INTRODUCTION

LV305 is a novel viral vector platform that encodes NY-ESO-1 and the co-stimulatory molecule ZVex to deliver high level expression of each with improved safety. This was developed as a NY-ESO-1 therapeutic vaccine entering a pivotal Phase 3 study. Previously presented data at ASCO 2016 showed that LV305 is safe, induces immune responses (IR) and appears to impact survival with 81% 1 year survival in NY-ESO-1 sarcoma patients following LV305 treatment.

The 2-year follow-up is presented to evaluate the impact of LV305 on survival and immune responses in soft tissue sarcoma including synovial sarcoma, a soft tissue subtype that has high expression of NY-ESO-1.

RATIONALE / BACKGROUND

NY-ESO-1 is a tumor-associated antigen whose function is unknown. It is expressed only in cancer and in normal testis in adults.

Expression (by IHC) is observed in many different malignancies with high expression of 70-100%, reported in the sarcoma subtypes: synovial sarcoma and myxoid/round cell liposarcoma and moderate expression in melanoma (24-45%), ovarian (14-43%), and NSCLC (11-29%).

NY-ESO-1 is an excellent immunologic target: preclinical and clinical data demonstrate cytotoxic T lymphocytes (CTLs) directed against NY-ESO-1 can specifically target and kill NY-ESO-1 antigen-bearing cancer cells with no off-target effects.

LV305 is a novel hybrid viral vector from the ZVex® platform that encodes NY-ESO-1 and LV305 is designed to target DCs in vivo and stimulate CD8+ T cells against this cancer target antigen.

TRIAL DESIGN

• Rationale: In this first-in-human study, we examine the safety, immunologic activity, and preliminary efficacy of LV305 in patients whose cancers expressed NY-ESO-1.

• Indication: Locally advanced, recurrent or metastatic melanoma, sarcoma, ovarian, or lung cancers (breast cancer allowed in Part I). All patients must be at least 18 years old.

• Treatment / Study Measurements:
  - Part I: Dose Escalation: 4 cohorts, 3 dose levels
  - Cohort 1: 10 (10 x 2 doses), Cohort 2: 10 (10 x 4 doses), Cohort 3: 10 (3 x 4 doses)
  - Part II: Patient expansion: the dose (10 x 4 doses) determined in Part I to be safe was used to treat additional cancer patients

LV305 administered q21d (Days 0, 21, 42, and 63) intradermally; 28d DLT window.

- Blood samples collected for safety and immunologic testing at multiple time points including neoadjuvant pre- and post-LV305.
- Disease status measured by IRCC criteria modified to use RECIST
- Follow-up 2 years monitoring safety, disease status, and LV305 persistence in blood

RESULTS

Table 1. Pretreatment Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Soft Tissue Sarcoma</th>
<th>Synovial Sarcoma</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.6 (25.67)</td>
<td>46.6 (25.67)</td>
<td>46.6 (25.67)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>9 (69.2%)</td>
<td>12 (62.2%)</td>
<td>21 (63.7%)</td>
</tr>
<tr>
<td>NY-ESO-1</td>
<td>8 (66.7%)</td>
<td>6 (33.3%)</td>
<td>14 (40.5%)</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>6 (50%)</td>
<td>6 (33.3%)</td>
<td>12 (35.3%)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>6 (50%)</td>
<td>6 (33.3%)</td>
<td>12 (35.3%)</td>
</tr>
<tr>
<td>Prior Chemotherapy</td>
<td>2 (16.7%)</td>
<td>3 (16.7%)</td>
<td>5 (15.2%)</td>
</tr>
<tr>
<td>Prior Therapy</td>
<td>1 (10%)</td>
<td>1 (10%)</td>
<td>2 (6.0%)</td>
</tr>
<tr>
<td>Relapsed, Locally Advanced</td>
<td>5 (41.7%)</td>
<td>3 (15.3%)</td>
<td>8 (24.2%)</td>
</tr>
<tr>
<td>Progression Metastatic</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>NY-ESO-1 Expression ≥ 1%</td>
<td>9 (75%)</td>
<td>3 (15.3%)</td>
<td>12 (35.3%)</td>
</tr>
<tr>
<td>≥1%</td>
<td>9 (75%)</td>
<td>3 (15.3%)</td>
<td>12 (35.3%)</td>
</tr>
</tbody>
</table>

Immune Biomarker Frequencies

- Anti-NY-ESO-1 Abs detected by ELISA against either the whole NY-ESO-1 protein or peptides: A 4-fold rise or new positive response was scored as positive (induced response)
- Anti-NY-ESO-1 CD4 and CD8 responses were determined to be positive by the following assays:
  - IFN-γ production detected by ELISPOT in separated T cell fractions
  - Intracellular cytokine staining for IFN-γ or TNFα after stimulation with NY-ESO-1 peptides
  - ELISPOT ≥50 spots & ≥2-fold rise and/or IFN-γ ≥2-fold over baseline were considered positive (induced response)

TEAEs Occurring in ≥ 2 Patients (All Dosed)

- All AEs were Grade 1 or 2. There were no Grade 3 TEAEs.
- There were no DLTs, treatment-related SAEs, or discontinuations due to TEAEs.
- TEAEs were primarily fatigue (12/24; 50%), injection site reaction (12/24; 50%), and myalgia (8/24; 33%).
- Related AEs were fatigue 30 (51.2%), injection-site pruritus 10 (25.6%), and myalgia 9 (25%).

Patient 151-006: Clinical Outcomes and Immune Response

- A 41 year-old patient with multiple recurrent metastatic synovial sarcoma at study entry. The original disease was an isolated mass in the lung that was treated with a wedge resection and adjuvant doxorubicin and bleomycin. Patient had multiple recurrences at several surgical resections and single-agent bleomycin and radiation therapy. Patient with further recurrence of advanced disease then treated with trastuzumab, with recurrence, and most recent prior to study entry a course of paclitaxel with progressive disease.
- Patient was enrolled into the LV305 study in May 2014 and experienced disease stabilization of growing disease and then objective tumor shrinkage with near complete response 3 years after study entry. Subsequent local regional or systemic anti-cancer therapy was administered after study start.
- NY-ESO-1 evidence of pre-existing anti-NY-ESO-1 antibodies and T cells (CD4+ and CD8+) with an induction of T cells following LV305 therapy.

SUMMARY

- LV305 is a well tolerated therapy with favorable toxicity and no Grade 3 adverse events.
- LV305 is in late-stage development as part of CBM305, a prime boost regimen entering a pivotal Phase 3 trial in soft tissue sarcoma patients.

Clinical Outcome: Immune Response Measurements

<table>
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<tr>
<th>Test Type</th>
<th>Methodology</th>
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<tbody>
<tr>
<td>ELISPOT</td>
<td>detection of IFN-γ production by T cells</td>
</tr>
<tr>
<td>Intracellular cytokine staining</td>
<td>detection of intracellular IFN-γ and TNFα</td>
</tr>
<tr>
<td>Antibody Assays</td>
<td>detection of anti-NY-ESO-1 Abs</td>
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Overall Survival: Baseline Immune Response versus Induced Immune Response

For STS the median OS for those patients who were pre-positive and post-positive (green curve) was NR (77.8, NR) versus for patients who were pre-negative and post-positive (red curve) was 23.7 (12.2, 26.3).

Overall Survival: Baseline Immune Response after LV305 Therapy in Patients with Advanced Sarcoma and Other Solid Tumors

Abstract #109

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