

A Phase 1 Trial of a Novel Vaccine Targeting NY-ESO-1 to the Dendritic Cell Receptor DEC-205 in Combination with Toll-like Receptor Agonists

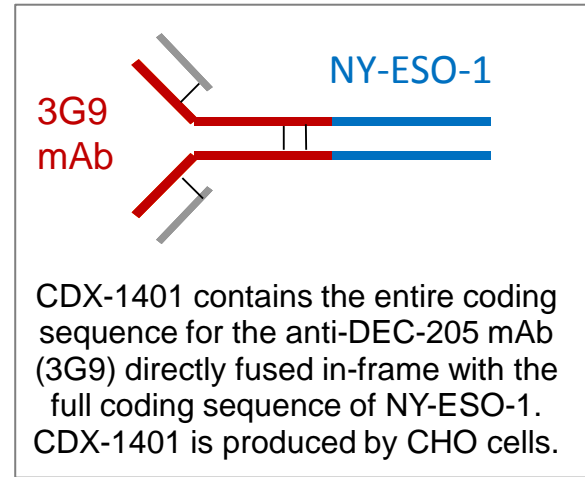
Madhav V. Dhodapkar¹; Biwei Zhao²; Ding Wang³; Richard Carvajal⁴; Mary Keohan⁴; Ellen Chuang⁵; Rachel Sanborn⁶; Jose Lutzky⁷; John Powderly⁸; Harriet Kluger¹; Mario Szol¹; Sheela Tejwani³; Andrea Crocker²; Laura Vitale²; Venky Ramakrishna²; Michael Yellin²; Thomas Davis²; Tibor Keler²

1. Yale Cancer Center, New Haven, CT; 2. Celldex Therapeutics, Needham, MA; 3. Henry Ford Health Systems, Detroit, MI; 4. Memorial Sloan-Kettering Cancer Center, New York, NY; 5. Weill Cornell Medical College, New York, NY; 6. Providence Portland Medical Center, Portland, OR; 7. Mt. Sinai Medical Center, Miami Beach, FL; 8. Carolina BioOncology Institute, Huntersville, NC

BACKGROUND

CDX-1401: A Recombinant mAb-NY-ESO-1 Fusion Protein

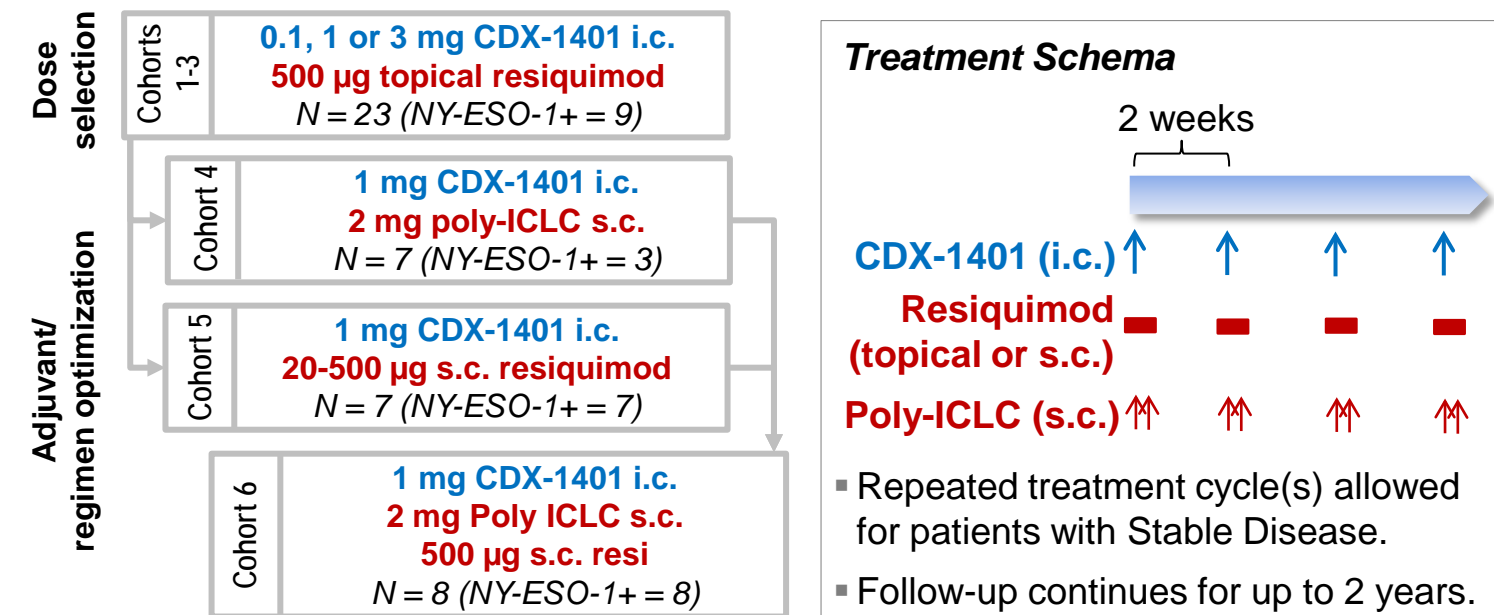
- NY-ESO-1 is a cancer-testis antigen associated with a number of cancers and validated as tumor rejection antigen.¹
- CDX-1401 binds directly to DEC-205 on dendritic cells and stimulates NY-ESO-1 specific CD4 and CD8 responses in preclinical models.²
- Combination with TLR agonists enhances immunity to NY-ESO-1.³



PHASE I CLINICAL STUDY

Open-Label, Dose-Escalation Study of CDX-1401

- Population:** Patients with malignancies known to express NY-ESO-1, progressive after available curative/salvage therapies.
- Objectives:** Safety, Dose selection, Immune response, Anti-tumor activity



NY-ESO-1 Tissue Analysis

| Tumor Type | n | Positive by Either IHC or PCR | Positive by Both IHC and PCR | Strongly Positive by IHC |
|--------------------|-----|-------------------------------|------------------------------|--------------------------|
| Melanoma | 57 | 19 (33%) | 15 (26%) | 10 (18%) |
| Colorectal | 38 | 13 (34%) | 4 (11%) | 6 (16%) |
| Lung | 38 | 9 (24%) | 4 (11%) | 8 (21%) |
| Sarcoma | 37 | 17 (46%) | 15 (41%) | 14 (38%) |
| Ovarian | 24 | 6 (25%) | 2 (8%) | 1 (4%) |
| Breast | 15 | 1 (7%) | 1 (7%) | 1 (7%) |
| Bladder/Urothelial | 13 | 3 (23%) | 1 (8%) | 1 (8%) |
| Other | 59 | 12 (20%) | 1 2% | 2 3% |
| All | 281 | 80 (28%) | 43 (15%) | 43 (15%) |

Results considered positive if NY-ESO-1 expression detected by either PCR (at any intensity) or IHC (≥5% of cells, ≥1+ intensity). Strongly positive defined as expression by IHC in ≥30% of cells.

Enrolled Patients

| | All Patients (n=45) |
|----------------------|---------------------|
| Male (n [%]) | 23 (51%) |
| Age (median [range]) | 64 [38-90] |
| Cancer type (n [%]) | |
| Melanoma | 21 (47%) |
| Ovarian | 6 (13%) |
| Sarcoma | 5 (11%) |
| NSCLC | 4 (9%) |
| Colorectal | 4 (9%) |
| Other | 5 (11%) |
| Distant metastases | 39 (87%) |
| NY-ESO-1 + | 27 (60%) |

Safety

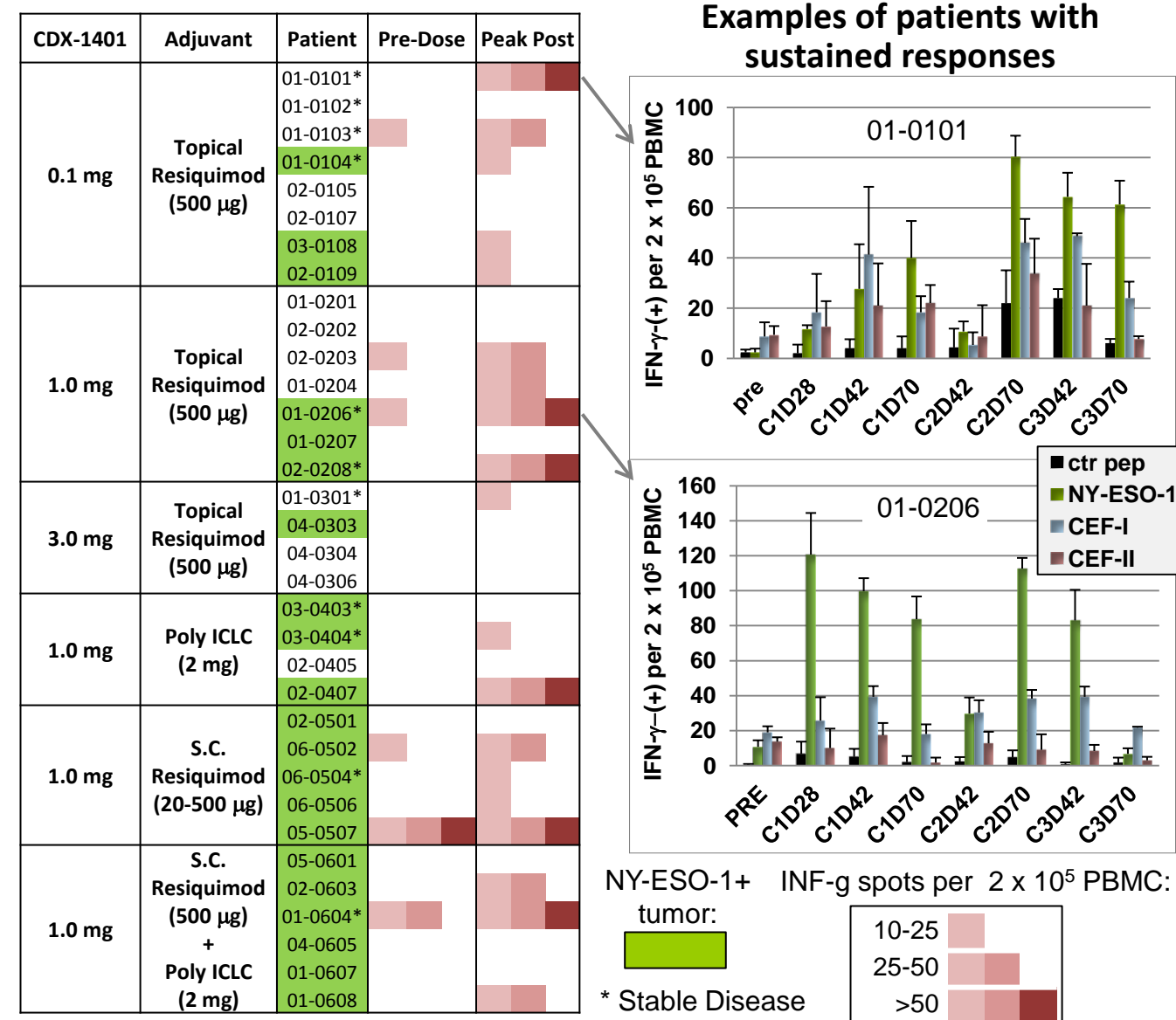
- No dose-limiting toxicity (DLT) or discontinuation of treatment due to toxicity.
- Treatment-related toxicities, all Grade 1-2, included administration site reaction (76%), fatigue (24%), nausea (9%) and chills (9%).

Clinical Outcome

- 41 patients completed at least one cycle
- 10 patients were retreated (median [range] = 10 [6 to 20] CDX-1401 doses)
- 13 patients had stable disease (median [range] = 6.7 [2.4+ to 13.4] months)
 - 7 had melanoma, 2 had colorectal cancer, and 4 had other tumor types
- 4 patients (3 melanoma/1 cholangiocarcinoma) had tumor shrinkage (-2, -8, -20 & -21%)
- 8 patients completed study follow-up at 2 years, while an additional 8 remain in follow up.

IMMUNE RESPONSE: CDX-1401 TREATED STUDY PATIENTS

INF γ ELISpot Analysis

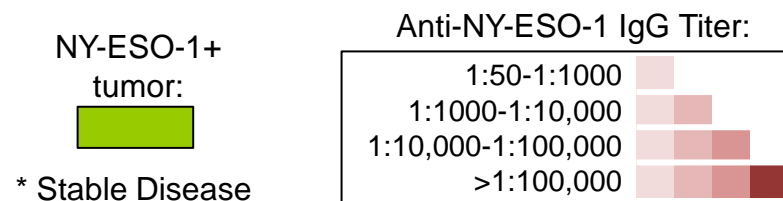


ELISpot: 34 patients had pre and post treatment PBMCs that were restimulated in vitro with NY-ESO-1 peptide pool and rhIL-2 for 7-days and tested in an IFN γ ELISpot assay. Effector lymphocytes were incubated with T-depleted APCs (5:1) loaded with an NY-ESO-1 peptide pool or a control peptide pool and plated in anti-IFN γ coated ELISpot plates. CEF/II peptides served as positive controls.

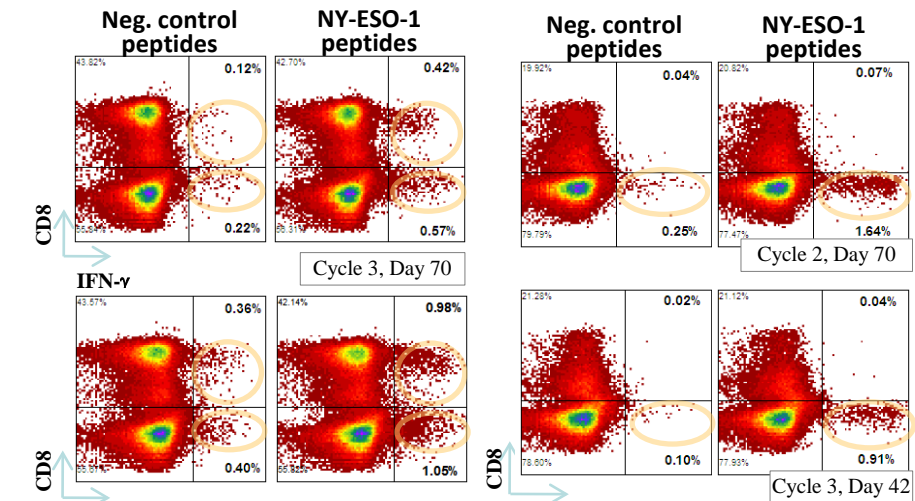
Anti-NY-ESO-1 Titers

| CDX-1401 | Adjuvant | Patient | Pre-Dose | Peak Post |
|----------|---|----------|----------|-----------|
| 0.1 mg | Topical Resiquimod (500 µg) | 01-0101* | | |
| | | 01-0102* | | |
| | | 01-0103* | | |
| | | 01-0104* | | |
| | | 02-0105 | | |
| | | 02-0107 | | |
| 1.0 mg | Topical Resiquimod (500 µg) | 01-0201 | | |
| | | 02-0202 | | |
| | | 02-0203 | | |
| | | 01-0204 | | |
| | | 01-0205* | | |
| | | 01-0206* | | |
| 3.0 mg | Topical Resiquimod (500 µg) | 01-0301* | | |
| | | 01-0302 | | |
| | | 04-0303 | | |
| | | 04-0304 | | |
| | | 03-0403* | | |
| | | 04-0306 | | |
| 1.0 mg | Poly ICLC (2 mg) | 02-0401 | | |
| | | 03-0403* | | |
| | | 03-0404* | | |
| | | 02-0405 | | |
| | | 02-0407 | | |
| | | 02-0501 | | |
| 1.0 mg | S.C. Resiquimod (20-500 µg) | 06-0502 | | |
| | | 05-0503 | | |
| | | 06-0504* | | |
| | | 03-0505 | | |
| | | 06-0506 | | |
| | | 05-0507 | | |
| 1.0 mg | S.C. Resiquimod (500 µg) + Poly ICLC (2 mg) | 05-0601 | | |
| | | 02-0603 | | |
| | | 01-0604* | | |
| | | 04-0605 | | |
| | | 05-0606 | | |
| | | 01-0607 | | |

Antibody ELISA: 42 patients had pre and post treatment sera that were tested for anti-NY-ESO-1 IgG responses by ELISA using full length recombinant NY-ESO-1. The titer was established by determining the end-point dilution.

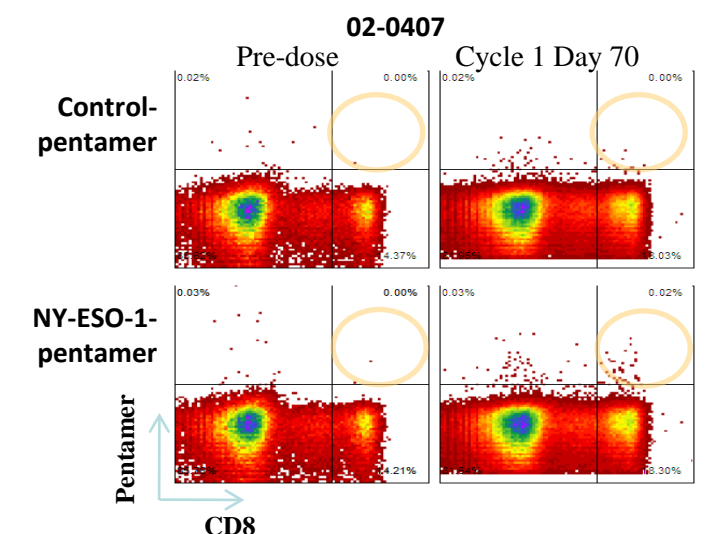


Intracellular Cytokine Staining of Selected Patients



ICS: Selected ELISpot positive patient PBMCs were tested by ICS using the same in vitro stimulation. Intracellular cytokine assay was performed by exposure of stimulated effectors to T-depleted APCs loaded with a NY-ESO-1 peptide pool or a control peptide pool for 1hr before addition of GolgiPlug.

NY-ESO-1 Pentamer Staining



Pentamer Staining: Pre and post PBMCs from vaccinated patients were thawed and stained directly with an A*0201/NY-ESO-1157-165 SLLMWITQV pentamer-RPE or a control A*0201/ AAXXYZZZ-Pentamer-RPE. Increase in antigen (SLLMWITQV)-specific CD8+ T cells were detected in the live CD3+ lymphocyte gate of post vaccinated patients.

SUMMARY AND CONCLUSIONS

- Administration of the dendritic cell targeted vaccine, CDX-1401, in combination with resiquimod and/or Poly ICLC is well tolerated with no DLT or Grade 3 toxicity.
- The targeted NY-ESO-1 protein induces robust immunity to NY-ESO-1 in advanced cancer patients, including augmentation of existing immunity.
 - 18/34 (53%) of evaluable patients had increase in T cell response to NY-ESO-1 as measured by ELISpot
 - All five ELISpot-positive patients tested by ICS showed an NY-ESO-1 specific CD4 response; two also had NY-ESO-1 specific CD8 response.
 - Circulating NY-ESO-1-specific pentamer-positive CD8+ cells were detected in 3/16 (19%) HLA-A2 patients.
 - 34/42 (81%) of patients had NY-ESO-1 specific IgG titers (up to 1:800,000) post vaccine; 29 patients (69%) had increasing titers post vaccine.
 - The anti-NY-ESO-1 response was primarily IgG1.
- Good immune responses were observed with both resiquimod and/or Poly ICLC.
- Thirteen patients had stable disease (2.4+ to 13.4 months). Ten were retreated, including 5 who received ≥3 cycles. The majority developed NY-ESO-1-specific immune responses, and significant tumor shrinkage was observed in two patients.
- Tissue screening confirmed significant rates of NY-ESO-1 expression in multiple cancer types.
- This study has identified a safe and immunogenic regimen for advancing into future studies.

References:
1. Nicholaou T, et al. Immunol. Cell Biol. (2006)
2. Tsuji, T, et al. J. Immunol. (2011)
3. Ramakrishna V, et al. J. Transl. Med. (2007)