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# A phase 1 clinical trial of NY-ESO-1 protein formulated with immunostimulatory complexes (ISCOM® adjuvant) in patients with minimal residual disease

Jonathan S. Cebon[1*], Ian D Davis[1], Phillip Parente[1], Weisan Chen[1], Mark Shackleton[1], Wendie Hopkins[1], Heather Goldie[1], Eugene Maraskovsky[1], Qiyuan Chen[1], Heather Jackson[1], Tsin Yee Tai[1], Grant McArthur[2], Peter MacCallum[2], Duncan MacGregor[3], Sue Sturrock[3], Simon Green[4], Andrew Cuthbertson[4], Darryl Maher[4], David Ryan[4], Michael McNamara[4], Debbie Drane[4], Lena Miloradovic[4], Achim Jungbluth[5], Gerd Ritter[5], Elisabeth Stockert[5], Yao-T. Chen[5], Eric Hoffman[5], Sacha Gnjatic[5], and Lloyd Old[5]

[1]Ludwig Institute for Cancer Research, Heidelberg, Australia
[2]Cancer Institute, Melbourne, Australia
[3]Austin & Repatriation Medical Centre, Heidelberg, Australia
[4]CSL Limited, Melbourne, Australia
[5]Ludwig Institute for Cancer Research, New York, NY
[*]Presenting author

## Abstract

Spontaneous antibody and cellular immune responses against the cancer testis antigen NY-ESO-1 occur in a subset of patients with NY-ESO-1 expressing tumors. NY-ESO-1 specific immune responses to injected HLA A2-restricted peptides of NY-ESO-1 have also been reported in patients with spontaneous NY-ESO-1 immunity. Furthermore, a number of Class-II epitopes to NY-ESO-1 presented on HLA DP4, DR53 and DR4 have been identified. The potential to stimulate both CD8+ and CD4+ T-cell responses following vaccination with full-length NY-ESO-1 protein formulated with ISCOM® (ImmunoStimulating COMplexeS, CSL Ltd, Australia) adjuvant was pursued in a Phase 1 study. The ISCOM® adjuvant is saponin-based and has been shown to stimulate antibody responses and induce T helper cell as well as cytotoxic T lymphocyte responses in a variety of animal models and human clinical trials. The objectives of the current study were to evaluate the safety and immunogenicity of an NY-ESO-1 ISCOM® vaccine.

Forty-six (46) patients with minimal residual disease and tumors that expressed NY-ESO-1 antigen by immunohistochemistry and/or RT-PCR were evaluated in the study. Patients received NY-ESO-1 ISCOM® or protein alone, administered IM on three occasions at monthly intervals. NY-ESO-1 ISCOM® protein doses were: 10 µg (n = 3), 30 µg (n = 3), and 100 µg (n = 20). A further 20 patients received 100 µg NY-ESO-1 protein alone. All patients except 10 in each of the 100 µg groups were HLA-A2 positive, and 2 patients in each group of 10 received placebo.

Patients were evaluated for toxicity each week. Immune function was assayed in all patients by Delayed Type Hypersensitivity (DTH) to NY-ESO-1 protein alone and by NY-ESO-1 antibody titre (ELISA). In HLA-A2 patients the number of reactive NY-ESO-1 CD8+ T cells was measured by HLA-A2 tetramers and by "Cytospot assay" for gamma-interferon production. Results: Grade 3 injection site pain occurred in three patients who received 100 µg. Grade 2 injection site pain, flu-like symptoms, fever and malaise were also noted, otherwise the vaccine was

generally very well tolerated. At the 100 µg dose of the NY-ESO-1 ISCOM® vaccine, enhanced DTH reactions (up to 60 mm redness and 25 mm induration) over baseline occurred. Antibody titres were significantly higher (>1:100,000) in patients immunized with ISCOM® formulation than with NY-ESO-1 protein alone. CD8+ cellular immune responses were observed in one of three NY-ESO-1 ISCOM® patients at the 10 µg dose (a patient with prior antibody response), and otherwise at the 100 µg dose, primarily in patients who received the vaccine with adjuvant. There was a good correlation between tetramer and cytospot findings but little or no correlation between DTH and the monitored ESO1b-specific CD8+ T-cell responses. One patient has shown evidence of a response to a new peptide epitope presented on HLA DR2. This patient also had evidence of a simultaneous response to epitopes presented on HLA A2 and HLA DP4.

Conclusion: NY-ESO-1 ISCOM® vaccine was safe, well tolerated and generated both humoral and cellular NY-ESO-1 specific responses. Future studies will focus on identifying responses to other epitopes as well as undertaking trials in patients with evaluable disease to immune and clinical responses.