® lung cancer vaccine	II	NewLink Genetics
IDM-2101	II	IDM Pharma
MelCancerVac	II	DanDrit
SAI-EGF	II	Center of Molecular Immunology
Tertomotide (GV-1001)	II	Pharmexa
TG-4010	II	Transgene
LungVax®	I/II	Avax Technologies
Vitespen (Oncophage®)	I/II	Antigenics
VX-001	I/II	Vaxon Biotech
CRS-207	I	Anza Therapeutics
GI-4000	I	GlobeImmune
INNO-305	I	Innovive Pharmaceuticals

erential cellular or humoral immune response (17). The vaccine is delivered subcutaneously at four points of the body and is designed to be taken up by cytotoxic T lymphocytes and T helper cells in order to potentiate the immune response. L-BLP-25 is currently in phase III clinical development for the treatment of NSCLC.

Preclinical Pharmacology

In vitro studies in human peripheral blood lymphocytes incubated with L-BLP-25 have demonstrated that two weekly stimulations can generate potent anti-MUC-1-specific T cell proliferation, as well as a class I-restricted cytotoxic response (18). Studies in C57BL/6 mice have also shown that immunization with L-BLP-25 induces a proliferative T cell response to the MUC-1 antigen by $CD4^+$ cells, with the production of interferon gamma (a T helper type 1 [Th1] response) (17).

More recent studies have provided evidence that delivery of L-BLP-25 in poly(D,L-lactic-co-glycolic acid) (PLGA) nanoparticles to dendritic cells can generate a potent Th1 response superior to that evoked upon delivery in a soluble form (19). PGLA nanoparticle delivery of L-BLP-25 in *Muc1* transgenic mice bearing *Muc1*-transfected Lewis lung carcinoma has also been shown to induce antitumor MUC-1-specific T cell responses (20).

Protective antitumor activity has been observed in mice immunized with a human *MUC1*-transfected mouse mammary adenocarcinoma cell line (GZHI). The protective antitumor activity mediated by L-BLP-25 (5 μg) correlated with anti-MUC-1-specific T cell proliferation, interferon gamma production and IgG_{2a} anti-MUC-1 antibodies, suggesting a Th1 response. In contrast, a lack of protection in mice immunized with negative control vaccines correlated with IgG_1 anti-MUC-1 antibody formation, low or no anti-MUC-1 IgG_{2a} and low antigen-specific T cell proliferation, consistent with a type 2 T cell (Th2) response to the tumor (21).

Safety

A multicenter, open-label phase I/II study conducted in Canada assessed the safety of L-BLP-25 in patients with unresectable stage IIIA and IIIB NSCLC (N = 16). A total of 81.25% of patients reported adverse events (AEs) during the first four vaccinations, with 53.9% experiencing an L-BLP-25-related AE (grade 1/2 AEs ≥ 10%: fatigue, dyspnea, insomnia, anorexia, headache, diarrhea, paresthesia, abdominal pain, influenza-like illness, urinary tract infection and peripheral neuropathy). No patients discontinued L-BLP-25 due to an AE and no grade 3/4 AEs related to L-BLP-25 were reported. Six patients (37.5%) had an injection-site reaction (22).

Clinical Studies

Phase I studies in NSCLC patients demonstrated that subcutaneous (s.c.) dosing of L-BLP-25 at 20 μg (n = 8) and 200 μg (n = 8) at weeks 0, 2, 5 and 9 was well tolerated; 9 patients developed erythematic injection-site

reactions. Both doses evoked class I-restricted cytotoxic T lymphocytes capable of destroying MUC-1-positive tumor cell lines (41.7% of patients). Median survival was 5.4 and 14.6 months, respectively, in patients receiving doses of 20 and 200 μg. Of 12 patients who completed all vaccinations, 4 had stable disease (23, 24).

Phase II studies in 8 NSCLC patients receiving L-BLP-25 at a higher dose of 1000 μg (given weekly for 7 weeks) provided further evidence for MUC-1-specific proliferative T cell responses (75%). Furthermore, there was no evidence of serious AEs, although all patients displayed injection-site reactions (23). In a subsequent follow-up study, 75% of patients in this study remained alive up to 8 months following entry into the study (25).

A phase IIb study in patients with stable or responsive stage IIIB/IV NSCLC following chemotherapy or chemotherapy with radiotherapy indicated a clinically meaningful benefit for patients receiving best supportive care with L-BLP-25 (single i.v. dose of cyclophosphamide followed by 8 weekly s.c. L-BLP-25 immunizations containing 1 mg of antigen, given at 6-week intervals; n = 88) compared with those receiving best supportive care alone (n = 83). Median survival for best supportive care + L-BLP-25 and best supportive care alone arms was recorded as 17.4 and 13.0 months, respectively. Two-year survival rates were 43.2% for best supportive care + L-BLP-25 *versus* 28.9% for best supportive care alone. For the subgroup of patients with stage IIIB locoregional disease, 2-year survival was 60% for L-BLP-25 + best supportive care and 37% for best supportive care only, and median survival in this group was 30.6 months *versus* 13.3 months. Although statistical significance was not achieved between the two arms, these data suggest a survival advantage for those receiving best supportive care + L-BLP-25 (26-28). FACT-L quality-of-life questionnaires (completed at randomization, weeks 4 and 8 and then every 12 weeks) also indicated that more patients in the best supportive care + L-BLP-25 arm demonstrated either a clinically meaningful improvement or did not change from baseline compared with patients in the best supportive care alone group (29).

The evaluation of L-BLP-25 is ongoing in clinical trials. A prospective open-label, controlled, randomized phase IIb study is currently being conducted in Canada and the U.K. to test the safety and efficacy of L-BLP-25 (1000 μg) for the treatment of patients with stage IIIB or IV NSCLC (30). A phase II safety study of L-BLP-25 in NSCLC patients with unresectable stage III disease is under way in Canada (31) and a phase III trial is recruiting patients to determine whether L-BLP-25 in addition to best supportive care is effective in prolonging the lives of patients with unresectable stage III NSCLC compared with best supportive care alone (32).

Pilot data from a trial in hormone-naïve prostate cancer patients with prostate-specific antigen (PSA) failure after radical prostatectomy suggested that further investigation of L-BLP-25 in this patient population is warranted. The study involved a single i.v. dose of cyclophosphamide, followed by vaccinations with L-BLP-25 for up to 1 year. After 8 weeks of treatment, 8 of 16 patients (50%) had stable or decreased PSA; however, PSA stability was not maintained to the final PSA measurement in this study. Interestingly, 6 of the 16 patients had > 50% prolongation of PSA doubling time compared to prestudy PSA doubling time (33).

Sources

Oncothyreon, Inc. (formerly Biomira); being developed in collaboration with Merck Serono.

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