# Cancer vaccines

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**Phase II trial to assess the activity of MVA5T4 (Trovax®) alone versus MVA5T4 plus granulocyte macrophage colony-stimulating factor (GM-CSF) in patients (pts) with progressive hormone refractory prostate cancer (HRPC)**

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**Background:** MVA 5T4 consists of the highly attenuated modified vaccinia Ankara virus containing the gene encoding the human tumour associated antigen (TAA) 5T4 under regulatory control of a modified promoter, mH5 More than 85% of prostate cancers overexpress the 5T4 antigen. GM-CSF is involved in the enhancement of T-cell priming via effects on dendritic cells. An immunotherapy approach was evaluated using MVA 5T4 alone or in combination with GM-CSF to look at the comparative potency of these approaches to elicit an immune response and to further determine the impact of such a response on signs of clinical benefit as defined by PSA reduction and delay in time to progression (TTP). The humoral and/or cellular immune response to 5T4 will be correlated to clinical outcome.
**Methods:** Eligibility included HRPC pts with progressive disease based on at least 1 of the following; (a) 3 consecutive rising PSA levels, or (b) new or progressive measurable disease, or (c) new or progressive metastatic lesions on bone scan; serum testosterone level ($\leqslant$50 $\mu$g/mL), withdrawal from anti-androgen therapy, any prior therapy regimen, Karnofsky performance status (KPS) $\geqslant$60% and adequate physiologic parameters. The dosage regimen of MVA 5T4 consisted of intramuscular injections ($5\times10^8$ pfu)on day 1 of week 1, 3, 6, 9, 17, 25, 33 and 41. GM-CSF is given at 250 $\mu$g/m$^2$ (maximum 500 $\mu$g) 14 days on, 14 days off by subcutaneous injection. Routine laboratory, PSA and imaging studies will occur every 8 weeks.
**Results:** 21 pts have been enrolled as of this review. Median age 70 (50−94) years. All pts received at least 2 prior therapies, including chemotherapy. Base-line PSA was 75.0 (4.0−2661.9). 1 pt was PSA only, 5 pts were PSA with bone involvement, 4 were PSA with measurable disease and 11 were PSA with bone involvment and measurable disease. All pts continue to receive therapy. Adverse events were assessed and included; grade 1 fever and bone pain. The clinical and immunologic analysis is in progress.
**Conclusion:** MVA 5T4 with or without GM-CSF is well tolerated in this group of patients. Reduction in PSA has been noted in 5/5 of the first patients treated with TroVax plus GM-CSF after only 2 weeks. The immune response along with clinical outcome will be presented. The study is still continuing to accrue.

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**Effective inhibition of the EGF/EGFR binding by anti-EGF antibodies increased survival of advanced NSCLC patients treated with the EGF cancer vaccine**

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**Background:** Previous studies have indicated that Epidermal Growth Factor (EGF) might be a suitable immunotherapeutic target in non-small cell lung cancer (NSCLC). Our approach consisted in active immunotherapy with the Epidermal Growth Factor. The aim of the present study was to characterize the humoral immune response and its relations with the clinical outcome of the treated patients.
**Methods:** Seventy-four NSCLC patients previously treated with first line chemotherapy were randomized to receive the EGF vaccine or best supportive care. Patients were vaccinated weekly for 4 weeks and then monthly. We choose 42 patients (26 vaccinated and 16 controls) to evaluate seric EGF concentration [EGF] and anti-EGF antibody titers. Then, we determined the capacity of the specific antibodies to inhibit the EGFR activation and the binding between EGF/EGFR.
**Results:** Eighty-four (84 %) of the vaccinated patients showed seroconvertion, while 56% of controls showed a 2 fold increase of the natural anti-EGF antibody titers. None of the controls developed a good antibody response (GAR) while 65% of vaccinated subjects did. In GAR patients, seric [EGF] was reduced below 168 pg/ml, which represents half of the mean [EGF] of healthy donors. In 58 % of vaccinated patients, the post-immune sera showed an EGF/EGFR binding inhibition capacity higher than 18% (range 18.9−60%). The mean EGF/EGFR inhibition percent of controls was significantly lower than the one from the vaccinated subjects at the same time points. In 46% of the vaccinated patients, post-immune sera inhibited more than 15% (range 16.31−62.5%) the EGFR phosphorylation induced by EGF as compared to day 0. Control patients showed a phosphorylation inhibition capacity lower than 10.4% at the same time points. A significant increase in survival was obtained for GAR patients in comparison to poor responders and control patients. A high correlation between anti-EGF antibody titers and EGFR phosphorylation inhibition was found. There was a significant increase of median survival for vaccinated patients in whom inhibition percent of EGF/EGFR binding was higher than 18% (13.17 months) as compared to those who did not achieve the referred inhibition capacity (5.63 months).
**Conclusions:** Immunization with EGF vaccine induced specific and neutralizing anti-EGF antibodies capable to inhibit EGFR phosphorylation. There is a significant correlation between the quality of anti-EGF antibodies and survival of advanced NSCLC.

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**Enhanced growth inhibition of HER-2/neu overexpressing tumor cells by combining HER-2/neu specific polyclonal antibodies and other HER-2/neu targeting treatments**

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**Background:** The HER-2/neu oncogene is overexpressed in 30% of breast cancer and other malignancies. As a transmembrane tyrosine kinase receptor this antigen can be targeted by different therapeutic approaches including HER-2/neu specific immunotherapy, passive transfer of HER-2/neu specific monoclonal antibody such as trastuzumab or of small molecules such as lapatinib, a dual EGFR(ErbB1)/HER-2/neu(ErbB2) tyrosine kinase inhibitor. We have developed a HER-2/neu antigen specific cancer immunotherapy (ASCI) that is based on the use of a recombinant HER-2/neu protein formulated in a strong GSK proprietary adjuvant. The HER-2/neu-ASCI has been shown previously to induce HER-2/neu specific T-cells and polyclonal antibodies with functional activity in animal models. The present studies illustrate that combination of the HER-2/neu specific polyclonal antibodies with the dual tyrosine kinase inhibitor lapatinib or with the humanized monoclonal antibody trastuzumab lead to enhanced growth inhibition of human tumor cells over-expressing HER-2/neu.
**Methods:** *In vitro* – HER-2/neu overexpressing cell lines were incubated with sub-optimal concentration of HER-2/neu specific polyclonal antibodies (pAb) and either lapatinib or trastuzumab. The % of growth inhibition was measured by 3H-thymidine incorporation. *In vivo* – BT474 tumor bearing SCID mice were treated with lapatinib or HER-2/neu specific polyclonal antibodies, or a combination of both. *In vivo* tumor growth was followed overtime.
**Results:** The *in vitro* combination of HER-2/neu specific polyclonal antibodies and lapatinib had at least an additive growth inhibitory effect on HER-2/neu overexpressing cell lines. Moreover, the combination of HER-2/neu specific polyclonal antibodies and trastuzumab also lead to improved growth inhibition, suggesting that inhibitory antibodies specific for other epitopes than the one recognized by trastuzumab have been generated by the immunization with the formulated HER-2/neu protein. In vivo, the administration of HER-2/neu specific polyclonal antibodies together with lapatinib was shown to enhance inhibition of BT474 tumor cell growth in mice.
**Conclusions:** Taken together these data provide evidence that combining different therapeutic approaches targeting the same HER-2/neu antigen could lead to a better control of the tumor growth which may translate into clinical benefit for the patient.

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**A recombinant HER2 protein evaluated for cancer immunotherapy: induction of specific antibodies and T-cells**

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**Background:** We designed an Antigen Specific Cancer Immunotherapeutic (ASCI) to induce a polyclonal antibody response and T-cells able to recognize HER2 epitopes.
**Methods:** The HER2 ASCI is a recombinant HER2 protein, including its extra and part of its intra-cellular domains (ECD/ICD), combined with