Public NY-ESO-1 Specific TCRs as Novel Biomarkers for Immune Monitoring of NY-ESO-1 Positive Cancer Patients

Poster #: P58

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ABSTRACT

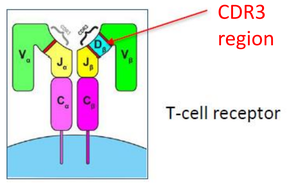
Background: T-cell clonotypes with T-cell receptors shared between patients (public TCRs [pTCR]) are involved in the immune response to chronic viral infections, however, their role in immune responses to cancer is largely unknown. We evaluated the association of NY-ESO-1 specific pTCR sequences with survival in solid tumor patients treated with LV305 or CMB305, which are active immunotherapies based on the dendritic cell targeting lentiviral vector platform ZVex®, expressing the cancer-testis antigen, NY-ESO-1.

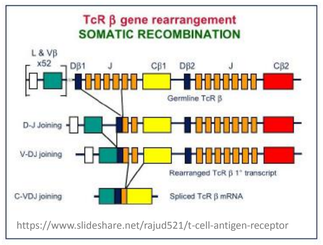
Methods: Peripheral blood mononuclear cells (PBMC) were collected before and after patients with NY-ESO-1 positive solid tumors, including soft tissue sarcomas, received therapy with dendritic cell targeting vaccine regimens LV305 (NCT02122861) or CMB305 (NCT0237125) (n=64). PBMC were subjected to deep sequencing to study the repertoire of the TCRVβ-CDR3 region.

Results: The TCR-Vβ CDR3 amino acid sequences of three NY-ESO-1 specific pTCR clones obtained through *in vitro* culture from a LV305 patient with a near complete response were fully conserved in 41/56 (73.2%) of LV305/CMB305 patients and 54% of 539 healthy blood donors. Induction of NY-ESO-1 pTCR on LV305 or CMB305 therapy (baseline negative to positive, or doubling of frequency) was observed in 31% of patients and was associated with a trend towards better overall survival. Querying TCR databases from multiple published clinical trials revealed NY-ESO-1 pTCR sequences in blood of patients with melanoma (6/13), renal cancer (1/3), and glioblastoma (6/13), and with a lower incidence in tumor biopsies. There is a trend of concordance between pTCR and ELISPOT.

Conclusion: We have identified NY-ESO-1 specific public TCRs in the PBMC of cancer patients undergoing active NY-ESO-1 targeting immunotherapy, as well as in healthy blood donors. In patients, the induction of pTCR appeared to be associated with better survival, whereas their presence in healthy blood donors may indicate frequent low-level baseline T-cell immunity against this cancer testis antigen. pTCR should be investigated as a prognostic or predictive biomarker of cancer immunotherapies targeting NY-ESO-1, and possibly other cancer-testis antigens.

BACKGROUND

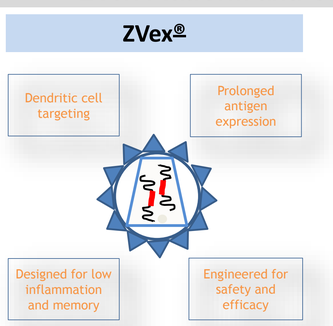




- Private TCRβ CDR3
  - Potential TCRβ CDR3 repertoire is ~5E11 for humans
  - approx. 3-4E6 realized in an individual*
- Public TCRβ CDR3
  - Shared between different individuals
  - Overlap 1.4E4 between individuals, HLA-independent
  - Originate from convergent evolution
  - May not require random nucleotide addition
- Public TCRs in Infectious Disease and Cancer
  - CMV, EBV, HIV
    - Benati et al., J Clin Invest. 2016
  - Melanoma, AML, breast cancer
    - Serana F et al, J Trans. Med 2009
    - Ochsenreither S et al, Cancer Immunol Immunother 2012
    - Munson DJ et al., PNAS 2016
  - NY-ESO-1 specific pTCR remains unreported

METHODS

ZVex Platform and Clinical Development

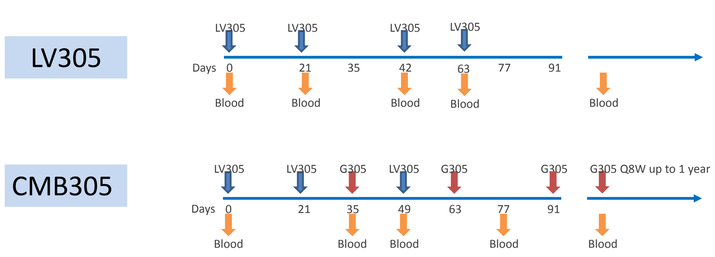


LV305:
ZVex/NY-ESO-1 (4x)

CMB305:
LV305 prime (3x) &
rec NY-ESO-1+GLA boost (4x)

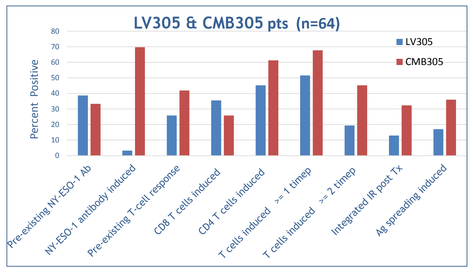
Two Ph1:
Soft tissue sarcoma
(Ovarian, NSCLC, Melanoma)

LV305 and CMB305 Clinical Trial Schema



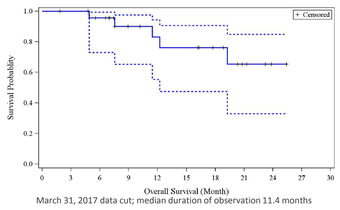
RESULTS

Immune Responses in LV305 and CMB305



NY-ESO-1 specific T cell and antibody responses induced by LV305 and CMB305:
T cell response was measured by ELISPOT; antibody response was measured by ELISA.
(Data presented at ASCO, 2017 by Pollack S.)

Clinical Responses in LV305 and CMB305



Standard Therapy for 2nd Line STS	
Study	OS
Pazopanib[1]	12.5 months
Eribulin[2]	13.5 months
Trabectedin[3]	12.4 months

[1] van def Graaf, et al., 2012, [2] Schoffski, P. et al, 2016, [3] Demetri, G. et al, 2016

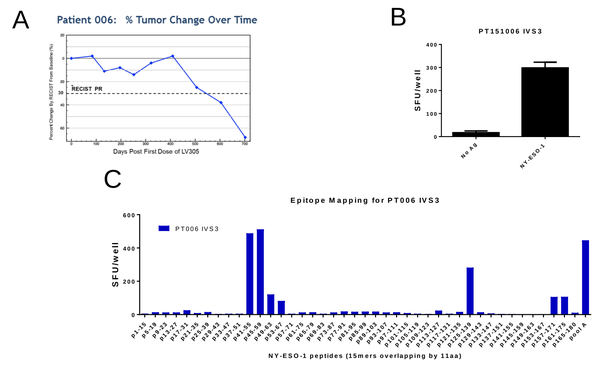
Standard Therapy for 2nd Line Synovial Sarcoma	
Study	OS
METASARC[1]	11.7 months

[1] Savina, et al., 2017 (synovial sarcoma)

OS compared favorably to historical data
-Data presented at ASCO, 2017 by Somaiah N.

Clinical Responses in LV305 (poster# P109 by Somaiah N et al. at SITC 2017)

Identification of NY-ESO-1 Specific pTCR from the Oligoclonal T-cell Culture from Near CR Patient



3 out of 5 top clones are public:
CASSLNRDYGYTF
CASSLNRDQPQHF
CASRLAGQETQYF

Shared TCRβ-CDR3 AA in Patients and Healthy Donors

Frequency in cancer and healthy donors

Three Public TCR (pTCR) sequences in PBMC	pTCR in pre-Tx PBMC	pTCR Induced
LV305	12/26	8/26
CMB305	15/29	9/29
Blood donors	289/539	na

Same CDR3 – different Vβ families

Patient ID	AminoAcid	V GeneName	D GeneName	J GeneName
PT006*	CASSLNRDQPQHF	TCRBV07-07	TCRBD01-01	TCRBJ01-05
PT016	CASSLNRDQPQHF	TCRBV07-09	TCRBD01-01	TCRBJ01-05
PT050	CASSLNRDQPQHF	TCRBV05-04	TCRBD02-01	TCRBJ01-05
PT119	CASSLNRDQPQHF	TCRBV07-08	TCRBD02-01	TCRBJ01-05

Few non-templated nucleotide additions

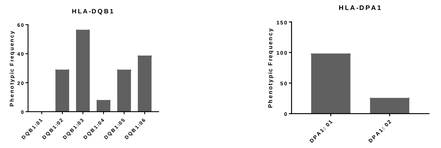
AminoAcid	CDR3 Length	V GeneName	D GeneName	J GeneName	V Deletion	N1 Insertion	D5 Deletion	D3 Deletion	N2 Insertion	J Deletion
CASSLNRDYGYTF	39nc	TCRBV07-08	TCRBD01-01	TCRBJ01-02	3	2	3	3	0	3
CASSLNRDQPQHF	39nc	TCRBV07-07	TCRBD01-01	TCRBJ01-05	3	2	3	3	2	7
CASRLAGQETQYF	39nc	TCRBV28-01	TCRBD02-01	TCRBJ02-05	6	0	3	3	0	2

HLA Analysis: Potential Class II Association

PT151006

PT151006		
HLA-A	*02:01	*24:02
HLA-B	*13:02P	*35:01
HLA-C	*04:01	*06:02
HLA-DRB1	*11:01	*13:01
HLA-DRB3	*02:02	-
HLA-DRB4	-	-
HLA-DRB5	-	-
HLA-DQB1	*03:01	*06:03P
HLA-DPB1	*04:01	-
HLA-DQA1	*01:03/10	*05:01:01G
HLA-DPA1	*01:03P	-

62 LV305 and CMB305 Patients



Detection of pTCR in TIL and Concordance between pTCR and ELISPOT

- Presence of pTCR in TIL
  - pTCR is detectable in the TIL of synovial sarcoma patient with near CR
  - Two NY-ESO-1 pTCR sequences were detected in the biopsy of a NY-ESO-1 positive MCC patient with CR, post 2x intratumoral treatment with TLR4 agonist G100
- Concordance of pTCR and ELISPOT (LV305 and CMB305 pts)
  - NY-ESO-1 pTCR assay detects 77.5% of ELISPOT positive patients
  - 57.1% of ELISPOT negative patients are positive in pTCR assay

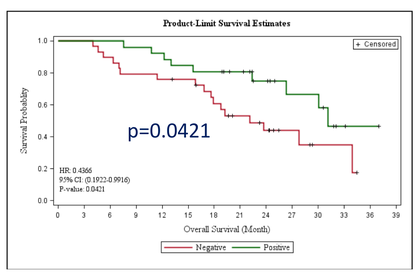
TCR-Vß CDR3: CASSLNRDQPQHF	PT151006 (SS, near CR post LV305)
Pre-Tx PBMC	0.0058%
Post-Tx PBMC	0.017%
TIL REP-PC12-04A1	0.000647%
TIL-PC12-04A1	0.002%
Fixed tumor	0.06%

	pTCR+	pTCR-	Total
ELISPOT+	31 (77.5%)	9 (22.5%)	40
ELISPOT-	8 (57.1%)	6 (42.9%)	14
Total	39	15	54

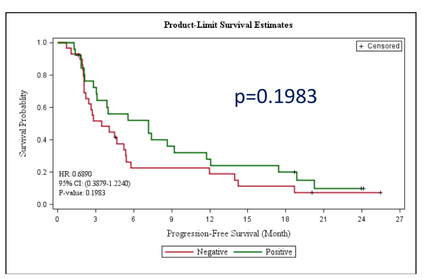
P=0.175, Fisher's exact test

Association between post-Tx pTCR and Clinical Responses

Overall Survival



Progression-free Survival



pTCR+: N=40; pTCR-: N=15

CONCLUSIONS

- NY-ESO-1 specific, public TCRβ-CDR3 sequences have been identified from a sarcoma patient with near complete response after LV305 therapy
- pTCR are shared by patients from different trials (LV305, CMB305, and G100) with different types of NY-ESO-1$^+$ cancers and detected in TIL
- Possibly HLA class 2 restricted
- Presence of pTCRs post-treatment with LV305/CMB305 is associated with improved clinical benefit in sarcoma and other cancer patients
- Potential use of NY-ESO-1 specific public TCRs as surrogate for ELISPOT in cancer vaccine trials?

IMMUNE DESIGN