

Tumor-reactive CD8⁺ T-cell responses after vaccination with NY-ESO-1 peptide, CpG 7909 and Montanide[®] ISA-51: association with survival

Julia Karbach¹, Sacha Gnjatic², Armin Bender³, Antje Neumann¹, Eckhart Weidmann¹, Jianda Yuan⁴, Cathy A. Ferrara⁵, Eric Hoffmann⁶, Lloyd J. Old², Nasser K. Altorki⁵ and Elke Jäger¹

¹Klinik für Onkologie und Hämatologie, Krankenhaus Nordwest, Frankfurt, Germany

²Ludwig Institute for Cancer Research, Branch at Memorial Sloan-Kettering Cancer Center, New York, NY 10065

³Klinik für Dermatologie und Allergologie, Universitätsklinikum Giessen und Marburg, Marburg, Germany

⁴Ludwig Center at Memorial Sloan-Kettering Cancer Center, New York, NY 10065

⁵Division of Thoracic Surgery, New York Presbyterian Hospital, Weill Medical College of Cornell University, New York, NY

⁶Ludwig Institute for Cancer Research, New York, NY

Peptide-based vaccines have led to the induction of antigen-specific CD8⁺ T-cell responses in patients with NY-ESO-1 positive cancers. However, vaccine-induced T-cell responses did not generally correlate with improved survival. Therefore, we tested whether a synthetic CpG 7909 ODN (deoxycytidyl-deoxyguanosin oligodeoxy-nucleotides) mixed with NY-ESO-1 peptide p157-165 and incomplete Freund's adjuvants (Montanide[®] ISA-51) led to enhanced NY-ESO-1 antigen-specific CD8⁺ immune responses in patients with NY-ESO-1 or LAGE-1 expressing tumors. Of 14 HLA-A2+ patients enrolled in the study, 5 patients withdrew prematurely because of progressive disease and 9 patients completed 1 cycle of immunization. Nine of 14 patients developed measurable and sustained antigen-specific CD8⁺ T-cell responses: Four had detectable CD8⁺ T-cells against NY-ESO-1 after only 2 vaccinations, whereas 5 patients showed a late-onset but durable induction of NY-ESO-1 p157-165 specific T-cell response during continued vaccination after 4 months. In 6 patients, vaccine-induced antigen-specific T-cells became detectable *ex vivo* and reached frequencies of up to 0.16 % of all circulating CD8⁺ T-cells. Postvaccine T-cell clones were shown to recognize and lyse NY-ESO-1 expressing tumor cell lines *in vitro*. In 6 of 9 patients developing NY-ESO-1-specific immune responses, a favorable clinical outcome with overall survival times of 43+, 42+, 42+, 39+, 36+ and 27+ months, respectively, was observed.

A major goal of active immunotherapy against cancer is the activation of antigen-specific and tumor-reactive CD8⁺ T-cells. To prevent tumor progression, high levels of activated, high affinity T-cells must be induced and maintained active over an extended period of time, and antigen-specific T-cells should have the capacity to recognize tumor targets. Previous clinical studies with NY-ESO-1 peptides indicated that primary NY-ESO-1 specific CD8⁺ T-cell responses can be induced by repeated weekly intradermal immunization and that T-cell responses are associated with disease stabiliza-

tion and regression of single metastases.¹ Modified protocols using high-dose and intensive-course immunization schedules have demonstrated enhanced immune responses leading to specific recognition of antigen-expressing tumor cells.²⁻⁴ To optimize peptide-based immunotherapy, different adjuvants were mixed with the antigenic peptides to improve their immunogenicity.⁵⁻¹⁰ Various studies have demonstrated the depot effect of incomplete Freund's adjuvant (Montanide[®] ISA-51) leading to a prolonged antigen exposure at the vaccination site followed by enhanced activation of the immune system.¹⁰⁻¹⁵ Different synthetic CpG oligodeoxynucleotides (ODNs) as adjuvants are currently under investigation. They have been shown to elicit proinflammatory cytokines and to stimulate DC activation through TLR9 triggering, which leads to enhanced antigen-specific T-cell responses.¹⁶⁻²³ A previous clinical study demonstrated enhanced Melan-A immunity when CpG 7909, a modified oligodeoxynucleotide for optimized stimulation in humans, was administered concurrently to the Melan-A plus Montanide ISA-51 vaccine.²⁴

This phase I clinical trial tested the coadministration of CpG 7909 and NY-ESO-1 peptide p157-165 mixed with Montanide ISA-51 to evaluate the toxicity and immunogenicity of this approach in HLA-A2 positive patients with

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Correspondence to: Elke Jäger, Klinik für Onkologie und Hämatologie, Krankenhaus Nordwest, Steinbacher Hohl 2-26, 60488 Frankfurt, Germany, Fax: +49-69-769932, E-mail: elke.jaeger@licr.org