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Vaccination of patients with advanced non-small cell lung cancer with an optimized hTERT cryptic peptide (Vx-001)

VAXON Biotech

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Abstract

Purpose: To evaluate the immunological and clinical efficacy of the optimized peptide TERT572Y (Vx-001) presented by HLA-A*0201 in patients with advanced non-small cell lung cancer (NSCLC).

Patients and methods: Twenty-two patients with residual (n=8) or progressive (n=14) advanced NSCLC following chemotherapy and/or radiotherapy received two subcutaneous injections of the optimized TERT572Y peptide followed by four injections of the native TERT572 peptide given every 3 weeks. Peptide-specific immune responses were monitored by Elispot assay and/or TERT572Y pentamer staining. Clinical outcome was compared with that of 22 case-matched historical control patients.

Results: Thirteen (59%) out of 22 patients completed the vaccination program. Adverse events (grade I) consisted primarily of local skin reactions. TERT572-specific CD8+ cells were detected in 16 (76.2%) out of 21 patients after the 2nd vaccination and 10 (90.9%) out of 11 patients after the 6th vaccination. Stable disease occurred in 8 (36.4%) patients with a median duration of 11.2 months. Patients with immunological response (n=16) had a significantly longer time to disease progression and overall survival than non-responders (n=5) (log-rank tests p=0.046 and p=0.012, respectively). The estimated median overall survival was 30.0 (range, 2.8-40.0) and 4.1 (range, 2.4-10.9) months for immunological responders and non-responders, respectively. Moreover, median overall survival was 30.6 months (95% CI:10.9-48.9) and 6.1 months (95% CI:4.4-7.8) for the vaccinated and case-matched historical control patients, respectively (p=0.074).

Conclusion: TERT572Y peptide vaccine is well tolerated and effective in eliciting a specific T-cell immunity which seems to be associated with prolonged patients' survival.

Introduction

Anti-tumor immunotherapy is mainly based on the activation of cytotoxic T lymphocytes (CTL) recognizing endogenously processed peptides derived from tumor antigens and presented at the cell surface in association with HLA class I molecules (HLA I). Dominant peptides exhibit high HLA I affinity and immunogenicity but most vaccines targeting dominant peptides gave relatively disappointing results in clinical studies due to the presence of tolerance. One simple way to break tolerance to tumor antigens is to use cryptic peptides. Indeed, we and others have shown that the T-cell repertoire specific for cryptic peptides partially or completely escapes tolerance mechanisms, suggesting that cryptic peptides would be good tumor vaccines provided they are rendered immunogenic. Cryptic peptides, which have low HLA-class I affinity and therefore are not immunogenic, have to be "optimized" by modifying their amino acid sequence to increase their HLA class I affinity thereby transforming them into high-affinity peptides capable of stimulating a specific T-cell response. We have previously developed and described such a method for optimizing cryptic peptides presented in association with HLA-A*0201.

The TElomerase Reverse Transcriptase subunit (TERT) is a promising target for cancer immunotherapy. Indeed, it is overexpressed in many human tumors and is therefore considered as a universal tumor antigen whereas most normal human tissues do not express TERT. TERT is overexpressed in more than 85% of NSCLC, and is associated with poor prognosis. TERT has recently been targeted in many tumors including NSCLC.

TERT572Y (Vx-001) is an HLA-A*0201-associated optimized cryptic peptide derived from TERT. TERT572Y was able to induce tumor immunity but not autoimmunity in HLA-A*0201 transgenic mice. *In vitro*, TERT572Y stimulated antitumor CTLs from both healthy donors and prostate cancer patients; CTLs killed TERT-expressing tumor cells but not TERT-expressing normal cells. Vx-001 has recently been tested in a phase I clinical study in 19 patients with advanced cancer. Vx-001 was safe (only grade I/II toxicity was observed) and immunogenic. TERT572 specific immune response was detected in 13 out of 14 evaluable patients. As part of an expanded safety, immunological and clinical evaluation program, 22 patients with advanced non-small cell lung cancer (NSCLC) were vaccinated with Vx-001 and their clinical outcome was compared with that of 22 case matched historical control patients with similar disease and treatment characteristics. Here we report that in vaccinated patients, the vaccine was safe and immunogenic, generating functional CTLs which recognize the native TERT572 peptide. More importantly, patients with early developed immunological response had a significantly better overall survival than those without an immunological response.

Vaccination protocol

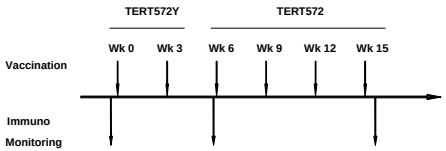
Objectives:

Primary : Safety and immunogenicity of Vx-001 vaccine

Secondary : Time to progression (TPP), overall survival and survival

Patients: HLA-A*0201 expressing NSCLC

Protocol:



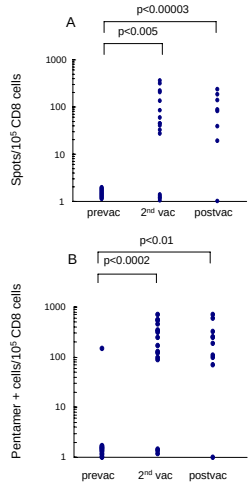
Patients demographics

Patient's characteristics	N (%) Vaccine	N (%) Control	p- value
Number of patients	22	22	
Age (years)			
median	58.5	62.0	0.985
min-max	48-76	47-72	
Sex			
male	17 (77.3)	19 (86.4)	0.434
female	5 (22.7)	3 (13.6)	
Histology			
Squamous cell	6 (27.3)	7 (31.8)	0.573
Adenocarcinoma	9 (40.9)	12 (54.5)	
Large cell	3 (13.6)	1 (4.5)	
Poor differentiated	4 (18.2)	2 (9.1)	
Stage			
III	6 (27.3)	5 (22.7)	0.728
IV	16 (72.7)	17 (77.3)	
Performance status (WHO)			
0	12 (54.5)	13 (59.1)	0.948
1	8 (36.4)	7 (31.8)	
2	2 (9.1)	2 (9.1)	
Line of treatment			
2nd	12 (54.5)	13 (59.1)	0.761
≥3rd	10 (45.5)	9 (40.9)	
Clinical status before vaccination			
SD	8 (36.4)	8 (36.4)	
PD	14 (63.6)	14 (63.6)	

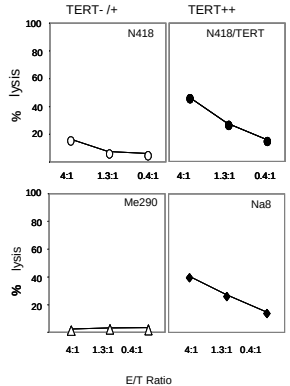
Safety in vaccinated patients

	N (%) of patients		
	Grade I	Grade II	Grade III/IV
Local skin reaction	8 (36.3%)	No	No
Anemia	3 (13.6%)	No	No
Neutropenia	1 (4.5%)	No	No
Thrombo cytopenia	3 (13.6%)	No	No
Fever	3 (13.6%)	No	No
Lumbago	2 (9.1%)	No	No
Fatigue	2 (9.1%)	1 (4.5%)	No
Nausea	No	1 (4.5%)	No

Immune response in vaccinated patients



TERT572 specific T cells detected in the blood of vaccinated patients by ELISpot assay(A) and Pentamer staining (B)

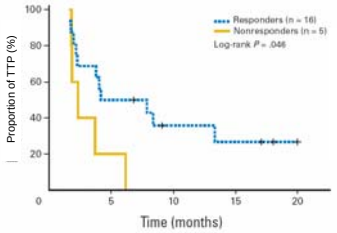


Killing of TERT expressing tumor cells by T cells induced in vaccinated patients

Clinical response of vaccinated patients

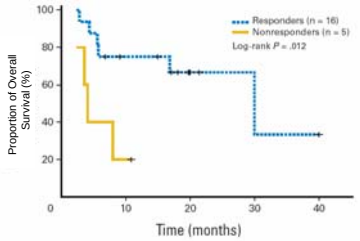
Correlation Between TTP and Early Immune Response

Median TTP = 4.2 vs 2.3 months



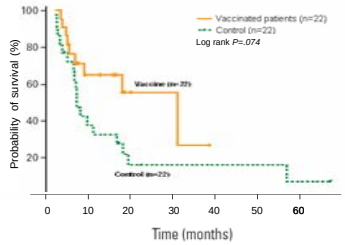
Correlation Between Overall Survival and Early Immune Response

Median Survival = 30 vs 4.1 months



Survival of Vaccinated Patients and Matched Controls

Median Survival = 30.6 vs 6.1 months



Conclusions

- Vx-001 was safe and immunogenic in almost all vaccinated patients.
- Patients who developed early immune response had a significantly better clinical outcome, TTP and survival than patients who didn't. This difference was observed between early immune responders and non-responders, despite similar stable disease patient ratio at inclusion.
- Based on these encouraging results, we are planning a controlled multicentric study to evaluate the clinical benefit of Vx-001 vaccination in NSCLC patients.

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