Immunotherapy with LV305 Enhances NY-ESO-1-specific T Cell Response and Enriches Tumor Antigen-specific TCR Sequences in Peripheral Blood

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ABSTRACT

LV305 is a lentiviral vector that expresses full-length NY-ESO-1, a cancer testis antigen. It is a replication-incompetent, integration-deficient, hybrid viral vector based on the 2SH11 platform to target dendritic cells (DC) in vivo via CD209 (DC-SIGN). Preclinical studies have demonstrated that LV305 induces NY-ESO-1-specific cytotoxic T lymphocytes (CTLs) and has potent anti-tumor effects. In a Phase I dose-escalation study presented at ASCO 2015, LV305 was administered to adult patients with previously treated, locally advanced, relapsed or metastatic soft tissue sarcomas, expressing NY-ESO-1 protein. Peripheral blood mononuclear cells (PBMC) were collected from patients at baseline, during, and post immunotherapy with LV305. ELISPOT demonstrated an induction or increase of NY-ESO-1-specific CD8+ TCD8+ T cells in the majority of patients. TCR repertoire analysis was performed in some patients where leukopheresis samples were available. The TCR sequences from PBMC were compared to the sequences from tumor infiltrating lymphocytes (TIL), where available, as well as T cell clones generated from PBMC through stimulation with NY-ESO-1. Results showed that NY-ESO-1 reactive T cell clones increased post-vaccination, consistent with the increase in antigen-specific T cell responses as measured by ELISPOT and tetramer staining. We identified two unique TCRi CD8 sequences that were increased in a significant portion of patients with different HLA-background post-treatment, suggesting that T cells with public TCR may have been expanded during treatment.

BACKGROUND

LV305 is a novel hybrid viral vector gene delivery system (2SH11) that expresses NY-ESO-1 and is designed to target DCs in vivo and stimulate CD8 T cell responses against this cancer testis antigen.

CLINICAL TRIAL DESIGN

Phase I dose-escalation study (NCT013239601)

- Indication: Locally advanced, recurrent or metastatic melanoma, sarcoma, ovarian, or lung cancers (breast cancer allowed in Phase I dose-escalation) expressing NY-ESO-1 at least one prior cancer therapy (2 for lung with low tumor burden)

- Treatment/Study Measurements:
  - Part 1: Dose Escalation - 4 cohorts, 3 dose levels, cohorts 1 & 2: 10^7 viral genomes x 3 doses, 1A (10^7 vg x 4), 2B (10^7 vg x 4), and 3 (10^7 vg x 4)
  - LV305 administered q2d intradermally, 26d DLT observation period
  - Blood samples collected for safety and immunologic testing at multiple time points including leukapheresis pre- and post-LV305
  - Disease status measured by RECIST criteria modified to use RECIST
  - Follow-up: 2 years monitoring safety, disease status and LV305 persistence in blood

CLINICAL RESPONSES

Dose Escalation: n=12 sarcoma pts

- Stable disease: 8 (66.6%) patients achieved a best response of SD (defined as stable for at least 4 weeks). Median duration of SD was 208 days [range: 139-347] days.
- 4 of 8 pts with evidence of growing disease at study entry stabilized their tumor growth following LV305.
- Pt 1 remained with SD for 347+ days and had tumor regression up to 14%.

IMMUNOLOGICAL ANALYSIS

Overall and NY-ESO-1-specific immune response

<table>
<thead>
<tr>
<th>T Cell Response</th>
<th>Immunohistochemistry</th>
<th>Flow Cytometry</th>
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<tr>
<td>CD8 T Cell</td>
<td>CD4 T Cell</td>
<td>CD4 and/or CD8</td>
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<tr>
<td>Pre-Tx</td>
<td>Post-Tx</td>
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LV305 induced T cells with increased polyfunctionality

- Cytokine production
- T cell proliferation
- T cell survival
- T cell migration

LV305 induced T cells against previously unrecognized epitopes of NY-ESO-1

- For direct IFN-gamma ELISPOT, PBMC were stimulated for 40hr with individual 10mer peptides of the NY-ESO-1 epitope pool, which contain 42 10mer peptides overlapping by 11 aa and span the full length protein.
- For IFN-gamma ELISPOT, PBMC were stimulated in vitro for one week in OpTiter T cell expansion medium in the presence of NY-ESO-1 peptide pool and cytokines (10-10 and 10-10 ng/ml).
- The expanded cells were stimulated with individual peptide overnight for the IFN-gamma ELISPOT.
- Bioses represent NY-ESO-1 epitopes that had increased T cell response following LV305

PRECLINICAL DATA

Dose-dependent induction of Polyfunctional CTls

- ELISPOT
- ICS

CONCLUSIONS

- LV305 is immunologically active in generating anti-NY-ESO-1 CD4 and CD8 T cells
- There is preliminary evidence of durable stable disease in a subset of patients
- LV305 induced T cells against previously unrecognized epitopes of NY-ESO-1
- TCRi sequences specific for NY-ESO-1 tumor antigen were enriched in post-Tx PBMC
- Evidence of induction/expansion of NY-ESO-1 specific public TCRi CD83 sequences by LV305