

A Phase 1 Trial of Intra-lymph Node Administration of a Novel Immunotherapeutic Regimen (MKC1106-MT) in Patients with Advanced Melanoma

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ABSTRACT

Background: MKC1106-MT is an immunotherapeutic consisting of recombinant plasmid pMEL-TYR containing Melan-A (MEL) and tyrosinase (TYR) antigen fragments and 2 peptide (E-MEL; E-TYR) analogs corresponding to an HLA-A*0201-restricted epitopes from each. **Methods:** Patients received a prime-boost with a fixed priming of the plasmid (2,400 µg/dose) via ultrasound guided injections into inguinal or axillary nodes on days 1, 4, 15 and 18 followed by peptide on days 29 and 32; cycles were repeated every 43 days. Either 100 mg/dose or 300 mg/dose of each peptide were given. Patients were HLA*0201+, and had stage IIIB/C or IV melanoma positive for MEL and TYR. Clinical evaluations occurred at baseline and the end of each cycle. Patients without disease progression received up to 8 cycles of treatment. Immune responses using PBMCs were measured days 29 and 39 of each cycle by MHC tetramer and IFN gamma ELISPOT for MEL and TYR epitopes. **Results:** 18 pts were enrolled: 7 in the low dose and 11 in the high dose peptide cohort. Therapy was well tolerated, with no DLTs. No differences in safety or immune responses were seen between the 2 cohorts. The most frequent treatment-related AEs were: fatigue (grade 1-2), chills (grade 1-2) and brief pain at injected sites (grade 1-2). At 1 year, 4 pts, all with nodal metastases showed ORs (1 CR, 2 PRs and 1 SD by RECIST) and all exhibited high baseline levels of MEL T cells. Among two biopsies of regressing lesions one had a dense infiltration of CD8+ T cells with ~1% TILs being specific for the MEL epitope targeted by MKC1106-MT. **Conclusions:** Repeated intra-lymph node administration of MKC1106-MT is feasible, safe, induces objective tumor regression and correlates with baseline immunity to MEL.

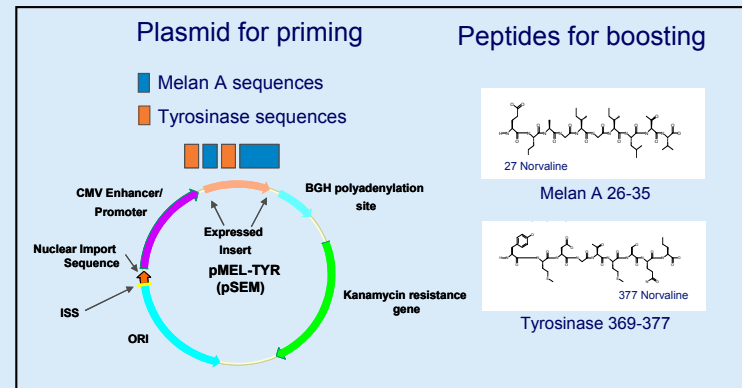
% tetramer MEL*total CD8* at baseline (median; range)	No OR	OR
Detectable	4/14 pts (0.25; 0.2-0.31)	4/4 (0.2; 0.11-0.23)
Low/None detectable	10/14 pts (0.06; 0-0.08)	0/4 pts

BACKGROUND

Investigational drug regimen

- A recombinant plasmid expressing fragments of two antigens, Melan A and tyrosinase (Fig.1), formulated as a sterile solution
- Two peptide analogues: Melan A 26-35 and tyrosinase 369-377 CTL epitopes, as sterile solution from lyophilized powders

Diagram of active pharmaceutical ingredients



CLINICAL TRIAL DESIGN

Primary objective

- Assess safety and tolerability of MKC1106-MT regimen

Secondary objectives

- Assess immune response* to Melan A and tyrosinase by tetramer and ELISPOT assays
- Study pMEL-TYR plasmid persistence and systemic accumulation
- To determine antigen (Melan A, tyrosinase and β2-microglobulin) expression in the tumor
- To assess preliminary evidence of clinical response

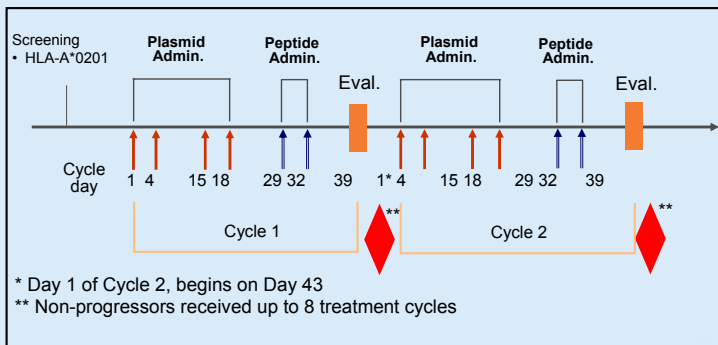
*Immune response defined as ≥ 2X increase in tetramer+ CD8 T cells over baseline

Open-label, multi-center design

Advanced, unresectable melanoma (stage IIIB,c or IV)	HLA- A*0201+	N=7 Low peptide dose cohort	
		100µg Melan A	100µg tyrosinase
Fixed dose plasmid (1,200µg bilaterally)	N=11 High peptide dose cohort	300µg Melan A	300µg tyrosinase
		Fixed dose plasmid (1,200µg bilaterally)	

Drug administration

- Bilateral bolus injection directly into inguinal lymph nodes
- Plasmid DNA-priming followed by peptide-boost



TRIAL RESULTS

Summary of patient demographics

Characteristics	Low dose	High dose	Overall
Number of Subjects	7	11	18
Mean age (years)	60.1 (46-74)	64.5 (47-81)	62.8 (46-81)
18 to 64	4	6	10
65 +	3	5	8
Male	6	9	15
Female	1	2	3
ECOG Performance Status			
0	3	9	12
1	4	2	6
Prior Cancer Therapy			
Chemotherapy (1-2 regimens)	3	4	7
Immunotherapy (1-4 regimens)	4	7	11
Radiation (2 regimens)	0	1	1

Safety summary

- The most frequently reported Treatment-Emergent Adverse Events were fatigue and chills (Grade 1 or 2), with 1 Dose Limiting Toxicity (Grade 3 fatigue).
- No difference in safety profile was observed between the low and high dose peptide cohorts.

Summary of integrated clinical and immune Data

Pts	Disease stage	Prior Therapies	Dose cohort	Treatment duration (Cycles)	RECIST (v1.0)†	Surgically Unresectable Stage IIIC, IV (M1a)			
						%Tetramer+ T cells ^a Baseline		%Tetramer+ T cells Peak	
						Mel	Tyr	Mel	Tyr
0001	IV (M1a)	Tremelimumab	Low	8	PR	0.23	0.04	0.20	0.07
0002	IV (M1a)	IFN	Low	2	PD	0	0	0.33 ↑	0.13 ↑
0006	IV (M1a)	IFN, DTIC, IL-2, Vindesine, Cisplatin,	High	8	PR*	0.17	0	0.85 ↑	0.30 ↑
0010	IIIC	IFN	High	2	SD**	0.06	0.03	0.08	0.05
0020	IV (M1a)	n/a	High	9	PR	0.11	0	0.87 ↑	0.41 ↑
0028	IV (M1a)	IFN, Carbo/Taxol	High	2	PD	0.07	0	0.54 ↑	0.06 ↑
0029	IV (M1a)	n/a	High	8	SD	0.23	0.03	0.40	0.05

† Best Overall Response
^a Lower limit of detection (LLD) is 0.03 % Tetramer+ CD8+ T cells / total CD8+ T cells; in blue, values at baseline > 3xLLD;
 * Initially reported as unconfirmed CR for cycle 7 as scans from subsequent scans were not yet available. Detailed clinical response assessment shown in later section.
 ** Stable disease for 2 cycles.

Pts	Disease stage	Dose cohort	Treatment duration (Cycles)	RECIST (v1.0)†	Surgically Unresectable Stage IV (M1b,c)			
					%Tetramer+ T cells ^a Baseline		%Tetramer+ T cells Peak	
					Mel	Tyr	Mel	Tyr
0003	IV (M1c)	Low	1	PD	0.04	0	0.10 ↑	0
0005	IV (M1c)	Low	0	PD	0.07	0.06	ND	ND
0008	IV (M1c)	Low	0	PD	0.20	0.04	ND	ND
0011	IV (M1c)	Low	0	PD	0.08	0	ND	ND
0015	IV (M1c)	Low	0	PD	0.04	0.07	0.10 ↑	0.04
0017	IV (M1b)	High	0	PD	0.20	0.03	ND	ND
0021	IV (M1c)	High	1	PD	0.31	0	0.39	0
0022	IV (M1c)	High	2	PD	0.07	0.32	0.11	0.77 ↑
0027	IV (M1c)	High	1	PD	0.30	0	0.64 ↑	0.13 ↑
0033	IV (M1c)	High	2	PD	0.06	0	0.15 ↑	0.03
0034	IV (M1b)	High	2	SD*	0.08	0	0.15	0

† Best Overall Response
^a Lower limit of detection (LLD) is 0.03 % Tetramer+ CD8+ T cells / total CD8+ T cells; in blue values at baseline > 3xLLD
 * Stable disease for 2 cycles.

Patient 0001 – Objective Tumor Response by Cycle (RECIST)

Cycle	Target Lesion	Non-Target Lesion	Overall
1	SD	IA*	SD
2	SD	SD	SD
3	SD	SD	SD
4	SD	SD	SD
5	SD	SD	SD
6	PR	SD	PR
7	PR	SD	PR
8	PR	SD	PR

* IA – Incomplete Assessment

Patient 0006 – Objective Tumor Response by Cycle (RECIST)

Cycle	Target Lesion	Non-Target Lesion	Overall
1	SD	none	SD
2	SD	none	SD
3	PR	none	PR
4	ND	none	ND
5	ND	none	ND
6	IA	none	IA
7	CR	none	CR*
8	IA	none	IA

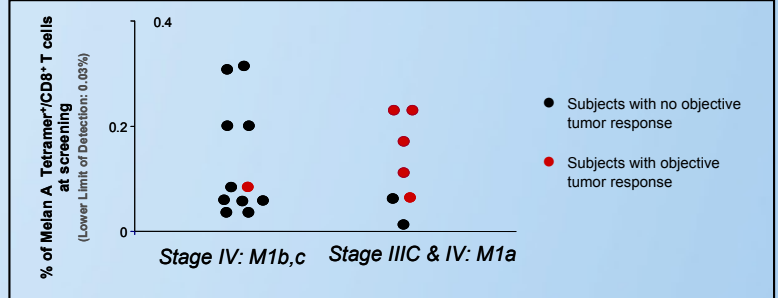
*Unconfirmed CR (confirmed PR) due to incomplete assessment at Cycle 8

Biopsies of regressing lesions in cycles 7 had a dense infiltration of CD8+ T cells with ~1% TILs being specific for the Melan A epitope

Patient 0020 – Objective Tumor Response by Cycle (RECIST)

Cycle	Target Lesion	Non-Target lesion	Overall
1	SD	SD	SD
2	SD	CR	SD
3	SD	CR	SD
4	SD	SD	SD
5	PR	CR	PR
6	SD	CR	SD
7	PR	CR	PR
8	PR	CR	PR
9	PR	PD	PD

Baseline immunity and clinical outcome



CONCLUSIONS

- Repeat intra-lymph node administration of the MKC1106-MT regimen was well-tolerated and no difference in safety profile was observed between the low and high dose peptide cohorts.
- Immunologic response, as measured by the tetramer assay in PBMC to either the Melan A or tyrosinase antigens, was achieved in 50% of all subjects.
- Plasmid pMEL-TYR levels were small or not detectable in most subjects over the course of treatment, indicating no systemic accumulation.
- Tumor objective response assessed by RECIST was achieved in 6 subjects: 3 PR and 3 SD. Overall, 4 subjects continued treatment through 8 cycles with 1 subject on study for 9 cycles (> 1year).
- All 4 subjects with tumor objective response and treated for ≥ 8 cycles had lymphatic disease and presence of Melan A specific T cells at baseline, suggesting such subjects are likely to benefit from this treatment.