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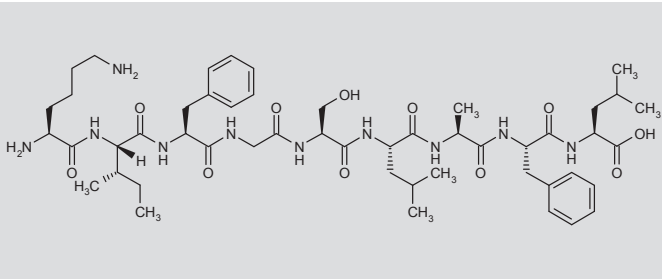
NEUVAX™

Anti-HER2/NEU/erbB-2 Vaccine
Treatment of HER2-Positive Cancers

E75

L-Lysyl-L-isoleucyl-L-phenylalanyl-glycyl-L-seryl-L-leucyl-L-alanyl-L-phenylalanyl-L-leucine

InChI: 1S/C50H78N10O11/c1-8-31(6)42(60-44(64)35(52)21-15-16-22-51)49(69)58-37(25-33-17-11-9-12-18-33)45(65)53-27-41(62)55-40(28-61)48(68)57-36(23-29(2)3)46(66)54-32(7)43(63)56-38(26-34-19-13-10-14-20-34)47(67)59-39(50(70)71)24-30(4)5/h9-14,17-20,29-32,35-40,42,61H,8,15-16,21-28,51-52H2,17H3,(H,53,65)(H,54,66)(H,55,62)(H,56,63)(H,57,68)(H,58,69)(H,59,67)(H,60,64)(H,70,71)/t31-,32-,35-,36-,37-,38-,39-,40-,42-/m0/s1



$C_{50}H_{78}N_{10}O_{11}$
Mol wt: 995.2147
CAS: 160212-35-1
EN: 302089

ABSTRACT

The HER2/NEU/erbB-2 oncogenic protein is a well-defined tumor-associated antigen that is overexpressed in several cancers, including breast and prostate cancers. A new vaccine candidate from Apthera, NeuVax™, consists of the HER2/NEU-derived immunogenic peptide E75, which induces a peptide-specific cytotoxic T-lymphocyte (CTL)-mediated immune response following intradermal administration. Clinical investigations to date have shown that the E75 vaccine plus granulocyte–macrophage colony-stimulating factor (GM-CSF) as adjuvant reduces recurrence rates in breast and prostate cancer patients, with minimal toxicity.

BACKGROUND

The American Cancer Society and Cancer Research UK have indicated that cancers of the prostate and breast are the most frequently diagnosed cancers in men and women, respectively (1-4). An estimated 192,370 new cases and 40,170 deaths from breast cancer and 192,280 new cases and 27,360 deaths from prostate cancer were reported in the U.S. during 2009 (1, 4). A U.K. report from 2009 using incidence and mortality data for 2001-2005 estimated that the lifetime risk of developing breast cancer is 1 in 1,014 for men and 1 in 9 for women, while the lifetime risk of being diagnosed with prostate cancer is 1 in 10 for men in the U.K. (2, 3).

Standard-of-care treatment approaches for breast cancer (such as surgery, radiation therapy, chemotherapy and hormonal therapies) are often successful but can be associated with treatment resistance, debilitating side effects and tumor recurrence (5). Targeted cancer therapies, which are directed at specific characteristics of the tumor cells, such as identifiable enzymes and growth factor receptors involved in cancer cell proliferation, apoptotic signaling pathways, angiogenesis and tumor-associated antigens (TAAs), are becoming increasingly popular treatment options in this field. Targeted pharmaceuticals can be tailored to specific tumor types and may be associated with less severe side effects, as they are more selective for tumor cells versus healthy nontumor cells (6).

The HER2/NEU oncogenic protein is a well-defined TAA that is overexpressed in breast, ovarian, non-small cell lung, colon and prostate cancers. Its overexpression has been shown to correlate with earlier relapse and poor prognosis (7). HER2/NEU-positive patients have a pre-existing immune response to HER2/NEU (8). Apthera is currently developing a peptide-based human tumor vaccine as an immunotherapeutic option for breast and prostate cancers. This vaccine consists of the E75 immunogenic peptide (a HER2/NEU-derived peptide [9, 10]), obtained by solid-phase synthesis in a peptide synthesizer, which induces a peptide-specific cytotoxic T-lymphocyte (CTL)-mediated immune response. This E75 vaccine (NeuVax™) is being developed to produce continuing and convenient activation of the immune system and therapeutic levels of CTLs upon once-monthly intradermal injection (11).

Apthera is completing phase II clinical trials with the E75 vaccine for the adjuvant treatment of early-stage, HER2/NEU-positive breast cancer (12), and a phase I/II trial is also under way in early-stage HER2-positive prostate cancer. Planning is under way for a large phase III clinical trial to prove the safety and efficacy of the product and prepare it for market. Apthera has indicated that the company will be seeking FDA approval for this agent as an adjuvant treatment for node-positive breast cancer in women with low to intermediate levels of HER2/NEU expression (13).

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PRECLINICAL PHARMACOLOGY

In vitro experiments have investigated cellular immunity in blood samples taken from patients at 8 weeks and up to 13-16 months after vaccination with escalating amounts of E75 (100, 500 and 1000 µg) mixed with 250 µg granulocyte–macrophage colony-stimulating factor (GM-CSF) as adjuvant (administered weekly for 4 weeks, followed by monthly boosts for a total of 10 injections). Seven of eight patients demonstrated significant delayed-type hypersensitivity (DTH) to E75. This vaccine strategy also induced both peptide-specific interferon gamma and epitope-specific cytotoxic lymphocytes (CTLs), which lyse HER2/NEU$^+$ tumors in stage IV patients (14, 15).

CLINICAL STUDIES

Breast cancer

A clinical study investigated the optimal biological dose (OBD), based on toxicity and immunological response, of the E75 vaccine administered as a preventive vaccine with GM-CSF in disease-free lymph node-positive (NP) and lymph node-negative (NN) breast cancer patients. Data from 99 patients receiving various doses of vaccine (48 NP and 51 NN) indicated that the OBD was 1000 µg of E75 vaccine plus 250 µg GM-CSF monthly x 6. On this dose regimen, patients (n = 29) demonstrated a significantly larger DTH response with local and systemic toxicity equivalent to that on suboptimal dosing regimens. When compared with clinical outcome, patients receiving the optimal dosing regimen also demonstrated fewer recurrences, despite more aggressive disease (16, 17).

Clinical investigations have been carried out in disease-free patients with a history of NP (n = 95) and NN breast cancer (n = 91). Patients received four or six monthly injections of 100, 500 or 1000 µg of intradermal E75 vaccine plus GM-CSF (125 or 250 µg for three, four or six monthly injections) over a period of 5 months. Human leukocyte antigen A2$^+$ (HLA-A2) and HLA-A3$^+$ patients were vaccinated (n = 101), with remaining patients serving as controls (n = 85). Data indicated that this vaccine strategy is safe and effective at stimulating HER2/NEU-specific immunity and significantly reduces the recurrence rate among vaccinated HLA-A2$^+$/A3$^+$ patients versus controls (recurrence rates reported as 5.6% and 14.2%, respectively, in this study at a median of 20 months of follow-up). E75 immunity was shown to decrease over time, with only 48% of patients maintaining significant residual immunity at 6 months, indicating the need for a booster program. At 26 months of follow-up, statistical significance between recurrence rates for vaccinated versus control groups was lost (8.3% vs. 14.8%), but a trend for prevention of breast cancer recurrence continued (18-21).

The potential benefits of booster vaccinations were further investigated in a total of 48 patients who were ≥ 6 months from completing their primary vaccination schedule. Boosters were offered every 6 months (1000 µg E75 peptide + 250 µg GM-CSF). Multiple boosters (n = 16) were well tolerated overall, with no grade 3-5 toxicities. There was a trend toward increased systemic toxicity from the first (grade 1-2 toxicity, 36%) to the second booster (grade 1-2 toxicity, 78%), with associated increased local reactions. Patients receiving later boosters (i.e., at a median of 13 months after the primary vaccination schedule) demonstrated more long-term increases in E75-induced CTLs (22, 23).

Another study evaluated the immunological response and recurrence patterns among those patients with clinical recurrence in the trial described above (NP, n = 95; NN, n = 91). When comparing 8 vaccinated recurrences (V-R) to 88 vaccinated nonrecurrent patients (V-NR), it was evident that the V-R group had more aggressive disease, with a significantly higher nodal stage (≥ N2, 75% vs. 5%) and higher-grade tumors (grade 3, 88% vs. 31%). In vitro and in vivo studies confirmed that there was no difference in immune response to the vaccine for V-R versus V-NR. V-R patients tended to have higher-grade tumors and hormone receptor negativity versus control (HLA-A2$^-$/A3$^-$) recurrent patients (C-R). When comparing these groups, V-R patients exhibited decreased mortality (V-R 12.5% vs. C-R 41.7%) and while bone-only recurrence was recorded at 50% among C-R patients, no bone-only recurrences were seen in V-R patients (24, 25).

Thirty-two patients from the NP and NN study described above were investigated further to assess correlations between serum monocyte chemotactic protein 1 (MCP-1) levels, prognosis and E75 vaccine-related immunity. Breast cancer patients with elevated levels of serum MCP-1 (> 250 pg/mL) demonstrated more favorable clinical prognostic variables (i.e., statistically significant later onset of disease, earlier stage of disease, fewer nodal metastases and less chemotherapy), along with evidence of pre-existing antitumor immunity in their peripheral blood T cells. Interestingly, repeated inoculation with the E75 + GM-CSF vaccine facilitated the induction of increased MCP-1 levels, which was most evident in those with the worst prognostic variables and correlated with vaccine-induced, peptide-specific immunity (26).

Blood samples from several NN patients from the above clinical investigations were processed to investigate the activity of regulatory CD4$^+$CD25$^+$ T cells (Treg), which are thought to support tumor growth and progression, following E75 vaccination. Flow cytometry identified that E75 vaccination significantly increased circulating activated CD4$^+$ T cells (1.23% prevaccination vs. 3.81% postvaccination) and significantly reduced Treg levels (5.31% vs. 1.81%). These effects were also associated with increased E75 vaccine-specific CD8$^+$ T cells and corresponding HER2/NEU$^+$ tumor cytotoxicity. Decreased levels of serum tumor growth factor β (TGF-β), a cytokine linked to Treg tumor support, were also observed in 57% of vaccinated patients (27, 28).

Prostate cancer

The ability of the E75 + GM-CSF vaccine to prevent post-prostatectomy prostate-specific antigen (PSA) recurrences in high-risk prostate cancer (HRPC) patients was investigated in a phase I study. HLA-A2$^+$ patients (n = 17) were vaccinated, whereas HLA-A2$^-$ patients (n = 10) were followed as clinical controls. Administration of the E75 vaccine in these patients induced only minor toxicities and effectively elicited an immune response against the HER2/NEU protein both in vitro and in vivo (assessed via DTH and CD8$^+$ levels). Despite the fact that HLA-A2$^+$ patients exhibited larger tumors, higher postoperative Gleason scores and more high-risk Center for Prostate Disease Research (CPDR) scores than HLA-A2$^-$ patients, disease-free survival was not different between these groups at a median follow-up of 23 months (29, 30). Conclusions from this study were further supported by median follow-up data at 58.2 months

(HLA-A2$^+$-vaccinated patients, n = 21; HLA-A2$^-$ control patients, n = 19); the PSA recurrence rate was not different between vaccinated (28%) and control (26%) groups (31).

SOURCES

Apthera, Inc. (US); licensed from The University of Texas M.D. Anderson Cancer Center, Houston, TX (US) and The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. (HJF), Rockville, MD (US); licensed to Kwang Dong Pharmaceutical Co., Ltd. (KR) for South Korea.

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