

A Phase III Multi-institutional Randomized Study of Immunization with gp100:209-217(210M) Peptide Followed by High Dose IL-2 vs High Dose IL-2 Alone in Patients With Metastatic Melanoma

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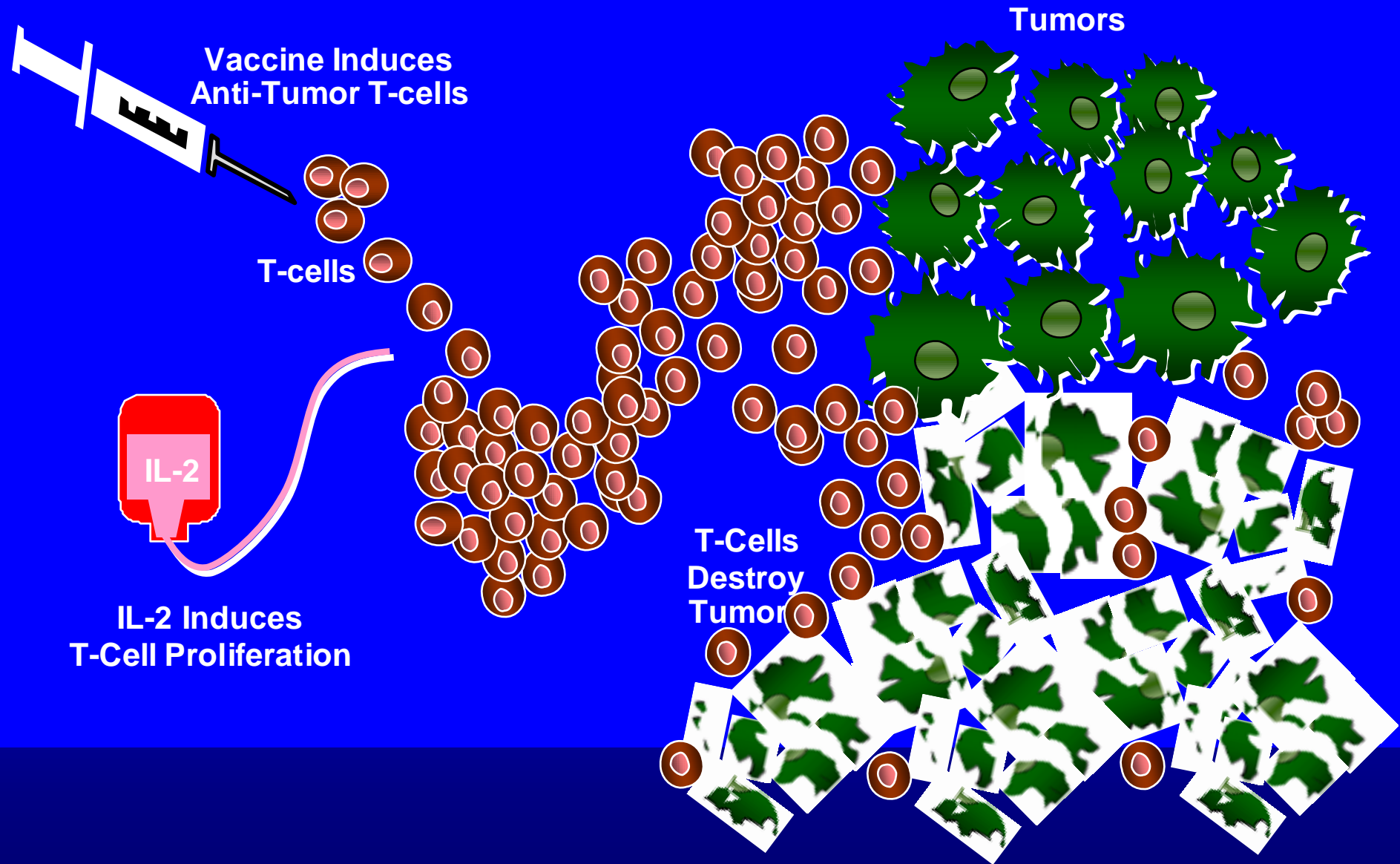
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Disclosures

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Rationale: Vaccine + IL-2 Induces Tumor Destruction



Background

Treatment of Patients with Metastatic Melanoma

- High-Dose IL-2 alone (600-720K) RR: 16% (6% CR).¹
- Melanoma vaccines RR: 3% (n=422).²
- gp100 209-217 (210M) in Montanide ISA 51: RR 0/32.²

1. Atkins M.B., et. al., J Clin Oncol 17: 2105-2116, 1999.
2. Rosenberg S.A., et. al., Nature Medicine 10: 909-915, 2004.

Background

Treatment of Patients with Metastatic Melanoma

- gp100 209-217 (210M) in Montanide ISA 51 + HD IL-2 (720K) every 3 weeks, RR 42% (13/31).¹
- gp100 209-217 (210M) in Montanide ISA 51 every 3 weeks + HD IL-2 (600K) on a variable schedule.²

Trial 1 (IL-2 C1 and C2 only) RR 23.8 % (n=42)

Trial 2 (IL-2 C3 and C4 only) RR 12.5 % (n=40)

Trial 3 (IL-2 C1 through C4) RR 12.8 % (n=39)

- Retrospective results Surgery Branch: HD IL-2 alone (n=305) RR 12.8 %; gp100 + HD IL-2 (n=49) RR 25.0 %.³

1. Rosenberg S.A., et. al., Nature Medicine 4: 321-327, 1998.

2. Sosman J.A., et. al., J Clin Oncol 26: 2292-2298, 2008.

3. Smith F.O., et. Al., Clin Cancer Res 14:5610-5618, 2008.

Objectives of Study

- Primary
 - Compare RR of HD IL-2 with and without gp100 vaccine.
- Secondary
 - Evaluate toxicity.
 - Compare disease and progression free survival.
 - Immunologic monitoring (PBL and serum)
 - QOL measurements (before and after 2 cycles of treatment)

Study Design

- Prospective, randomized (1:1), multi-institutional.
- Stratified for cutaneous / SQ disease only vs. all other.
- Arm A: HD IL-2 (720K) IV q 8hrs, max 12 doses, repeated every 3 weeks.
- Arm B: gp100 209-217 (210M) in Montanide ISA 51 SQ and HD IL-2 as in Arm A, starting day after vaccine.
- Response assessment (WHO criteria) after 2 cycles of treatment.
- Re-treatment with 2 cycles when disease stable.
- IL-2 obtained commercially.
- gp100 and Montanide provided by CTEP, NCI (IND holder).

Statistical Design

- Assume IL-2 RR 15% and IL-2 plus gp100 RR 35%.
- Need 83 patients per arm to detect RR difference with overall $\alpha = 0.05$ (two tailed) and power 80%.
- Accrue 185 patients to account for non evaluable patients.
- One interim analysis by DSMB at mid point.

Study Monitoring

- Central pathology review (NCI).
- Central HLA genotyping (NHLBI).
- Central blinded review of radiographic response (NCI).
- Central data collection, monitoring and statistics by EMMES Corporation, Rockville, MD.
- Independent Data Safety Monitoring Board.

Inclusion Criteria

- Cutaneous melanoma.
- Stage IV or locally advanced stage III.
- Measurable disease (CT, MRI, PE).
- HLA-A0201.
- Eligible for HD IL-2 (no major medical illnesses).
- ECOG 0 or 1.
- No brain metastases.
- No prior HD IL-2 or gp100 209-217 (210M).

Results: Enrollment

- Enrollment period: 2000-2007.
- Number of sites: 21
- Patients enrolled: 185

	<u>IL-2</u>	<u>IL-2 + gp100</u>
Randomized	94	91
Withdrew	1	3
Ineligible	0	2

Results: Patient Characteristics

Baseline Characteristics	Category	IL-2 %	IL-2 + gp100 %	P Value
Gender	Male	67	63	NS
	Female	33	37	
Age (years)	Mean	50.3	46.9	0.033
Race	White	97	99	NS
	Hispanic	2	1	
	Other	1	0	
ECOG Performance Status	0	83	84	NS
	1	17	16	
Prior Treatment	Prior Surgery	49	45	NS
	Prior IFN	22	26	
	Prior Chemo	6	6	
	Prior RT	8	7	
	Prior IL-2 (Low dose)	4	6	

Results: Patient Characteristics

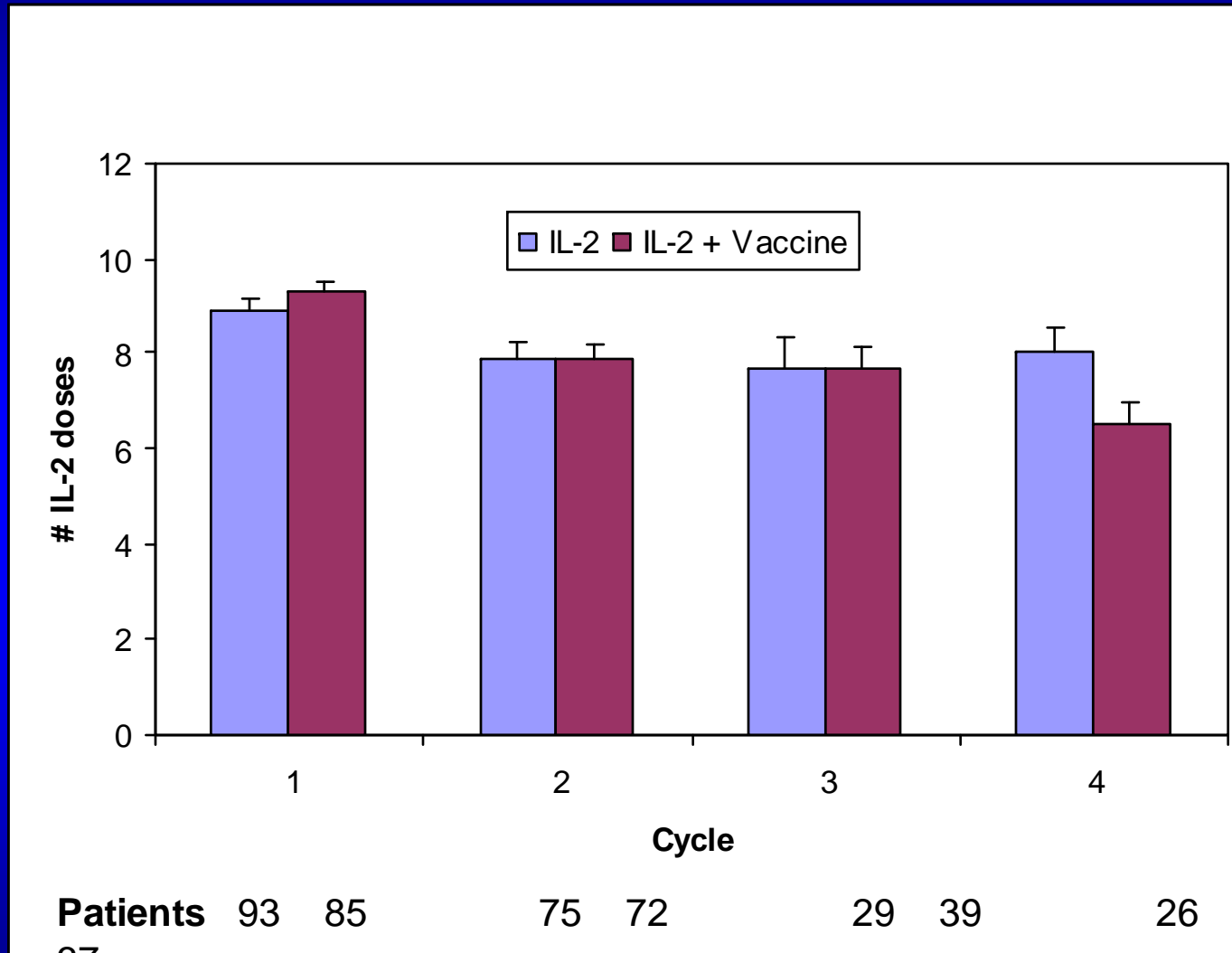
Baseline Characteristics	Category	IL-2 %	IL-2 + gp100 %	P Value
Stratification Factor	Cutan / SQ disease only	9	9	NS
	Any other site	91	91	
Stage	III locally advanced	3	5	NS
Stage	IV M1a	28	25	NS
	M1b	32	39	
	M1c	40	36	

Treatment: Patients per Cycle

Treatment Cycle	Number of Patients	
	IL-2	IL-2 + gp100
1	93	86*
2	75	74
3	29	40
4	26	37
5	6	16
6	5	15
7	4	7
8	4	7
9	1	2
10	1	2
All Cycles	244	287

* 1 patient received only vaccine

Treatment: IL-2 Doses (mean)



Toxicity: Grades 3-5, all Cycles

CTC v.2 Category	IL-2 %	IL-2 + gp100 %	P Value
Blood/Bone Marrow	35	48	NS
Metabolic / Laboratory	21	42	0.002
Hepatic	39	39	NS
Cardiovascular (General)	27	36	NS
Constitutional Symptoms	16	28	NS
Neurology	12	26	0.018
Pulmonary	21	22	NS
Gastrointestinal	18	21	NS
Renal / Genitourinary	15	19	NS
Cardiovascular (Arrhythmia)	4	19	0.002
Pain	11	13	NS
Infection / Febrile Neutropenia	6	8	NS
Dermatology / Skin	6	7	NS
Musculoskeletal	3	7	NS
Death (n)	1	2	

Toxicity: Grades 3-4, Cycles 1 & 2

CTC v.2 Category	IL-2 %	IL-2 + gp100 %	P Value
Cardiovascular (Arrhythmia)	2	15	0.002
AV Block	1	2	
Sinus bradycardia	0	2	
Sinus tachycardia	1	6	
Supraventricular	1	5	
Ventricular	2	1	
Other	1	1	

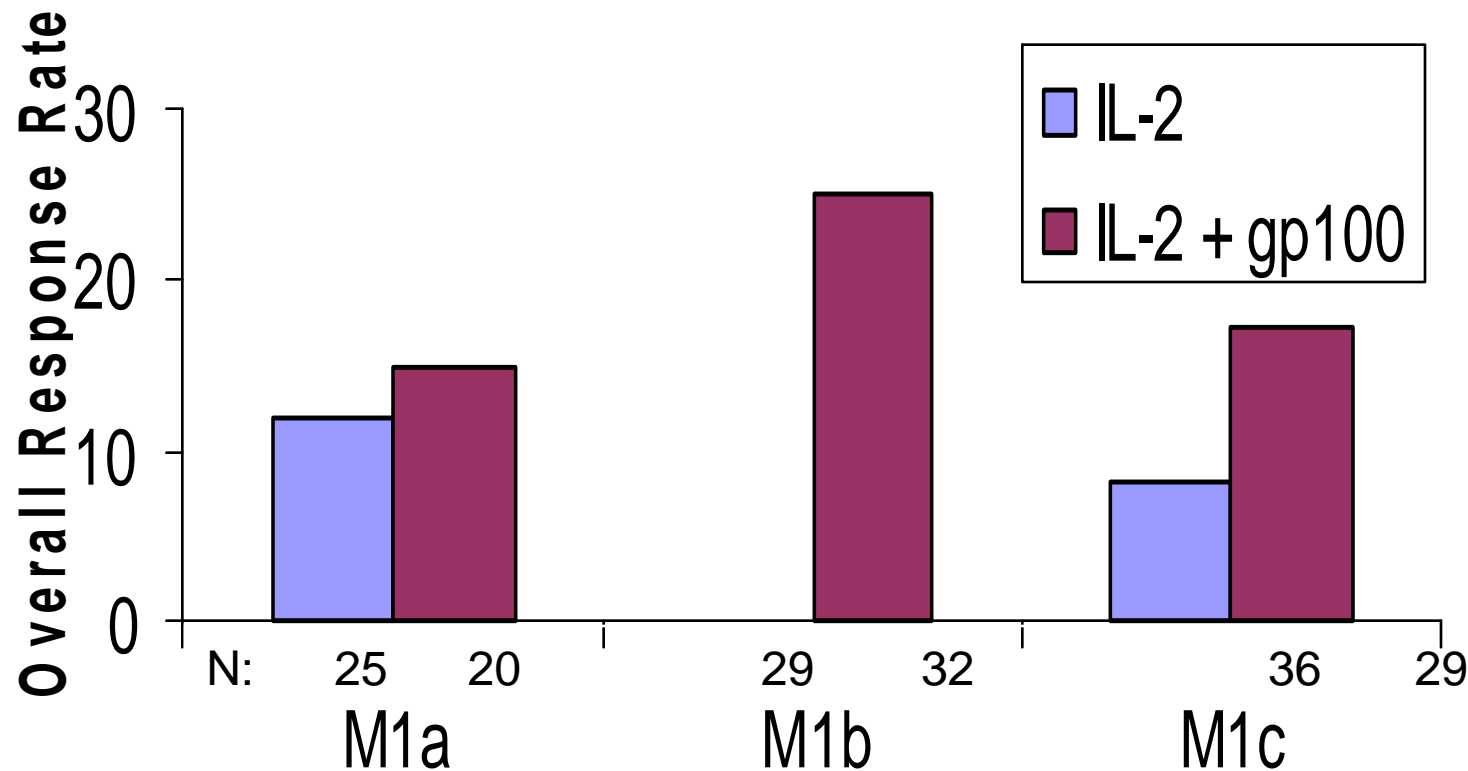
Investigator Assessed Response

Response	IL-2	IL-2 + gp100	P Value
	N=93 (%)	N=86 (%)	
CR	2 (2.2)	12 (14.0)	0.003
PR	7 (7.5)	7 (8.1)	
CR + PR	9 (9.7)	19 (22.1)	0.022
SD	26 (28.0)	28 (32.6)	
PD	58 (62.4)	39 (45.3)	

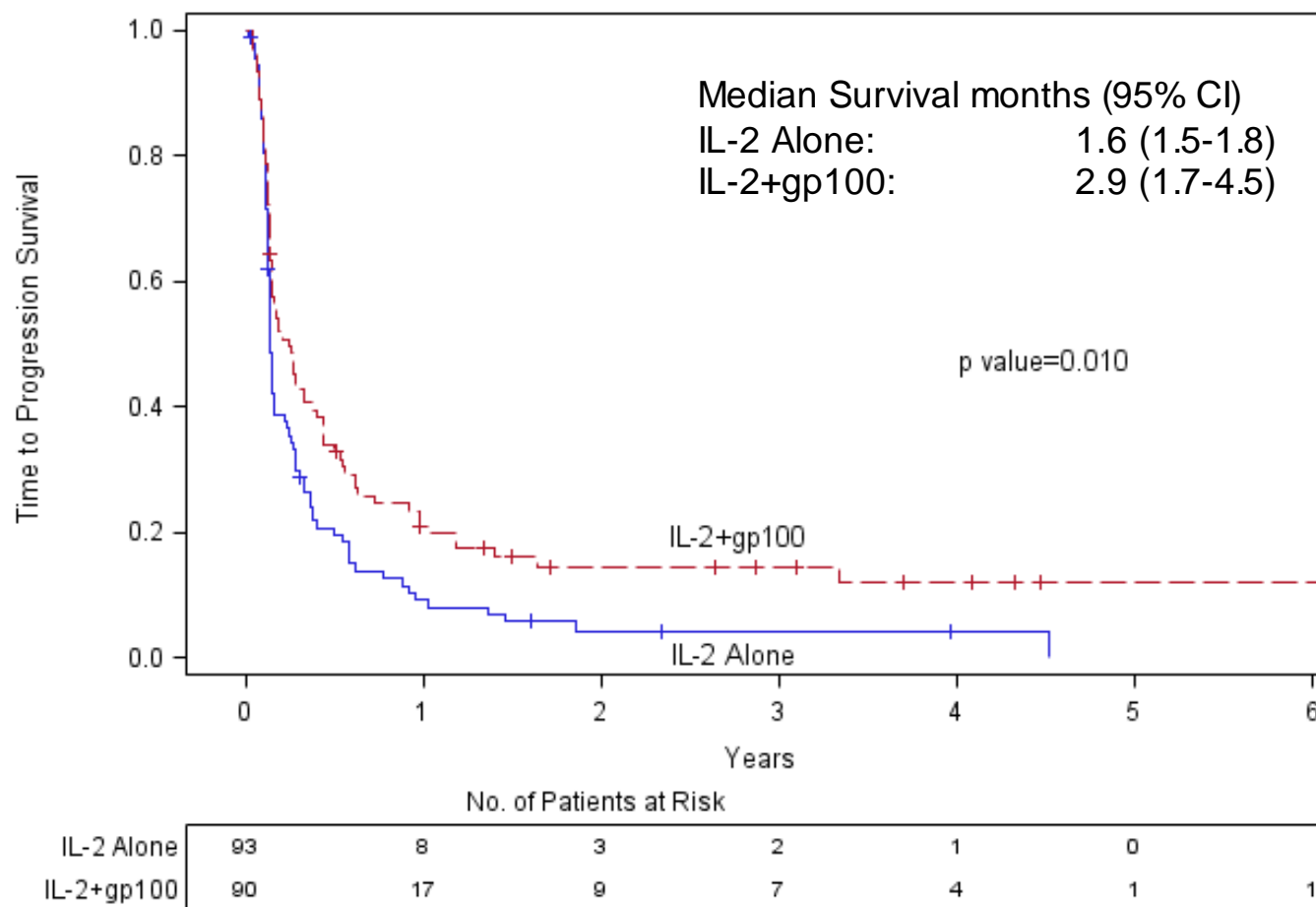
Central Response Assessment

Response	IL-2 N=93 (%)	IL-2 + gp100 N=86 (%)	P Value
CR	1 (1.1)	10 (11.6)	0.004
PR	5 (5.4)	6 (7.0)	
CR + PR	6 (6.5)	16 (18.6)	0.013
SD + PD	87 (93.5)	70 (81.4)	

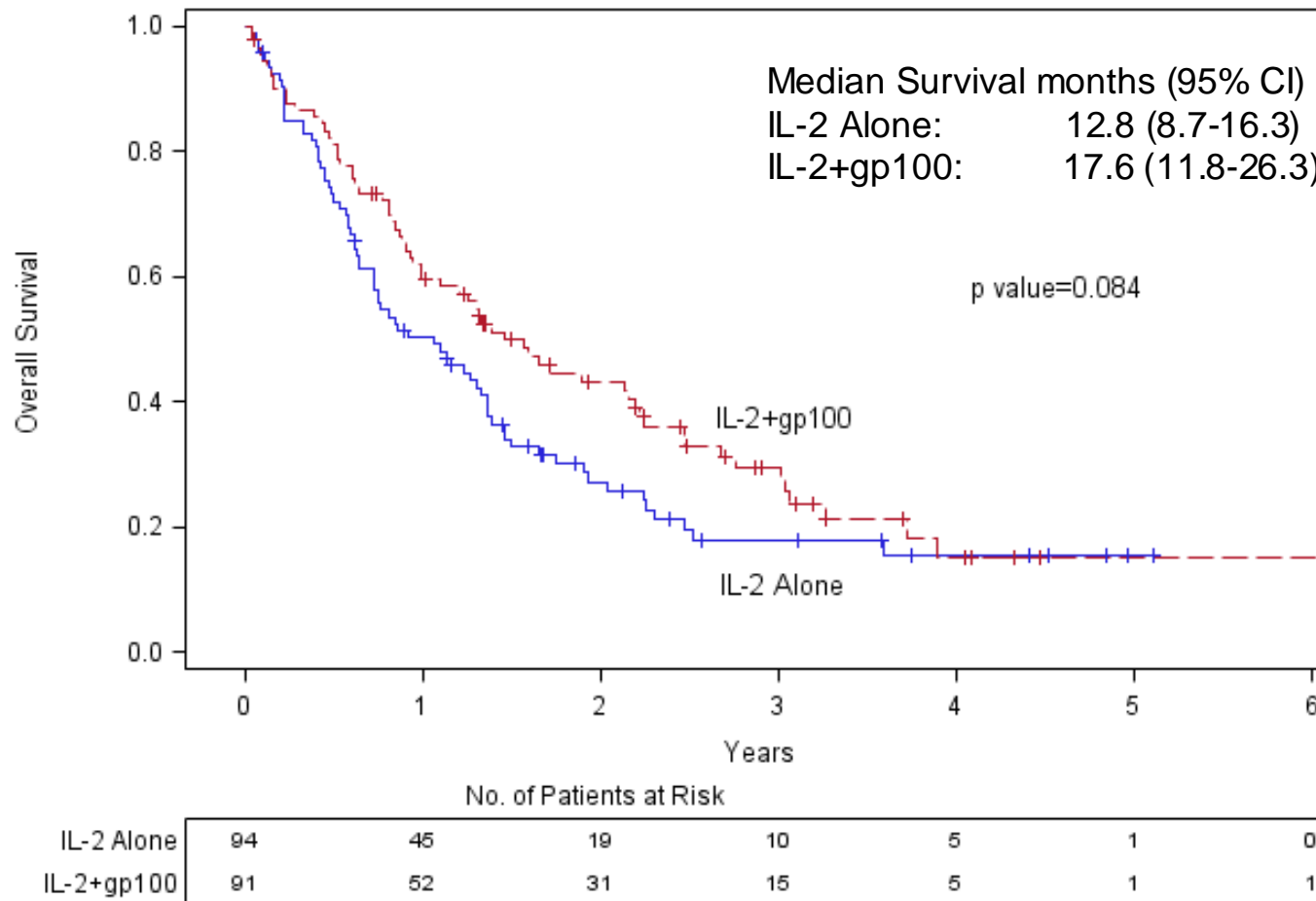
Overall Response in Stage IV M1a, M1b, and M1c Patients



Progression Free Survival



Overall Survival



Summary

- Pretreatment patient characteristics were well balanced except for a trend of younger patients in the vaccine arm.
- Within each cycle of treatment the number of IL-2 doses received was similar in both study arms.
- Adverse events were largely related to HD IL-2. More Grade 3-4 arrhythmias in the vaccine arm (unadjusted $p=0.002$).

Summary

- Investigator assessed Response Rate in the vaccine arm is significantly higher: 22.1% vs. 9.7% ($p=0.022$).
- Central review Response Rate in the vaccine arm is significantly higher: 18.6% vs. 6.5% ($p=0.013$).
- Patients with lung metastases (M1b) and liver/visceral metastases (M1c) accounted for the majority of the response difference.
- Progression Free Survival is significantly higher in the vaccine arm: 2.9 vs. 1.6 months ($p=0.01$).
- Trend for greater Overall Survival in the vaccine arm: 17.6 vs. 12.8 months ($p=0.084$). Median follow up for surviving patients is 28.7 months.

Conclusions

- gp100 209-217 (210M) in Montanide ISA 51 enhances the clinical activity of HD IL-2 in patients with metastatic melanoma.
- Rational combinations of vaccines and immunomodulatory agents like IL-2 need to be further studied in the treatment of patients with metastatic melanoma.

Thank you

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