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

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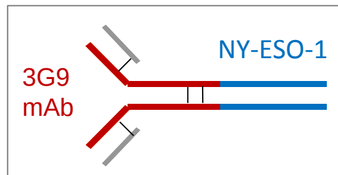
BACKGROUND

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-ES0-1 specific CD4 and CD8 responses in preclinical models.[2]
- Combination with TLR agonists enhances immunity to NY-ESO-1.[3]



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. CDX-1401 is produced by CHO cells.

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

Dose selection

Cohorts 1-3: **0.1, 1 or 3 mg CDX-1401 i.c. 500 µg topical resiquimod** *N = 23 (NY-ESO-1+ = 9)*

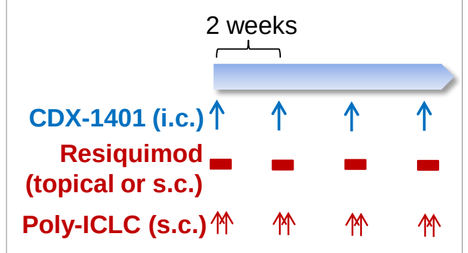
Adjuvant/ regimen optimization

Cohort 4: **1 mg CDX-1401 i.c. 2 mg poly-ICLC s.c.** *N = 7 (NY-ESO-1+ = 3)*

Cohort 5: **1 mg CDX-1401 i.c. 20-500 µg s.c. resiquimod** *N = 7 (NY-ESO-1+ = 7)*

Cohort 6: **1 mg CDX-1401 i.c. 2 mg Poly ICLC s.c. 500 µg s.c. resi** *N = 8 (NY-ESO-1+ = 8)*

Treatment Schema



- Repeated treatment cycle(s) allowed for patients with Stable Disease.
- Follow-up continues for up to 2 years.

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 cholangiocarcioma) had tumor shrinkage (-2, -8, -20 & -21%)
- 8 patients completed study follow-up at 2 years, while an additional 8 remain in follow up.

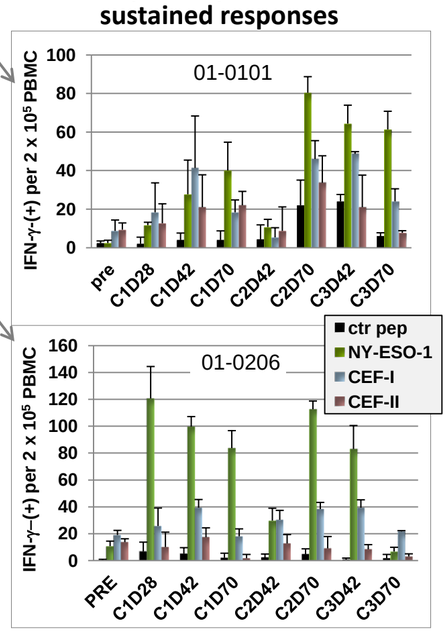
References:
1. Nicholaou T. et al. Immunol. Cell Biol. (2006)
2. Tsuji, T. et al . J. Immunol. (2011)
3. Ramakrishna V. et al. J. Transl. Med. (2007)

IMMUNE RESPONSE: CDX-1401 TREATED STUDY PATIENTS

INFγ ELISpot Analysis

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		
		03-0108		
		02-0109		
1.0 mg	Topical Resiquimod (500 µg)	01-0201		
		02-0202		
		02-0203		
		01-0204		
		01-0206*		
		01-0207		
		02-0208*		
3.0 mg	Topical Resiquimod (500 µg)	01-0301*		
		04-0303		
		04-0304		
		04-0306		
1.0 mg	Poly ICLC (2 mg)	03-0403*		
		03-0404*		
		02-0405		
		02-0407		
1.0 mg	S.C. Resiquimod (20-500 µg)	02-0501		
		06-0502		
		06-0504*		
		06-0506		
		05-0507		
1.0 mg	S.C. Resiquimod (500 µg) + Poly ICLC (2 mg)	05-0601		
		02-0603		
		01-0604*		
		04-0605		
		01-0607		
		01-0608		

Examples of patients with sustained responses



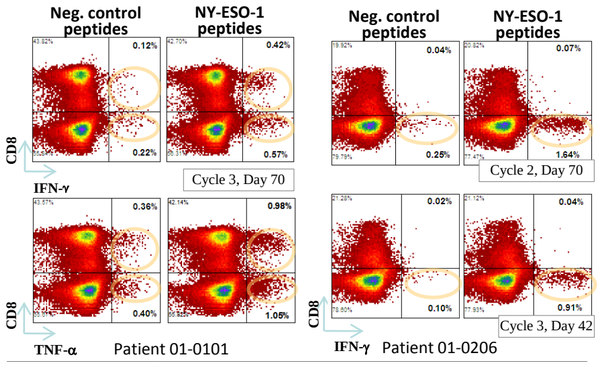
NY-ESO-1+ tumor:

* Stable Disease

INF-g spots per 2 x 10^5 PBMC: 10-25, 25-50, >50

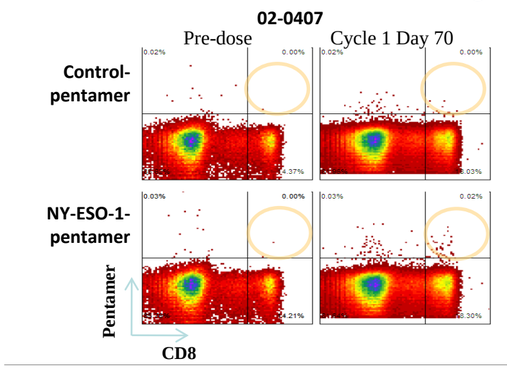
ELIspot: 34 patients had pre and post treatment PBMCs that were restimulated in vitro with NY-ESO-1 peptide pool and rhuIL-2 for 7-days and tested in an IFNγ ELISpot assay. Effector lymphocytes were incubated with T-depleted APCs (5:1) loaded with an NY-ESO-1 peptide pool or a control peptide pool and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

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/ AAXXYYZZZ-Pentamer-RPE. Increase in antigen (SLLMWITQV)-specific CD8+ T cells were detected in the live CD3+ lymphocyte gate of post vaccinated patients.*

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		
		01-0106*		
		02-0107		
		03-0108		
		02-0109		
1.0 mg	Topical Resiquimod (500 µg)	01-0201		
		02-0202		
		02-0203		
		01-0204		
		01-0205*		
		01-0206*		
		01-0207		
		02-0208*		
3.0 mg	Topical Resiquimod (500 µg)	01-0301*		
		01-0302		
		04-0303		
		04-0304		
		03-0305		
		04-0306		
1.0 mg	Poly ICLC (2 mg)	02-0401		
		03-0403*		
		03-0404*		
		02-0405		
		02-0407		
1.0 mg	S.C. Resiquimod (20-500 µg)	02-0501		
		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		
		01-0608		

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.

NY-ESO-1+ tumor:

* Stable Disease

Anti-NY-ESO-1 IgG Titer: 1:50-1:1000, 1:1000-1:10,000, 1:10,000-1:100,000, >1:100,000

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.