Abstract ID: 2785040

A PHASE 2 STUDY OF CMB305 AND ATEZOLIZUMAB IN NY-ESO-1+ SOFT TISSUE SARCOMA: INTERIM ANALYSIS OF IMMUNOGENICITY, TUMOR CONTROL AND SURVIVAL

Chawla, S.[1], Van Tine, BA.[2], Pollack, S.[3], Ganjoo, K.[4], Elias, A.[5], Riedel, RF.[6], Attia, S.[7], Choy, E.[8], Okuno, S.[9], Agulnik, M.[10], von Mehren, M.[11], Livingston, M.[12], Keedy, V.[13], Verschraegen, C.[14], Philip, T.[15], Bohac, C.[16], Lu, H.[16], Chen, M.[16], Maki, R.[15]

[1]Sarcoma Oncology Center, Santa Monica, CA, [2]Washington University, St Louis, MO, [3]Fred Hutchinson Cancer Center, Seattle, WA, [4]Stanford University, Palo Alto, CA, [5]University of Colorado, Denver, CO, [6]Duke University, Durham, NC, [7]Mayo Clinic, Jacksonville, FL, [8]Dana Farber Cancer Institute, Boston, MA, [9]Mayo Clinic, Rochester, MN, [10]Northwestern University, Chicago, IL, [11]Fox Chase Cancer Center, Philadelphia, PA, [1]Carolinas Healthcare System, Charlotte, NC, [13]Vanderbilt University, Nashville, TN, [14]Ohio State University Medical Center, Columbus, OH, [15]Northwell Health System, New Hyde Park, NY, [16]Immune Design, Seattle, WA and San Francisco, CA

INTRODUCTION

CMB305 is an active immunotherapy designed to generate and expand anti-NY-ESO-1 immune response (IR). CMB305 consists of a dendritic cell-targeting lentiviral vector encoding NY-ESO-1 (LV305), and a boost with an NY-ESO-1 recombinant protein plus GLA-SE (G305), a TLR-4 agonist. Phase 1 studies of LV305 and CMB305 showed this approach is safe, generates IR and appears to impact survival with 81% 1-year survival in NY-ESO-1+ sarcoma patients following LV305 treatment. This Phase 2 study was designed to evaluate:

- Whether CMB305 has activity in a randomized setting
- Whether addition of CMB305 improves activity of atezolizumab in a tumor type where checkpoint inhibitors have limited single agent activity

STUDY DESIGN

This is a randomized, open-label, Phase 2 study of CMB305 in combination with atezolizumab (C+A) or with atezolizumab alone (A) in patients with in NY-ESO-1$^+$ synovial sarcoma and myxoid round cell liposarcoma who have had an inadequate response, relapse, and/or unacceptable toxicity with one or more prior systemic, surgical, or radiation cancer therapies. Safety run-in (3 + 3 design in each arm) was followed by a stratified by histology randomization between arms. Eighty-nine (89) patients were enrolled (88 dosed) at 15 sites in the United States. Tumor biopsies were optional. No formal comparison analysis was planned between treatment arms.

INTERIM ANALYSIS (IA)

- Exploratory analysis of progression-free survival rate (PFR) at 6 months for the first 36 patients enrolled after the safety run-in was performed
- No formal interim analysis was performed for efficacy
- Final analysis will be conducted when 72 deaths have occurred or earlier as determined by Sponsor

STUDY OBJECTIVES

Primary Objectives

- Overall survival (OS) and progression-free survival (PFS)

Secondary Objectives

- Safety, PFS rate at 3 and 6 months, immune response in the tumor tissue and peripheral blood, time to next treatment (TTNT) and distant metastasis free survival (DMFS)

Exploratory Objectives

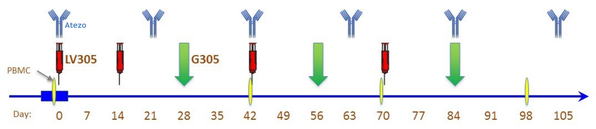
- Compare efficacy assessments: ORR, Disease Control Rate, PFS, OS

METHODS

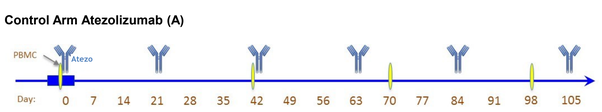
Treatment: Arm C+A: CMB305 (LV305 Intradermal Days 0, 14, 42, 70 + G305 Intramuscular Days 28, 56, 84 then q6wk up to one year) + atezolizumab (1200 mg IV q3wk); Arm A: atezolizumab alone (Figure 1).

Figure 1. CMB305 Treatment and Biomarker Schedule

A. Combination Treatment Arm CMB305 + Atezolizumab (C+A)

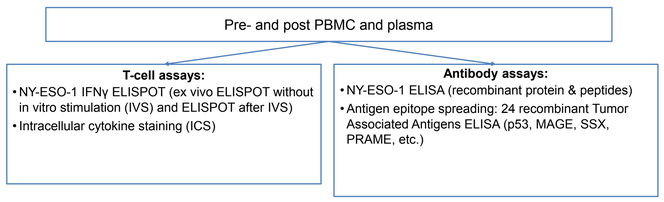


B. Control Arm Atezolizumab (A)



Abbreviations: PBMC = peripheral blood mononuclear cell

Figure 2. NY-ESO-1 Immune Response Assessment



RESULTS

Preliminary Clinical Efficacy of CMB305+Atezolizumab in NY-ESO-1+ STS Patients

- Patients in Arm C+A are a more advanced, refractory STS population compared to A alone (Table 1)
  - Higher % of ECOG PS1, metastatic disease, synovial sarcomas, Grade 3 at diagnosis, ≥2 prior lines of chemo
  - Safety run-in – 13 patients were excluded from PFS IA due to lack of stratification by histology

Table 1. Demographics and Disease Characteristics

Demographics/Characteristics	Interim Analysis* (n=36)		Safety Population (n=88)	
	Atezo (n=18)	CMB305 + Atezo (n=18)	Atezo (n=43)	CMB305 + Atezo (n=45)
Median age, yrs	43.0	46.5	47.0	48.0
Female, %	50	38.9	44.2	42.2
ECOG Performance Status 1, %	44.4	55.6	46.5	57.8
Synovial sarcoma, %	55.6	61.1	67.4	73.3
Metastatic disease, %	72.2	100	79.1	97.8
Time from diagnosis, median (range), mos	26.1 (7.7, 186)	27.4 (3.7,78.1)	21.4 (0.5, 300.1)	34.8 (3.7, 295.1)
>2 lesions at baseline, %	83.3	100	83.7	95.6
≥2 prior lines of systemic anti-cancer therapy, %	53.3	76.5	48.6	61.1
Progression at study entry, %	50	50	51.2	48.9
NY-ESO-1 expression 50-100%, %	94.5	88.9	90.7	86.7
Grade 3 at Diagnosis	38.9	61.1	32.6	46.7

*The IA of PFS included the first 36 patients with a median 7.0 months follow up (first 13 patients in safety run-in are excluded from IA as they were not stratified by histology)

- Combination C+A demonstrated partial responses (Table 2), better disease control (Table 2, Figure 2) and a trend to a longer PFS (Table 2) than A alone
- Overall Survival (OS) data is immature at the time of IA

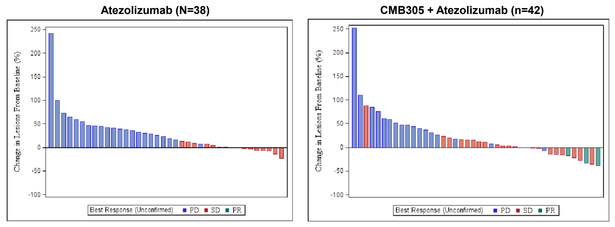
Table 2. Preliminary Clinical Efficacy in Patients on Arm A and Arm C+A

Outcomes	Interim Analysis (n=36)		Safety Population (n=88)	
	Atezo (n=18)	CMB305 + Atezo (n=18)	Atezo (n=43*)	CMB305 + Atezo (n=45*)
Median Duration of Observation, mos	8.9	7.7	5.1	5.3
Median Progression Free Survival, mos (95% CI)	1.4 (1.3-1.9)	2.6 (1.4-2.8)	Not reported	Not reported
PFS Rate 6 months (%)	16.7	16.7	Not reported	Not reported
Partial Response (%)	0	1 (5.6)	0	3** (6.8)
Disease Control Rate (%)	5 (27.8)	11 (61.1)	16 (38.1)	25 (56.8)
Time to Next Treatment (mos)***	6.3	9.0	Not reported	Not reported

*1 patient in each Arm did not have post baseline tumor assessment
**1 patient with unconfirmed PR
***For TTNT 10 patients in A and 8 patients in C+A received subsequent therapy after progression

Data extraction date: 21 July 2017

Figure 3. Target Lesion Change from Baseline in Patients on Arm A and Arm C+A



Safety of CMB305+Atezolizumab Combination in NY-ESO-1+ STS Patients (Safety Populaton)

- Combination C+A is well tolerated and no new safety signal has been identified for the combination (Table 3)

Table 3. Treatment Related Adverse Events Arm A and Arm C+A

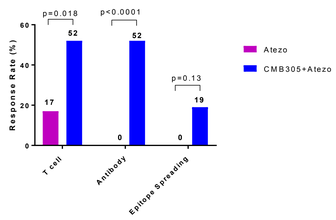
Patients with At Least One Treatment Related TEAEs	Safety Population (n=88)	
	Atezo* (n=43)	CMB305 + Atezo** (n=45)
Grade 1, n (%)	13 (30.2)	18 (40)
Grade 2, n (%)	5 (11.6)	10 (22)
Grade 3, n (%)	3 (7.0)	3 (6.7)
Grade 4, n (%)	1 (2.3)	1 (2.2)
Grade 5, n (%)	0	0

* TEAEs related to atezolizumab; ** TEAEs related to CMB305 and/or atezolizumab
Most common (>10%) TEAEs related to CMB305: diarrhea, fatigue, injection site pain; Grade 3 TEAEs related to CMB305: lymphopenia, thrombocytopenia, influenza like illness; No Grade 4 TEAEs related to CMB305 were reported; Grade 4 pneumonitis on Arm A+C was related to atezolizumab

Exploratory Analysis of Immune Response (IR)

- Patients with collected and analyzable peripheral blood samples (N=60) are included in IR analysis
- Combination C+A resulted in stronger induction of anti-NY-ESO-1 specific antibodies (Ab) and T cell responses than A alone (Figure 4)
- Antigen epitope spreading was observed on Arm C+A (Figure 4)

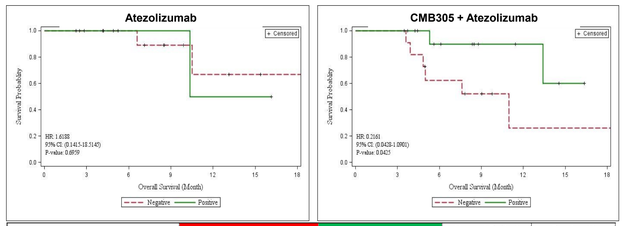
Figure 4. Induction of NY-ESO-1 Specific Ab and T cell Responses and Antigen Epitope Spreading



Induction of NY-ESO-1 specific T cells was defined as a ≥ 2 fold increase in ELISPOT; Induction of NY-ESO-1 specific Ab was defined as ≥ 4 fold increase in ELISA. Antigen epitope spreading was defined as Ab response to tumor antigens other than NY-ESO-1.

- Preliminary biomarker analysis shows a trend to a better OS in C+A patients with induced anti-NY-ESO-1 T Cells (Figure 5) and anti-NY-ESO-1 Abs (Figure 6) than A alone
- Presence of baseline anti-NY-ESO-1 T cells may be associated with a better survival on C+A arm (data not shown)

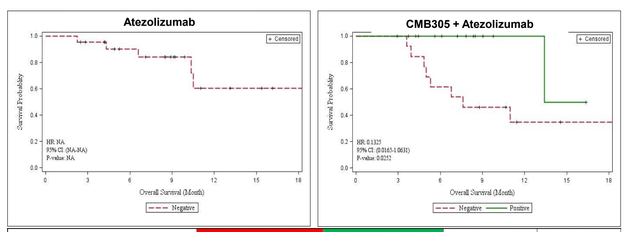
Figure 5. OS in Patients With (Green) and Without (Red) Induced anti-NY-ESO-1 T Cells



	Induced T cell Negative	Induced T cell Positive	Hazard Ratio *	P value **
All Patients, mos (95% CI)	11.0 (7.6, NR) (n=27)	NR (10.3, NR) (n=16)	0.47	0.26
CMB305 + Atezolizumab, mos (95% CI)	11.0 (3.9, 18.6) (n=12, 48%)	NR (5.3, NR) (n=13, 52%)	0.22	0.04
Atezolizumab , mos (95% CI)	NR (6.6, NR) (n=15, 83%)	NR (10.3, NR) (n=3, 17%)	1.62	0.70

* Kaplan-Meier method; ** not adjusted for multiplicity of analyses; NR – Not reached

Figure 6. OS in Patients With (Green) and Without (Red) Induced anti-NY-ESO-1 Antibodies



	Induced Antibody Negative	Induced Antibody Positive	Hazard Ratio *	P value **
All Patients, mos (95% CI)	18.6 (7.6, NR) (n=36)	NA (13.4, NR) (n=14)	0.23	0.12
CMB305 + Atezolizumab, mos (95% CI)	7.6 (4.8, 18.6) (n=13, 48%)	NR (13.4, NR) (n=14, 52%)	0.132	0.025
Atezolizumab , mos (95% CI)	NR (10.3, NR) (n=23, 100%)	0 (n=0, 0%)	NA	NA

* Kaplan-Meier method; ** not adjusted for multiplicity of analyses; NR - Not Reached; NA - Not Applicable

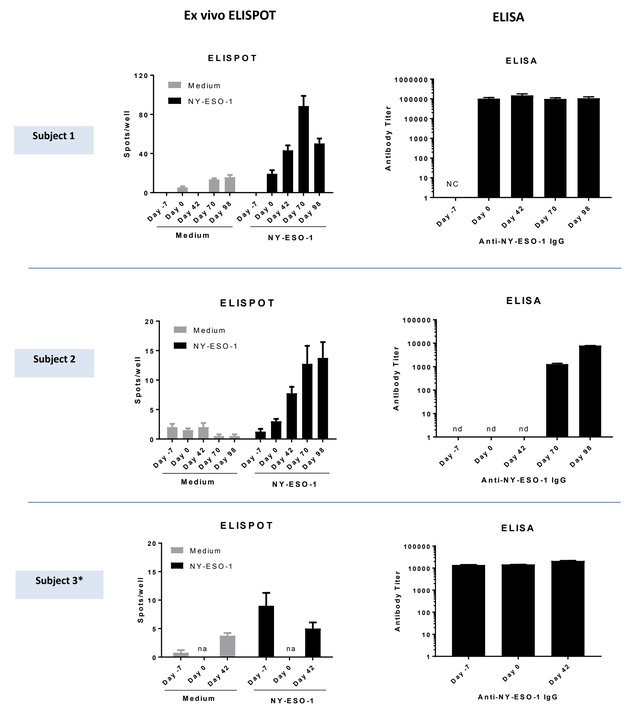
- Patients with PR treated on combination C+A had advanced metastatic disease after multiple prior lines of therapy (Table 4)
- These patients had evidence of preexisting anti-NY-ESO-1 immunity and induction of anti-NY-ESO-1 IR while on combination C+A therapy (Figure 6). T cell immune response included both CD4 and CD8 cells based on intracellular cytokine staining (data not shown)

Table 4. Characteristics of Patients with PR

Patient	NY-ESO-1 expression	Disease status at study entry	Prior therapy	Tumor burden at study entry	Timing of Partial Response	Timing of Progressive Disease	Current Status
Subject 1							
25 yr, M, Synovial sarcoma	78%	Metastatic/ Progressive	Tumor excision, XRT, AIM, pazopanib	Target sum 39 mm Non-target multiple lung nodules	16 weeks	32 weeks	Alive 15 months on Atezo
Subject 2							
34 yr, F, Synovial sarcoma	100%	Metastatic/ Progressive Relapsed	Lobectomy, tumor resection, XRT, AIM, pazopanib	Target sum 36 mm Non-target multiple lung nodules	12 weeks	Not yet	Alive 7 months on Atezo
Subject 3 (unconfirmed PR)							
35 yr, M, Synovial sarcoma	100%	Metastatic/ Progressive Relapsed	Tumor excision, XRT, AIM	Target sum 92 mm Non-target pleural mets	6 weeks	12 weeks	Death 16 weeks Cancer related after Pneumonia/Pneumonitis

XRT – radiation therapy, AIM – doxorubicin/ifosfamide

Figure 7. Induction of anti-NY-ESO-1 specific T cells and Antibody Responses in 3 Patients with PR



T cell response was measured by ELISPOT. Cryopreserved PBMC thawed and plated at 300,000 cells/well (quadruplicate) into ELISPOT plate, incubated overnight (medium alone; negative control) or stimulated with NY-ESO-1 overlapping peptides (a mixture of 43 15mer peptides, overlapping by 11aa, from JPT Peptide Technologies, Berlin). Shown are the mean±SEM of spots per well. Antibody response was measured by ELISA using recombinant NY-ESO-1 protein and serially diluted plasma samples.
*1 patient with unconfirmed PR; NC = not collected; na = not analyzable; nd = not detectable

- Tumor biopsy IHC staining showed that STS baseline and post treatment PD-L1 expression is low and restricted to immune cells and not on tumor cells (Table 5)
- Paired biopsies showed evidence of a possible increase of CD8 tumor infiltrating lymphocytes (TILs) on C+ A arm (Table 6a and Table 6b)

Table 5. Baseline and Induced PD-L1 Expression in Tumor Tissue

Pre-treatment biopsies		
	All patients (n=69)	
PDL1 + (score 0-3)	7/69 (10.1%) (max score 2)	
Paired pre/post-treatment biopsies		
	Atezo (n=8)	CMB305 + Atezo (n=6)
PDL1 + (score 0-3) pre	1/8 (score 1)	1/6 (score 1)
PDL1 + (score 0-3) post	0/8	2/6 (score 1)

Sections (4μm) were prepared from formalin-fixed, paraffin-embedded (FFPE) tumor blocks from pre-Tx and post-Tx biopsies. PD-L1/CD274 IHC was performed using an anti-human PD-L1 rabbit monoclonal antibody (Roche/Ventana, clone SP142). A normal tonsil tissue slide was included as control. Membranous PD-L1 expression was scored for the tumor cell (TC) and tumor infiltrating immune cells (IC) components as % PDL1-positive cells. Specimens were scored as IHC 0, 1, 2, or 3 if <1%, ≥ 1% but <5%, ≥ 5% but <10%, or ≥ 10% of cells per area were PD-L1 positive, respectively.
(Herbst RS et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014 Nov 27;515(7528):563-7.)

Table 6a. CD8 TILs in Baseline Biopsies (central tumor) – Arm A and Arm C+A

	Atezo (N=31)	COM305+Atezo (N=31)	All patients (N=62)
CD8 TIL (%)*	0.20 ± 0.10	0.30 ± 0.19	0.25 ± 0.11

* (mean±sem); CD8 (mAb clone C8/144B, Dako) IHC was performed on FFPE tumor sections (4μm) from pre-Tx or archival tumor biopsies, on a Ventana Benchmark XT using CC1 antigen retrieval and Ultraview (Ventana) detection technology. The central tumor (Cn) area was defined based on pathologist annotated HE staining pathology report. The CD8 TIL in Cn region of interest was quantified by automatic random subsampling of a minimum of 100 tiles and >35% of the region of interest. Shown are the percentages of tumor area stained positive for CD8 signal

Table 6b. Patients With an Increase of CD8 TILs From Baseline (paired biopsy, central tumor) in Arm A and Arm C+A

	Atezo (n=8)	CMB305 + Atezo (n=8)
# of Patients with Increased CD8 (fold of change)	3/8 (2.0, 2.6, 3.1)	4/8 (3.0, 6.6, 17.1, >50)

The CD8 TIL in central tumor (Cn) region was quantified in pre-Tx (baseline) and post-Tx biopsies.
A ≥2-fold increase from baseline is considered positive.

CONCLUSIONS

Interim analysis indicates that addition of CMB305 to atezolizumab may result in clinical efficacy improved over atezolizumab alone in NY-ESO-1+ STS patients with low/absent PD-L1.

Clinical

- Despite more advanced patients with worse prognostic factors were enrolled to the combination arm there were partial responses, higher disease control rate and a trend to a better PFS
- Overall survival data is immature for this interim analysis
- Addition of CMB305 to atezolizumab is well tolerated and no new safety signal was detected

Immunologic

- C+A combination induced a more robust anti-NY-ESO-1 immune response including stronger T cell induction than A alone, antibody induction (not seen on Arm A), faster immune response than CMB305 monotherapy (based on historic data comparison)
- Exploratory analysis found that induction of anti-NY-ESO-1 T cell and antibody IR may be associated with a better OS on C+A arm when compared to patients without induction of IR
- Baseline and on treatment PD-L1 expression is low in NY-ESO-1 STS and restricted to immune cells and not on tumor cells
- Tumor biopsies showed evidence of CD8 tumor infiltrating lymphocytes (TILs) with possibly increased infiltration on C+A combination

santchawla@sarcomaoncologycenter.com; chet.bohac@immunedesign.com