Vaccination with GM2-KLH-QS21 does not improve outcome of melanomas patients in EORTC study

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Results of an EORTC study published in the *Journal of Clinical Oncology* show that vaccination with GM2/KLH-QS-21 does not benefit patients with stage II melanoma. Vaccination with GM2/KLH-QS-21 stimulates the production of antibodies to the GM2 ganglioside, an antigen expressed by many melanomas. Serological response to GM2 was shown to be a positive prognostic factor in patients with melanoma and was the rationale for this trial.

The idea of treating cancer with a vaccine has been around since the first vaccines against infectious disease were developed. The GM2 ganglioside, an antigen expressed in most melanomas but with limited expression in normal tissues, was thought to offer a suitable target for such therapeutic vaccination. Previous studies had shown that serological response against GM2 was a favorable prognostic factor. The five and ten year survival rates for patients with melanoma having primary tumors with a Breslow thickness greater than 1.5 mm are just of 74% and 61%, respectively, so EORTC trial 18961 was launched to compare vaccination to observation in these patients.

Prof. Alexander M.M. Eggermont of the Institut Gustave Roussy, Villejuif, Paris-Sud, and Université Paris-Sud, Kremlin Bicêtre, France and Coordinator of this study says, "These results clearly indicate that we do not fully comprehend the impact, on the whole, of multiple vaccinations. The effects of such vaccinations might well be detrimental

as was clear at the time of the interim analysis that stopped this trial. Now that we have entered a new era in immunotherapy in melanoma with checkpoint inhibitors like anti-CTLA4, and especially with anti-PD1/PDL1, a new opportunity for vaccine development may have arrived."

In this phase III EORTC 18961 trial, 1314 patients with stage II melanoma (primary melanoma thicker than 1.5 mm, T3-4N0M0; AJCC Stage II) were randomized to either vaccination with GM2-KLH-QS21, 657 patients, or observation, 657 patients. The vaccination treatment consisted of subcutaneous injections given once a week during the first month, then once every three months for the first two years, and once every six months during the third year.

Analyses were by intent to treat, and at a median follow-up of 1.8 years the trial was stopped for futility and patients did not receive further vaccinations. For relapse-free survival, the primary endpoint, the hazard ratio (HR) was 1.00 and P = 0.99, and an unfavorable outcome was seen for patients in the vaccination arm compared to the observation arm in terms of overall survival (HR 1.66; P=0.02). Following the IDMC recommendations, all patients in the vaccination arm stopped their treatment.

At final analysis, the median follow-up was 4.2 years. There were 400 relapses, nine deaths without relapse, and a total of 236 deaths. Decreases in both the relapse-free, 1.2%, and overall, 2.1%, survival rates were observed in the vaccination arm at 4 years. For these two endpoints, the estimated HRs were 1.03 and 1.16, respectively.

Toxicity was acceptable; 4.6% of patients went off study because of toxicity.

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