

A phase I/II study of a multivalent dendritic cell vaccine in patients with metastatic melanoma.

I. Gorin¹, M. Prince², J. Grob³, M-T. Leccia⁴, T. Lesimple⁵, E. Ferrière⁶, N. Bercovici⁶, E. Tartour⁷, R. Taylor⁶, C. Robert⁸

¹ Hôpital Tarnier-Cochin, Paris, France ; ² Peter MacCallum Cancer Centre, East Melbourne, Australia ; ³ Hôpital Ste Marguerite, Marseille, France ;

⁴ Hôpital Michallon, Grenoble, France ; ⁵ Centre Eugène Marquis, Rennes, France ; ⁶ IDM S.A., Paris, France ;

⁷ Hôpital Européen Georges Pompidou, Paris, France ; ⁸ Institut Gustave Roussy, Villejuif, France.

INTRODUCTION

Melanoma: Definition and Incidence

◆ Most serious form of skin cancer that arises in melanocytes.

◆ Accounts for about 5% of all skin cancer cases, but causes 70% of skin cancer-related deaths.

◆ Melanoma is the 7th most frequent cancer in US. Incidence is about 54 000 new cases per year in US (Ref: NCI ; www.cancer.gov) and 60 000 in Europe (Ref: Ferlay et al, 2001) and is increasing worldwide.

Rationale for Dendritic Cells (DCs) loaded vaccine in melanoma patients

◆ DCs are the most potent antigen presenting cells that activate specific T cells, inducing cytotoxicity against tumour cells and memory immune response.

◆ DCs loaded with antigen *ex vivo* may induce an effective tumor specific immune response.

◆ Cell lysate made from three melanoma cell lines from different disease stages is expected to present multiple specific known and unknown tumour antigens that may prevent tumor escape.

◆ DCs are attractive adjuvants for vaccination studies in cancer.

1 Uvidem® Clinical Study

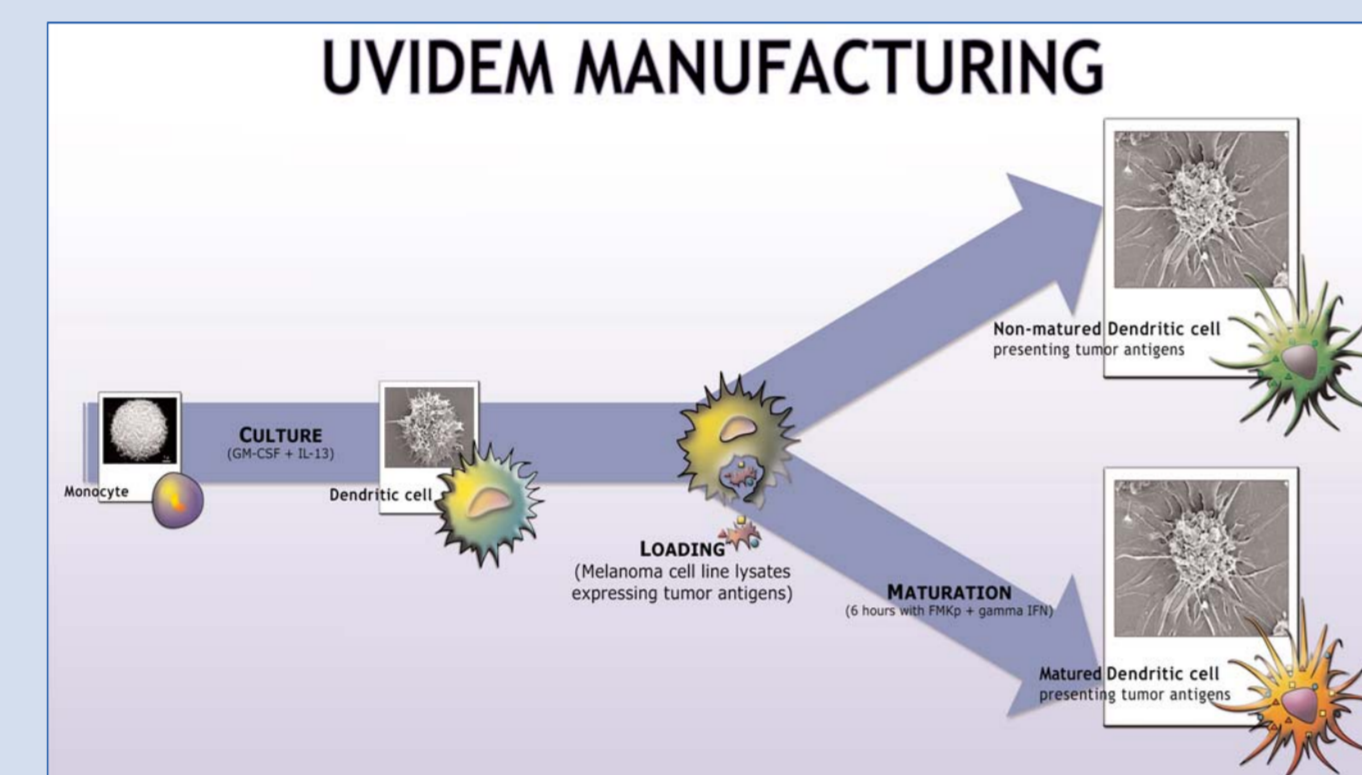
In a phase I/II study, stage IV metastatic melanoma patients were treated with either matured or non matured autologous monocyte-derived DCs loaded *ex vivo* with lysate produced from three allogeneic melanoma tumor cell lines (M44, Colo829 and SK-MEL-28).

Objectives of the clinical study were:

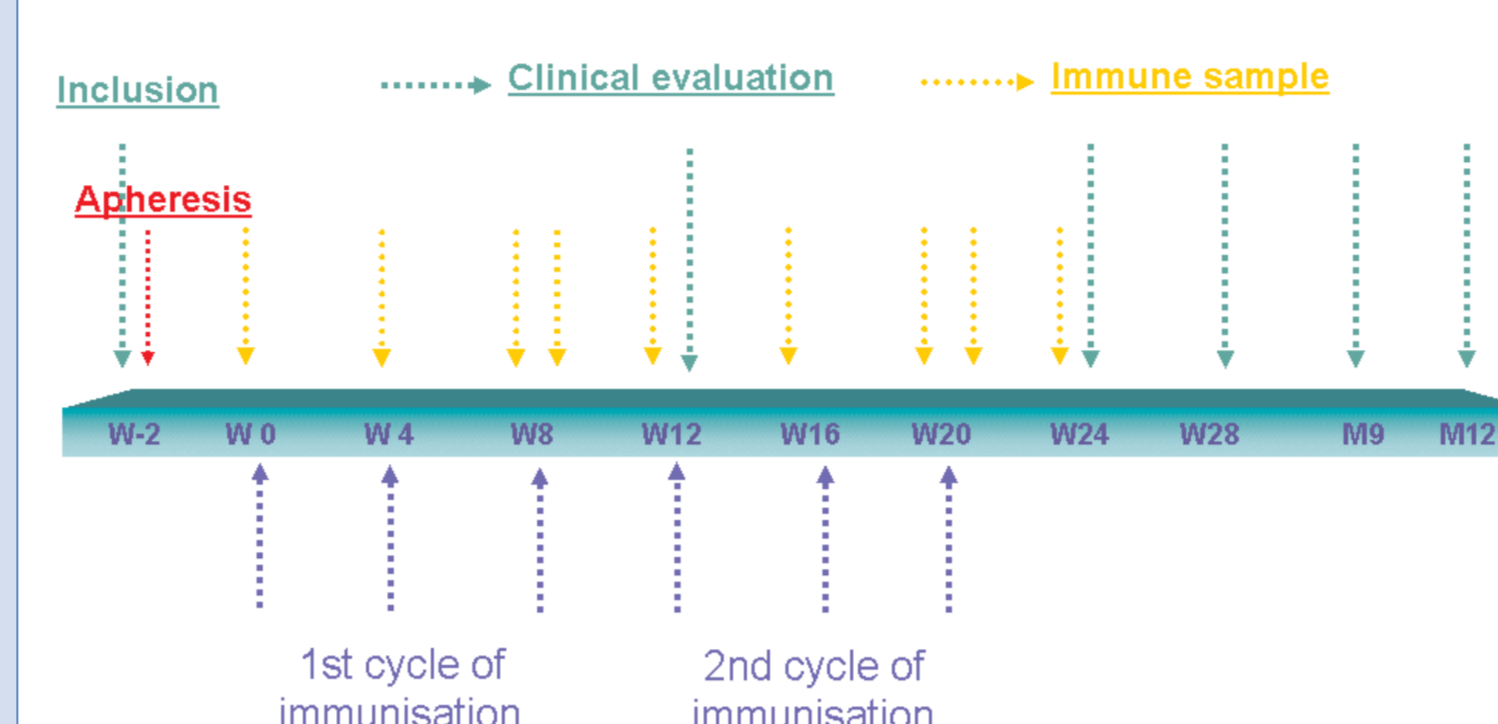
◆ To assess the safety of immunisations with lysate pulsed DCs

◆ To compare the immune response rate between patients immunized with loaded DCs or matured loaded DCs

◆ To assess the clinical activity of UVIDEM



Treatment and Patient Follow-up Schedule



- Doses :**
- ◆ Number of doses injected n=194
 - ◆ Average number of cells per immunization: 25.2 x 10⁶ DC (SD=11.1 X 10⁶)
 - ◆ Average purity: 91.85 % (SD=8.2 %)
 - ◆ Average viability: 80.28 % (SD=12.7 %)
- Route & Treatment Schedule :**
- ◆ Two cycles of 3 immunizations with monthly sub-cutaneous (2) and intra-dermal (4) injections
- Patient Follow-up:**
- ◆ Clinical evaluation with tumors evaluation by appropriate scan / X-rays at W0, W12 and W24
 - ◆ Immune sample (50 ml blood or partial apheresis) for immune-monitoring by ELISpot assay for IFN-γ secretion and proliferation assay

2 Patients Characteristics

Major Patient eligibility criteria

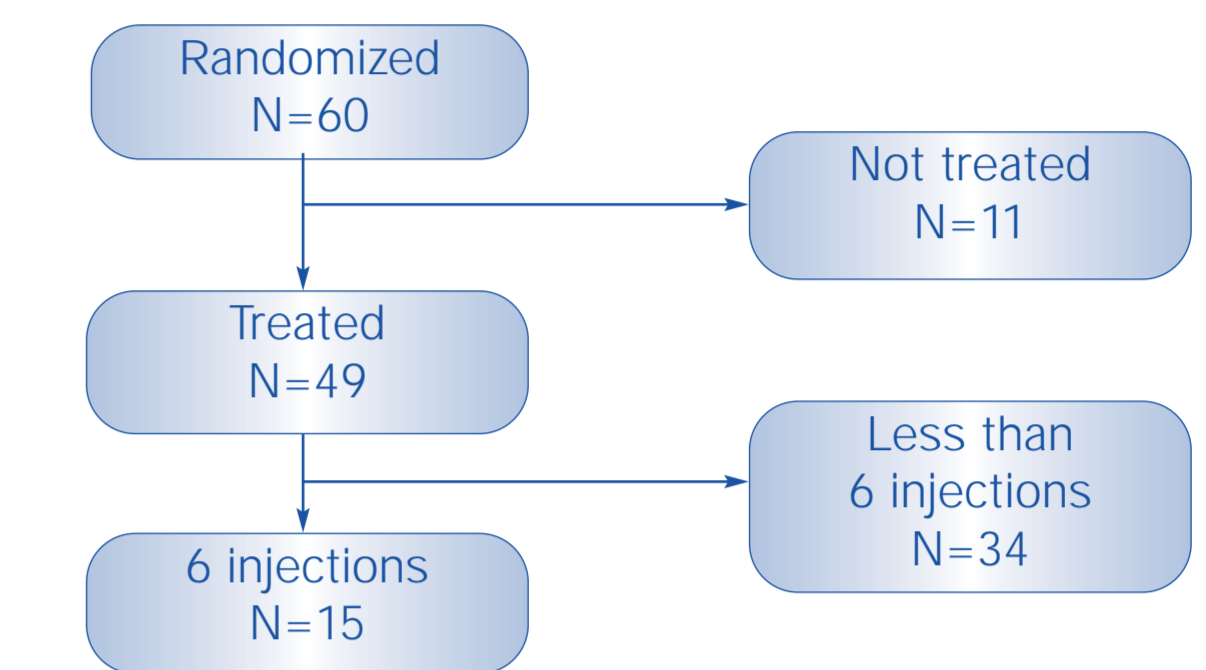
Inclusion criteria:

- ◆ Patient with a histologically proven malignant cutaneous melanoma stage IV with measurable lesions
- ◆ Patient without prior chemotherapy, or after a first line of chemotherapy.
- ◆ Prior immunotherapy permitted (except for vaccination with one or several melanoma antigens).
- ◆ Life expectancy > 6 months

Exclusion criteria:

- ◆ Cerebral or bone metastasis
- ◆ Bone marrow graft, splenectomy
- ◆ History of autoimmune disease or active autoimmune disease
- ◆ Radiotherapy or chronic systemic immunosuppressive treatment
- ◆ Positive serology (HIV, HTLV, Hep B and C)
- ◆ Contraindication to apheresis

- ◆ 12 centres : 10 in France and 2 in Australia, were involved in this study.
- ◆ 60 patients included: 30 patients in each treatment arm.



Treated Patient Characteristics

Demographics of patients included and treated with at least one dose		
N		49
Age		57 (30 - 77)
Gender	Male:	61% (30 pts)
	Female:	39% (19 pts)
ECOG (Performance Status)	ECOG 0:	86% (42 pts)
	ECOG 1:	14% (7 pts)
Visceral (liver, lung) involvement	Lung:	58% (25 pts)
	Liver:	42% (18 pts)
LDH (Average)		490 U/L
Number of lesions	<5 lesions:	25% (17 pts)
	>5 lesions:	65% (31 pts)
Prior Treatment with Chemotherapy	0 line:	35% (17 pts)
	>1 line:	65% (32 pts)

3 Clinical Study Results

Safety Results

- ◆ A total of 472 AEs were reported in 52 patients (8 patients had none)
- ◆ 24 SAEs were reported in 22 patients. No SAE related to the product or the protocol
- ◆ Most AE mild or moderate (Grade I+II =87%)
- ◆ Most frequent AE (classified by Organ System) were:
 - ◆ General disorders and administration site conditions (38%)
 - ◆ Musculoskeletal and connective tissue disorders (12%)
 - ◆ Gastrointestinal disorders (12%)
 - ◆ Nervous system disorders (10%)
- ◆ Most frequent AE related to treatment were:
 - ◆ Injection site erythema (27%)
 - ◆ Injection site pain (5%)
 - ◆ Pyrexia (5%)
 - ◆ Injection site pruritus (4%)
 - ◆ Fatigue (4%)
 - ◆ Influenza like illness (4%)
 - ◆ Injection site induration (4%)
- ➔ only 2/182 related adverse events were >Grade II: none were Gr IV

Clinical Responses

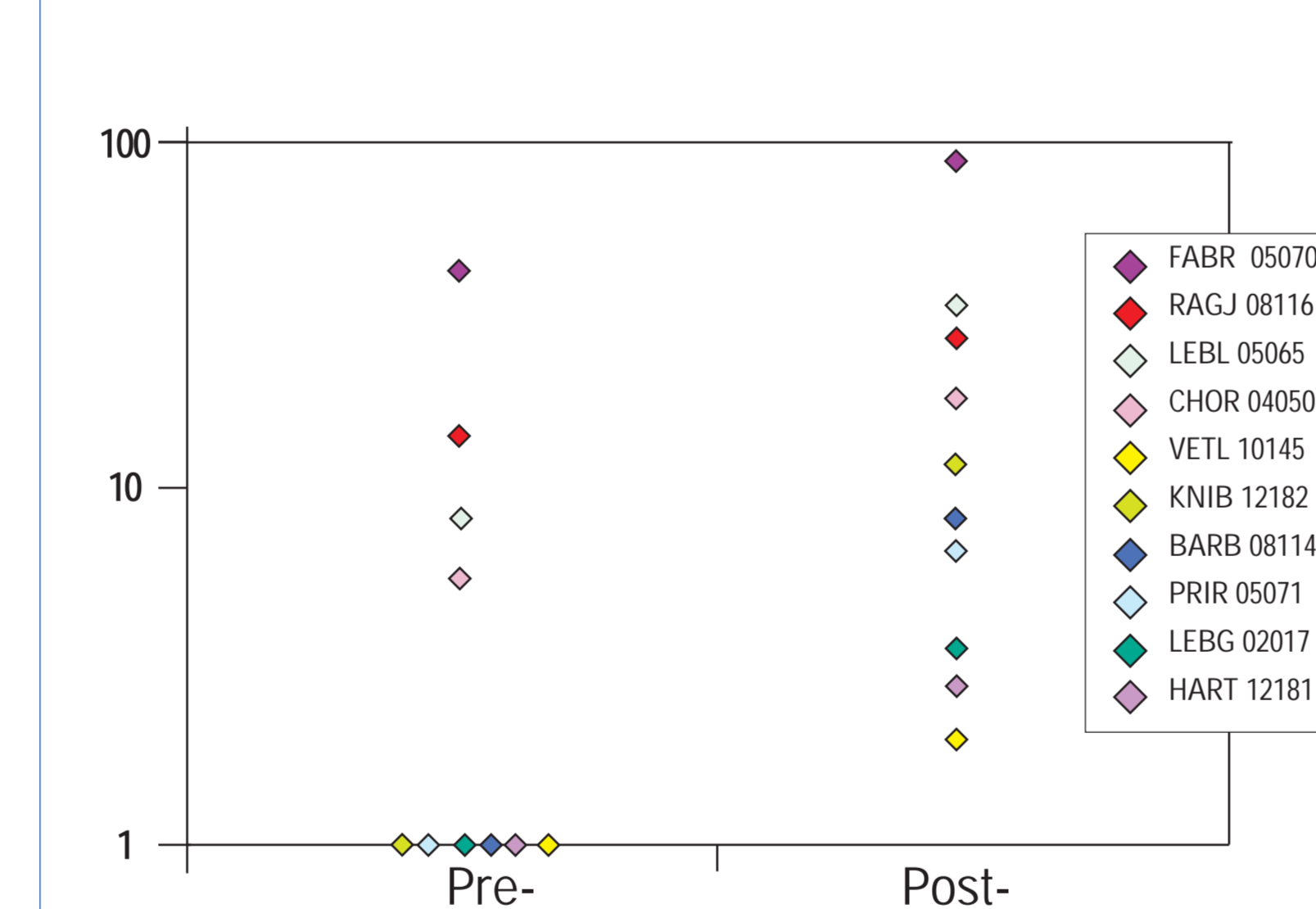
	Total treated population N=49	Immune responders N=14	Non immune responders (+ non analyzed patients) N=35	P (Fischer)
Best response according to RECIST criteria	45 PD (91%) 4 SD (9%)	10 PD (72%) 4 SD (28%)	35 PD (100%)	0.0002
Disease stabilization	10 (20%)	8 (57%)	2 (5%)	
No Disease Stabilization	39 (80%)	6 (43%)	33 (95%)	

- ◆ Some stabilizations occurred late, after initial progression on study
- ◆ Disease stabilization in 10 patients (20% of the treated population)
- ◆ 8 out of the 14 immune responders (57%) had a stabilization of their disease
- ◆ 100% of the patients who had a stabilization received 6 injections

Immune Responses

- ◆ Vaccine specific T cells immune response of patients were evaluated by Elispot assay for IFN-γ secretion and proliferation assay, before and at different time-points post vaccination.

T-cell proliferation to melanoma cell line-derived lysate

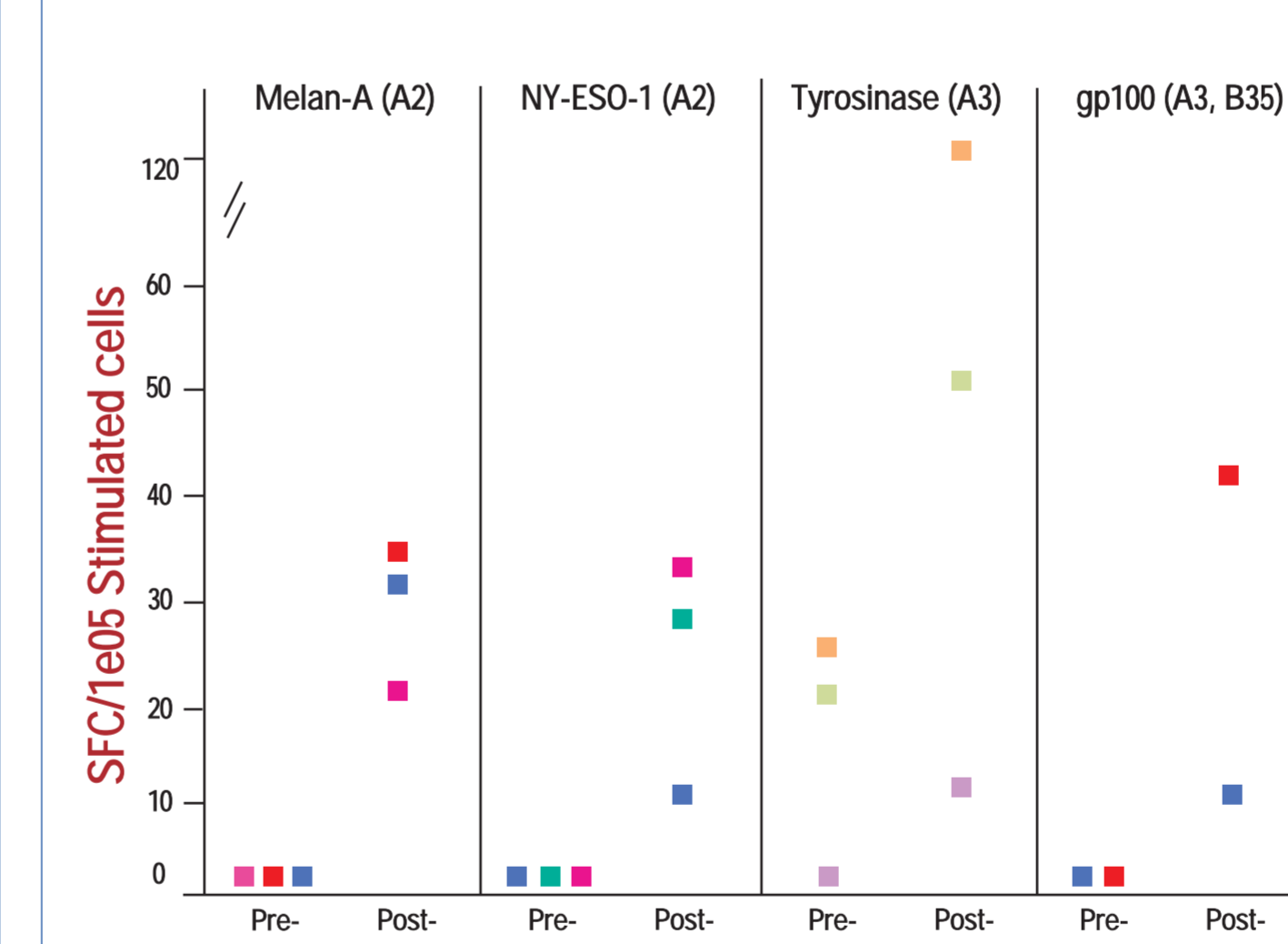


- ➔ Results are expressed as a stimulation index (SI = mean cpm [PBMC + Ag]/ mean cpm [PBMC]).
- ➔ Positivity of the IR determined with a rank test (p<0.05).
- ➔ Responding patients have a significantly increased response over the baseline (p<0.05, rank test).
- ➔ Each color represents a different patient. 10 patients responding to the Mel-201 lysate are shown.

- ➔ 77% of patients (10/13) receiving 6 vaccinations and evaluable for immune response showed appearance or increase of immune response against vaccine antigens after treatment.
- ➔ The rate of immune response is significantly higher in patients who received 6 injections compared to those who received less than 6 injections

	Total # of patients analyzed	Responding/Non Responding	Immune response rate	P (Fisher)
	40	14 R 26 non-R	35%	p= 0.0002
Patients with less than 6 injections analyzed	27	4 R 23 non-R	15%	
Patients with 6 injections analyzed	13	10 R 3 non-R	77%	

IFN-γ secretion (Elispot assay after restimulation) to MHC-Class-I-restricted TAA-derived peptides



- ➔ Results are expressed as Spot Forming Cells (SFC) among 1e05 stimulated cells.
- ➔ Positivity of the IR determined with a student test (p<0.05). Responding patients have > 2 fold increased response over baseline.
- ➔ Each color represents a different patient. 7 patients responding to at least 1 TAA-derived peptide are shown. 3 patients responded both to lysate and peptides (■, ■, ■)

CONCLUSIONS

According to protocol objectives:

- ◆ Treatment is feasible
- ◆ Treatment is well tolerated: most AEs were mild and not related to treatment
- ◆ Treatment induced an immune response in some patients, not significantly associated with matured or non matured dendritic cells
- ◆ No Complete or Partial Response according to RECIST criteria but disease stabilization in 10 patients

Other conclusions:

- ◆ There was a correlation between number of doses injected and immune response
- ◆ 77% of patients (10/13) receiving 6 vaccinations and evaluable for immune response showed appearance or increase of immune response against vaccine antigens after treatment
- ◆ Vaccine approaches may have a delayed effect

Next steps:

- ➔ Test the approach in adjuvant setting and/or in less advanced patients (more immunocompetent and a better life expectancy)
- ➔ Schedule doses closer together to increase likelihood that all planned doses will be completed

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