Immune Response, Safety, and Survival Impact from CMB305 in NY-ESO-1+ Recurrent Soft Tissue Sarcomas (C131 Study)

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Abstract 2951

ABSTRACT

- **Background.** CMB305 is an active immunotherapy regimen designed to generate and expand anti-NY-ESO-1 T and B cells. It consists of priming with a dendritic cell-targeting lentiviral vector encoding NY-ESO-1, and a boost with NY-ESO-1 recombinant protein plus the TLR-4 agonist. This first-in-human study of CMB305 examined the safety, immune response (IR), and efficacy in patients with NY-ESO-1 positive (+) solid tumors. At ASCO 2017, the median overall survival (OS) for soft tissue sarcoma (STS) was not reached (12-month OS rate 83%).
- **Methods.** Adults with previously treated NY-ESO-1+ solid tumors were enrolled in a 3+3 dose-escalation with an expansion phase 1b study. The CMB305 regimen included 4 intradermal injections of the prime, alternating with 3 intramuscular boost injections over 3 months, then bimonthly boost injections up to 1 year. An updated STS survival analysis was performed.
- **Results.** As of 24 August 2018, 25 patients with STS (15 synovial sarcoma [SS], 8 myxoid/round cell liposarcoma [MRCL], 2 spindle cell) were evaluable for safety; 24 patients were evaluable for IR and efficacy. All patients received prior therapy for advanced disease, 56% received ≥2 prior chemotherapy regimens. No dose-limiting toxicities were observed. Most treatment-related adverse events were Grade 1 or 2, and there were no Grade 4 or 5 events. The best tumor response was stable disease (SD) in 8/15 (53%) SS patients and 6/8 (75%) MRCL patients with evidence of tumor growth arrest. The median progression-free survival (PFS) was 3.9 months (2.1, 7.5) for STS and 3.7 months (2.1, 7.8) for SS. Median OS was 29.2 months (15.5, NR) for STS and 29.2 months (12.2, NR) for SS. The presence of anti-NY-ESO-1 antibodies (Ab) at baseline (29.4% of patients) was associated with longer survival. Anti-NY-ESO-1 specific T cells and antibody developed in 45.5% and 66.7% STS patients, respectively. Patients with baseline and induced anti-NY-ESO-1 IR (T-cells and/or antibodies) had a trend to improved clinical outcomes. T-cell receptor sequencing indicated increased clonality and antigen spreading was observed.
- **Conclusions.** CMB305 is well tolerated, broadly immunogenic, and impacts patient survival favorably when compared with approved agents for recurrent STS. These results support a randomized phase 3 trial evaluating CMB305 in the maintenance setting after first-line therapy in SS patients. .

BACKGROUND / RATIONALE

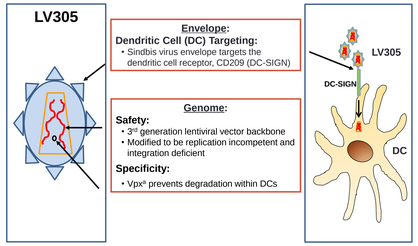
Advanced Solid Tumors, Immunotherapy and NY-ESO-1

- The cancer/testis antigen, NY-ESO-1, is frequently expressed in certain STS, can be expressed in other solid tumors, and may be associated with poor prognosis.[a]
- Cancers with expression of NY-ESO-1 are not uncommon with variable presentation, behavior, and outcome.[b]
- Effective targeting of NY-ESO-1 with novel immunotherapy in the appropriate patient population could lead to prolonged benefit.[c]
- 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.
- There remains an urgent medical need to develop sarcoma subtype-specific immunotherapies; targeting NY-ESO-1 in synovial sarcomas is a rational approach based on the high level of expression in this type of sarcoma.

[a] Iura, M., et al., 2017; [b] Brennan, M., et al., 2014; [c] D'Angelo, S. 2016

Figure 1. LV305, A Modified Dendritic Cell Tropic 3rd Generation Lentiviral Vector

- LV305 is a novel hybrid viral vector from the ZVex™ platform that expresses NY-ESO-1 **RNA and is designed** to target dendritic cells (DCs) ***in vivo*** and stimulate CD8 T cells against NY-ESO-1



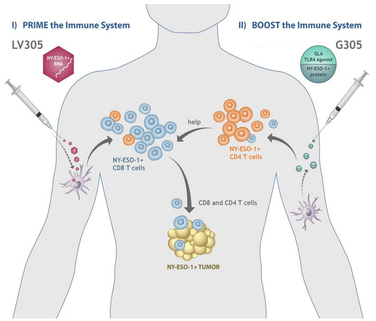
[a] Vpx is an additional accessory protein found naturally in HIV-2 but is absent in HIV-1. Vpx is packaged into LV305 vector during particle formation in the production process. Vpx counteracts the restriction in human DCs by promoting the degradation of SAMHD1 allowing LV305 to transduce human DCs.

CMB305: Prime-Boost Immunotherapy Targeting NY-ESO-1

CMB305 is a prime-boost immunotherapy targeting NY-ESO-1 that combines LV305 priming with sequential doses of G305 boosting.

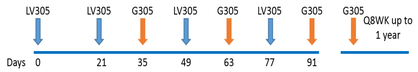
- **LV305 priming**:
  - DC targeting lentiviral vector encoding full length NY-ESO-1 RNA
  - Integration deficient, replication incompetent
  - Induces and expands NY-ESO-1 specific CD8 and CD4 T cells
- **G305 boosting**:
  - Potent TLR-4 agonist co-formulated with NY-ESO-1 full length protein
  - Enhances LV305 T-cell immunogenicity and triggers anti-NY-ESO-1 antibodies
- No *ex vivo* manipulation or HLA matching required

Figure 2. CMB305 Prime Boost Targeting NY-ESO-1



STUDY DESIGN

Figure 3. CMB305 Schedule



Rationale

- This Phase 1b study evaluated the safety, tolerability, immune response, preliminary efficacy, and biomarker data of CMB305 in patients whose cancers expressed NY-ESO-1.

Eligibility

- Recurrent locally advanced, relapsed and/or metastatic solid tumors, limited tumor burden (<10 cm)
- ECOG Performance Score 0–1
- NY-ESO-1+ by IHC
- Received prior therapy

Treatment and Study Measurements

- Part 1, Dose Escalation: 2 cohorts, 2 dose levels
- Part 2, Patient Expansion (Arm A and Arm B): LV305 ($1x10^{10}$ vg) 4 doses + G305 3 doses (5 µg/250 µg) determined in Part 1 to be safe
- Adverse events (AEs) and serious adverse events (SAEs) were reported up to 30 days after the last dose; dose limiting toxicities were observed for 49 days (42 + 7 days)
- Tumor response was measured by irRC criteria modified to use RECIST v1.1
- Follow-up visits for tumor response every 2 months until disease progression, then survival follow-up ever 3 months up to 5 years.

Part 1 Dose Escalation

Cohort	LV305 Dose (vg per dose)	G305 Dose (GLA/Ag)
1	10^9 ID	5 µg/250 µg IM
2	10^{10} ID	5 µg/250 µg IM

- **Primary Objective**—Safety

Part 2 Expansion

- **Arm A**: ID route; up to 9 each NSCLC, ovarian cancer, synovial sarcoma or MRCL
- **Arm B:** SC route, 9 synovial or MRCL
- **Objectives**:
  - Safety
  - Efficacy
  - Immune response and biomarkers

ID=Intradermal; IM=Intramuscular; vg = vector genome; Ag = antigen NY-ESO-1

NSCLC = non-small cell lung cancer; ID = intradermal; MRCL = myxoid/round cell liposarcoma; SC = subcutaenous.

STUDY RESULTS

Patient Characteristics

Table 1. Study Population

Safety Population	N = 50
Soft Tissue Sarcoma	**34**
Synovial sarcoma	21[a]
MRCL	11[b]
Spindle cell	2[c]
Osteosarcoma	1
Ovarian	11
Non-small cell lung carcinoma	4

MRCL = myxoid/round cell liposarcoma
[a]Arm A (n=14); Arm B (n=7)
[b]Arm A (n=9); Arm B (n=2)
[c]Arm A (n=2); Arm B (n=0)

Table 2. Demographics and Disease Characteristics – STS Patients

	STS Patients (N = 25)[a]
Median age (range)	45.9 years (20–76)
Female, n (%)	8 (32)
Male, n (%)	17 (68)
ECOG Performance Status 1, n (%)	14 (56)
Metastatic disease, n (%)	22 (88)
Median time from diagnosis (range)	**34 months (10–131)**
Prior chemotherapy	**23 (92)**
Median lines of chemotherapy	2.0
≥2 prior lines of chemotherapy, n (%)	**14 (56)**
Disease progression at study entry, n (%)	14 (56)
NY-ESO-1 expression 50–100 %, n (%)	20 (80)

ECOG = Eastern Cooperative Oncology Group; STS = soft tissue sarcoma
[a]Arm A only, Arm B not included

Summary of Safety

- The most common treatment-related TEAEs included fatigue, injection-site pain, influenza-like illness, myalgia, and injection-site reactions (all self-limited).
- Grade 3 treatment-related TEAEs were reported in one patient each and included fatigue (1), prostatic pain (1), and pneumonitis (1).
- Two patients had treatment-related SAEs: prostatic pain in a patient with metastatic synovial sarcoma, and pneumonitis in a non-small cell lung cancer patient; the pneumonitis was attributed by IMDZ to the patient's previous history of pneumonitis while on pembrolizumab and not related to CMB305.

Table 3. Summary of Adverse Events

All (N = 50)	
	Related TEAEs
Patients with at least one TEAE, n (%)	37 (74)
TEAEs by NCI CTC	
Grade 1–2	33 (68)
Grade 3	3 (6.0)
Grade 4	0
Grade 5	0
Serious TEAEs	2 (4.0)

CTC = Common Toxicity Criteria; NCI = National Cancer Institute; TEAE = treatment emergent adverse event.

Efficacy Outcomes with CMB305 in Soft Tissue Sarcoma

- Patients with progressive disease (PD) at study entry experienced durable tumor growth arrest.

Table 4. Disease Control – STS versus Synovial Sarcoma (All STS)

All Patients with STS versus Synovial Sarcoma		
	STS (N = 25)	Synovial Sarcoma (N = 14)
Overall response rate, N (%)	0	0
Stable disease, N (%)	17 (68)	8 (57)
PFS, median months	3.9	3.7
(95% CI)	(2.1 – 7.8)	(2.1 – 7.4)
6-month PFS rate, %	33.3	30.8
12-month PFS rate, %	20.8	23.1

CI = confidence interval; PFS = progression-free survival; STS = soft tissue sarcoma

Table 5. Disease Control – STS versus Synovial Sarcoma (STS Patients with Progressive Disease)

Patients with Progressive Disease at Study Entry		
	STS (N = 14)	Synovial Sarcoma (N = 8)
Stable disease, N (%)	9 (64)	4 (50)
PFS, median months	3.1[a]	3.9
PFS, median months (SD[b] on study)	7.4	12.6

PFS = progression-free survival; PD = progressive disease; SD = stable disease; STS = soft tissue sarcoma
[a] Anti-NY-ESO-1 immunity has been observed in patients with disease control.
- One patient with pre-existing immunity without induction of immunity during treatment, one patient without pre-existing immunity with induction of immunity during treatment, and one patient with pre-existing immunity without induction of immunity during treatment

[b] Tumor response was measured by irRC.

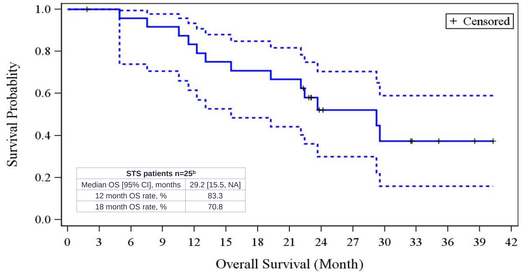
Overall Survival with CMB305 in STS

Summary from Published Literature for 2nd Line STS or Synovial Sarcoma

- Published overall survival data in STS patients treated with pazopanib[a] (12.5 months), eribulin[b] (13.5 months), and trabectedin[c] (12.4 months)
- Published overall survival data in synovial sarcoma patients in the METASARC[d] study (11.7 months)

[a]van def Graaf, et al., 2012, [b]Schoffski, P, et al, 2016, [c]Demetri, G. et al, 2016; [d]Savina, et al., 2017 (synovial sarcoma)

Figure 4. CMB305 Overall Survival – STS Patients[a]



[a] 24 August 2018 data cut; median duration of observation was 23 months.
[b] Median OS (95% CI) for synovial sarcoma was 29.2 months (95% CI 12.2, NA; Arm A n=14).

SUMMARY

- Therapy with CMB305 is well tolerated.
- Overall survival compares favorably with published data for patients with recurrent/metastatic STS.
- Median OS of 29.2 months, for both STS and synovial sarcoma patients, has been reached.
- Disease control has been observed in more than half of STS patients, including durable tumor growth arrest in patients who had disease progression prior to CMB305 therapy.
- CMB305 generates broad anti-NY-ESO-1 immune responses (T cells and antibodies) and triggers antigen spreading.
- Anti-NY-ESO-1 immune biomarkers identify cancer patients who have prolonged survival following CMB305 therapy.
- An evaluation of CMB305 is warranted in synovial sarcoma patients stratified by pre-existing NY-ESO-1 antibody in a pivotal Phase 3 study.
- A randomized Phase 3 trial to evaluate CMB305 monotherapy versus placebo in patients with NY-ESO-1+ locally advanced unresectable or metastatic synovial sarcoma opened in June 2018 by Immune Design.
- For information, see ClinicalTrials.gov Identifier: NCT03520959. Contact: Chet Bohac, MD: MedicalMonitor1702@immunedesign.com

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NY-ESO-1 Immune Response (IR) Assessment

Pre- and post-peripheral blood and plasma
(Blood collection on Days 0, 35, 49, 63, 77, 112, 168)

T-cell assays[a]:
- NY-ESO-1 IFNγ ELISpot (CD4 & CD8 T-cell bead separation, 2-3 week in vitro stimulation)
- TCR repertoire sequencing (Vβ-CDR3): clonality, "public" NY-ESO-1 TCR

Antibody assays[b]:
- NY-ESO-1 ELISA (recombinant protein & peptides)
- Antigen spreading: 24 recombinant tumor associated antigens ELISA (p53, MAGE, SSX, PRAME, etc.)

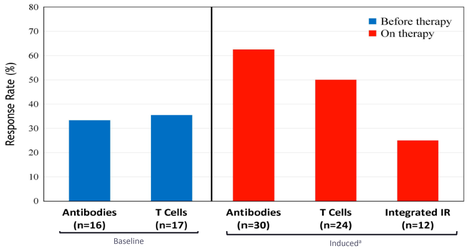
ELISA = enzyme-linked immunosorbent assay; ELISpot = enzyme-linked immunospot; TCR = T-cell receptor

[a]Anti-NY-ESO-1 CD4 and CD8 responses were determined to be positive by the following assays: IFNγ production detected by ELISPOT in separated T-cell fractions intracellular cytokine staining (ICS) for IFNγ or TNFα after stimulation with NY-ESO-1 peptides ELISPOT >50 spots & >2-fold rise and/or ICS >2-fold over baseline were considered positive (induced response)
[b]Anti-NY-ESO-1 antibodies detected by ELISA against either the whole NY-ESO-1 protein or to peptides. A 4-fold rise or newly positive response was scored as positive (induced response).

Anti-NY-ESO-1 Baseline and CMB305 Induced Immunity

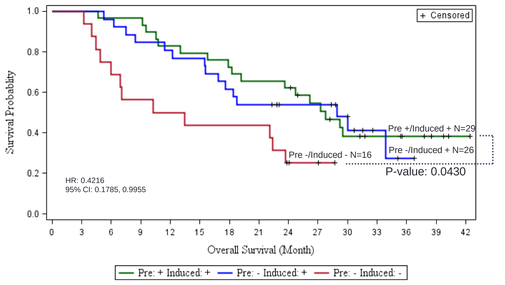
- CMB305 generates strong and broad anti-NY-ESO-1 IR (Figure 5)
  - Stronger T-cell response (ELISpot)
  - Antibody induction
  - 25% patients with induction of integrated IR
  - Evidence of antigen spreading in 4/18 (22%) patients
- Induction of anti-NY-ESO-1 IR is associated with a better overall survival (Figure 6)

Figure 5. Anti-NY-ESO-1 Baseline and CMB305 Induced Immunity



All tumor types (n = 48): 34 sarcoma, 11 ovarian, 3 non-small cell lung cancer
[a]Includes all patients whether or not there were pre-existing antibodies or T cells. Integrated immune response (IR) includes patients having both induction of antibodies and T cells.

Figure 6. NY-ESO-1 Immunity Survival in Studies with LV305[a]



[a] An exploratory biomarker analysis was performed in all patients enrolled (Arm A, Arm B, and patients on LV305 monotherapy including ID/IM and SC dosing) who had biomarker samples collected (n=71). 55/71 patients (77.4%) of patients had an induced anti-NY-ESO-1 immune response on LV305 or CMB305 therapy assessed by one of the antibody or T-cell assays.

ACKNOWLEDGEMENTS

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