Early Development of CDX-1401, A Novel Vaccine Targeting NY-ESO-1 to the Dendritic Cell Receptor DEC-205, in Combination with Toll-like Receptor Agonists

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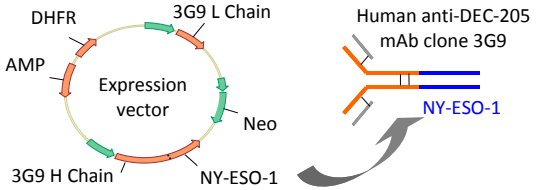
BACKGROUND

Cancer-testis antigen NY-ESO-1

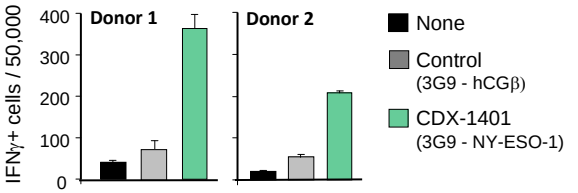
- Normal tissue expression restricted to germ cells (i.e. testis)
- Frequently expressed in a broad range of tumors including lung, breast, ovarian, bladder, liver cancers, melanoma and myeloma.
- Spontaneous immune responses to NY-ESO-1 have been reported in ~ half of patients with NY-ESO-1 expressing cancers.
- Approach under development in collaboration with Ludwig Institute for Cancer Research NY.

CDX-1401: 3G9 - NY-ESO-1 Fusion Protein



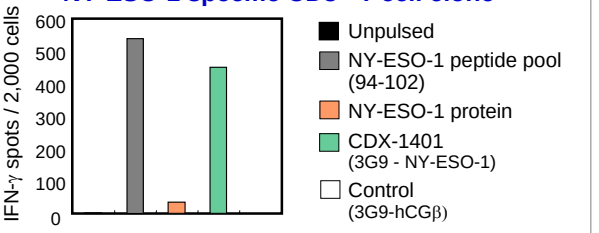
CDX-1401 contains the entire coding sequence for the anti-DEC-205 mAb (3G9) directly fused in-frame with the full coding sequence of NY-ESO-1. The antibody fusion protein is produced by transfected CHO cells.

NY-ESO-1 Sensitized CD8+ T cells Recognize NY-ESO-1 Presented by DCs via DEC-205



Day 5 Mo-DCs treated with test proteins, matured overnight with R-848 [0.5 mM] + Poly-ICLC [5mg/ml], irradiated (35 Gy) and added to autologous purified T cells. Cultures were maintained in low dose IL-7 (d1, 10 ng/ml) and IL-2 (d2, 20 ng/ml). Stimulations spread over 4-5 weeks. T cells were enriched for CD8+ T cells before analysis by IFNγ ELISpot assay.

CDX-1401 mediates efficient stimulation of NY-ESO-1 specific CD8+ T cell clone



DCs were pulsed O/N with test proteins and incubated with HLA-B35 restricted and NY-ESO-1 specific CD8 T cell clone (UC98F11). IFN-γ ELISPOT was evaluated after 24 hour incubation. Assay performed by Takemasa Tsuji, Sacha Gnjatic, and Gerd Ritter from Ludwig Institute for Cancer Research NY.

PHASE I CLINICAL STUDY

Indication: Malignancies known to express NY-ESO-1, progressive after available curative/salvage therapies.
Objectives: Safety, Immune response, Dose Selection, Anti-tumor activity
Study Treatment: CDX-1401 (0.1, 1.0, or 3.0 mg) administered intracutaneously once every two weeks x 4, plus the TLR7/8 agonist, resiquimod (250 mg of 0.2% gel), applied topically on the day of and the day after CDX-1401 administration.

Baseline Characteristics

	All Patients (n=20)
Male	11 (55%)
Age (median [range])	60 (48-79)
Cancer type (n [%])	
Melanoma	14 (70%)
Ovarian	3 (15%)
Other	3 (15%)
NY-ESO-1 Expression*	6 (35%)

* Tumor tissue analyzed by IHC and PCR at a central laboratory. Results not available for 3 patients.

Safety

- No dose-limiting toxicity (DLT)
- Treatment-related toxicities, all Grade 1-2, included administration site reaction (79%), fatigue (21%), decreased appetite (16%), nausea (11%), arthralgia (11%), and headache (11%).

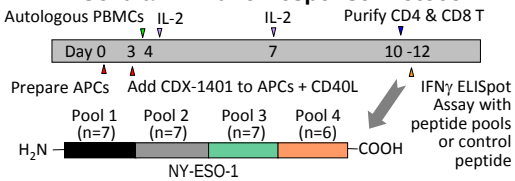
NY-ESO-1 Antibody Responses

- Pre-existing anti-NY-ESO-1 antibody titers were noted in four patients; all had tumors expressing NY-ESO-1.
- A significant increase in titer was induced in 2 patients with pre-existing immunity; the other 2 had baseline titers >1:200,000.
- Humoral response was induced in 8/16 (50%) of the remaining patients; of these, 4/5 (80%) who received >1 treatment cycle achieved a humoral response.
- Responses were most frequent for the 1 mg dose and onset earlier for the 3 mg dose.

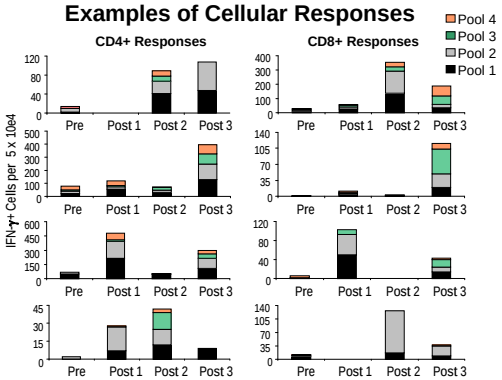
FLAG-tagged NY-ESO-1 antigen is captured to an ELISA plate with anti-FLAG antibody, then blocked with Casein buffer. Patient serum is diluted 1:50 in Casein buffer and added to the blocked plate. Antibodies bound to the NY-ESO-1 are detected with HRP conjugated goat anti-human IgG and the color is developed with TMB substrate.

NY-ESO-1 Cellular Responses

Cellular Immune Response Protocol



Examples of Cellular Responses



- 7/18 (39%) patients across all dose levels developed T-cell responses, including both CD4+ and CD8+ responses (4), CD8+ responses (2), and CD4+ response (1).
- T-cell responses were mapped to peptides across different regions of NY-ESO-1 molecule.

CONCLUSIONS

- Targeting NY-ESO-1 to dendritic cells using CDX-1401 with topical resiquimod can induce robust NY-ESO-1 immunity in advanced cancer patients, including humoral responses, cellular responses with generation of both CD4+ and CD8+ T cells against multiple regions of the protein, and augmentation of existing immunity.
- CDX-1401 is well-tolerated with no DLT or Grade 3 toxicity.
- 6 patients with stable disease (range: 4.7 to 11.5+ months) have been retreated, including 4 who received ≥3 cycles. The majority developed NY-ESO-1-specific immune responses.
- Additional cohorts will evaluate CDX-1401 with subcutaneus TLR agonists including poly-ICLC and/or resiquimod.