A Randomized Placebo-Controlled Phase III Trial of Yeast Derived GM-CSF VS Peptide Vaccination VS GM-CSF Plus Peptide Vaccination VS Placebo in Patients with "No Evidence of Disease" after Complete Surgical Resection of "Locally Advanced" and/or Stage IV Melanoma: A trial of the ECOG-ACRIN Cancer Research Group (E4697)

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SUPPLEMENTARY MATERIALS

Supplemental Text

Methods

Eligibility criteria:

Other eligibility criteria included: age ≥18 years; known HLA-A2 status serologically defined; ECOG performance status of 0-1; adequate organ function; no other malignancy within the past 5 years (except lobular carcinoma in situ (LCIS) of the breast, other CIS, atypical melanocytic hyperplasia, Clark's level I melanoma, basal cell or squamous cell skin cancer); no active infection requiring IV antibiotics; no other significant medical, surgical, or psychiatric condition or requirement for medication that precludes study compliance; ability to self-administer or arrange for administration of subcutaneous injections; no autoimmune disorder or immunosuppressive medication; not pregnant or nursing; use of effective contraception during and for 18 months after study participation; no concurrent systemic corticosteroids, topical steroids or steroid-containing inhalers (concurrent replacement doses of steroids for adrenal insufficiency allowed); no prior treatment with GM-CSF, MART-1:27-35 peptide, tyrosinase:368-376(370D), or gp100:209-217(210M) antigen; no prior adjuvant therapy or limb perfusion after resection(s) that rendered the patient disease-free. Serologic testing of HLA status was sufficient. Subtyping (e.g., HLA-A0201) was not required. One prior systemic regimen after a prior surgery was allowed, but no systemic therapy was allowed following the most recent surgery. Patients had to wait at least 30 days since prior radiotherapy.

Interim statistical analysis:

To preserve the overall type I error rate, critical values at the interim analyses were determined using a truncated version of the Lan-DeMets spending function corresponding to the O'Brien-Fleming boundary. Early stopping for futility was conducted using Jennison-Turnbull repeated confidence interval (RCI) method. This design would also provide 80% power to detect 40% relative increase in OS in PV-treated patients (projected 5-year survival: 20% in PV- group and 28% in PV+ group) and 25% relative increase in median RFS (9 months in PV- group and 12 months in PV+ group) using cure rate model. Interim futility analysis was conducted using conditional power method for RFS.

Results

Treatment Characteristics and Study Discontinuation

Ineligibility was fairly balanced between arms: arm A: 7; arm B: 11; arm C: 14; arm D: 6; arm E: 19; arm F 18. Reasons for ineligibility included: not NED at baseline: 22; did not meet staging or prior treatment criteria: 33; timelines not met, scans not done, history of other malignancy, use of steroids, other: 22. Separate analysis using only eligible patients did not materially change the outcome of the study. This rate of ineligibility is not different from other adjuvant trials in cooperative groups during this era. Reasons include the complex design of the study, because of which we were rigorous in our eligibility review. The one pathology error is not rare in melanoma.

Number of patients not starting therapy was <u>not</u> balanced; arm A: 5; arm B: 1; arm C: 2; arm D: 3; arm E: 4; arm F: 18. Reasons for not starting therapy included:

withdrawal/refusal: 6; no data submitted: 17; disease progression prior to treatment: 4; eligibility/compliance issues: 6.

After the study was activated, pathology reports and other patient information were centrally reviewed for 766 patients. The proportion of concordance between randomization and central review for the 3 stratification factors was 99.8% for HLA-A2 status, 88.1% for site of metastases and 77.9% for number of metastatic lesions. The major error discovered for coding of site of metastases was not scoring lymph nodes as metastatic. The major error for number of metastatic lesions was counting individual nodes as metastases rather than counting a nodal basin as one site of metastasis. Staging was not required at the time of randomization; patients were centrally staged.

Table S1: Reasons for not starting assigned therapy (n=33) and for ineligibility (n=75)

Treatment arm	**Reasons for not starting protocol therapy**
A (n=5)	Withdrawal (2) No data submitted (3)
B (n=1)	No data submitted (1)
C (n=2)	Withdrawal (1) No data submitted (1)
D (n=3)	Withdrawal (1) Disease progressed before treatment started (1) No data submitted (1)
E (n=4)	Patient had recurrence before the start of protocol therapy (1) No data submitted (3)
F (n=18)	Withdrawal (1) Breast cancer in 1998 (1) Subcutaneous disease on whole body PET scan (1) Confusion about primary (1) Not able to travel from a displaced location (due to hurricane) (1) Not eligible, no satellite or intransit lesions (1) Patient had recurrence before the start of protocol therapy (2) Patient was not compliant (1) Patient refused (1) No data submitted (8)
Treatment arm	**Reasons for ineligibility**
A (n=7)	Patient not NED at study entry (4) Patient did not meet staging criteria (2) PS done post reg. Patient non-ulcerated and had 1 node positive (1)
B (n=11)	Patient not NED at study entry (2) Patient does not meet staging criteria (1) Patient did not have extra nodal extension of tumor (one sentinel node pos for melanoma at 1st presentation) (1) Solitary nodal recurrence in previously unresected nodal basin-not ulcerated (1) R Lung nodule removed via chemo but not by surgery per op report 3/17/03 (1) No path report submitted for excision done on 9/8/03 (1) Bilirubin not done within 4 weeks prior to registration (1) Patient had visc disease but imaging > 2 weeks prior to registration (1) LDH > ULN does not meet elig requirement (1) Received prior antibiotics and incomplete nodal dissection (1)
C (n=14)	Patient not NED at study entry (3) Patient did not meet staging criteria (3) Scans are outside the 4 week window (1) Patient not randomized within 16 weeks of surgical resection (1) No PET CT or bone scan done at baseline. Alk. Phos > ULN (1) Surgical resection > 112 days from registration (1) Regional recurrence in untreated nodal basin-primary not said to be ulcerated (1) Patient had lymphoma not melanoma (1) Axillary node dissection not done (1) LDH did not meet eligibility requirements, patient used steroid nasal spray (1)
D (n=6)	Patient not NED at study entry (1) Patient did not meet staging criteria (3) Bone scan done prior to registration (1) Recurred before treatment started (1)
E (n=19)	Patient not NED at study entry (6) Patient did not meet staging criteria (8) Scans are outside the 4 week window (1) Chest CT > weeks before reg (1) No pre-registration labs done (1) Patient took Flonase (steroid) at baseline (1) Recurred before treatment started (1)

F (n=18)	Patient not NED at study entry (6) Patient did not meet staging criteria (4) Patient not randomized within 16 weeks of last surgical resection (1) Brain CT > 8 weeks from registration (2) Had breast cancer in 1998 (1) No complete node dissection-pt recurred in node (1) Patient used steroid inhaler at baseline (1) Margins involved at baseline (1) Recurred before treatment started (1)

Table S2: Treatment Characteristics in Treated Patients

Number of patients who completed the GM-CSF/Placebo therapy in each cycle

Cycle	Arm A	Arm B	Arm C	Arm D	Arm E	Arm F	Total
1	100	108	106	102	185	170	771
2	99	105	103	102	176	167	752
3	92	98	98	96	168	160	712
4	87	85	86	92	154	136	640
5	85	82	80	84	146	130	607
6	79	77	78	81	133	118	566
7	74	71	70	75	125	109	524
8	70	70	64	73	119	101	497
9	67	67	60	72	115	101	482
10	64	63	57	68	109	92	453
11	60	58	53	65	107	87	430
12	58	59	52	61	101	83	414
13	52	54	47	56	95	77	381
14	1	3	2	1	5	4	16
15	1	3	2	1	4	3	14
16	1	1	1	1	2	2	8
17	1	1	0	1	0	2	5
18	1	0	0	0	0	1	2
19	1	0	0	0	0	1	2
Total	103	108	106	104	185	171	777

Note: 1) Of the 815 patients, 782 of them received at least one dose of protocol therapy, treatment data were not submitted for 5 patients, and 777 patients were included in Tables S2A and S2B. 2) The maximal number of cycles was 19 for patients who developed resectable recurrent disease while on treatment, and it was 13 cycles for other patients. Patients who received >=13 cycles were considered as completing the protocol therapy.

Total number of GM-CSF/Placebo cycles patients completed during the whole study

Total # of cycles	Arm A	Arm B	Arm C	Arm D	Arm E	Arm F	Total
1	2	1	2	1	9	3	18
2	8	7	5	4	8	8	40
3	3	10	11	7	14	20	65
4	1	2	6	7	8	9	33
5	5	5	4	3	12	12	41
6	8	6	7	6	8	9	44
7	3	3	6	2	5	6	25
8	1	5	3	2	4	2	17
9	5	6	4	3	6	9	33
10	6	4	4	4	3	6	27
11	3	0	2	4	6	3	18
12	6	5	5	5	7	6	34
13	51	51	45	55	90	74	366
14	0	0	0	0	1	1	2
15	0	2	1	0	2	1	6
16	0	0	1	0	2	0	3
17	0	1	0	1	0	1	3
19	1	0	0	0	0	1	2
Total	103	108	106	104	185	171	777
>=13 cycles (%)	52 (50.5)	54 (50.0)	47 (44.3)	56 (53.8)	95 (51.4)	78 (45.6)	382 (49.2)

Note: P>0.05 for comparison of % of >=13 cycles between treatment arms by Chi square test.

Table S3: Number of OS and RFS Events by Treatment Arm

Events	Arm A (n=109)	Arm B (n=111)	Arm C (n=109)	Arm D (n=107)	Arm E (n=190)	Arm F (n=189)	Total (n=815)
OS							
Alive	54	52	50	51	83	82	372
Dead	55	59	59	56	107	107	443
Dead with recurrence	51	57	57	54	96	104	419
Dead without recurrence	4	2	2	2	11	3	24
RFS							
No RFS events	33	36	30	30	50	45	224
RFS events	76	75	79	77	140	144	591
Recurrence							
No recurrence	37	38	32	32	61	48	248
Recurrence	72	73	77	75	129	141	567

Table S4: Univariate stratified Cox Regression Analysis for OS

Variables	Level	HR	95% CI		P-value
GM-CSF (n=815)	Yes vs. No	0.94	0.78	1.14	0.528
(stratified on HLA-A2, site and number of metastases)			0.77	1.15*	
Peptide (n=436)	Yes vs. No	0.93	0.71	1.21	0.598
(stratified on GM-CSF, site and number of metastases)					
Treatment in HLA-A2 positive patients (n=436)	B vs. A	1.15	0.79	1.67	0.462
(stratified on site and number of metastases)	C vs. A	1.13	0.78	1.64	0.516
	D vs. A	1.12	0.77	1.64	0.550
Treatment in HLA-A2 negative patients (n=379)	F vs. E	1.06	0.80	1.39	0.690
(stratified on site and number of metastases)					
HLA-A2 in patients without peptide (n=595)	Positive vs.	0.97	0.77	1.22	0.792
(stratified on GM-CSF, site and number of metastases)					

Note:
1) HR>1 indicated an increased hazard for death (i.e., worse survival).
2) PH assumption was met for all models by Schoenfeld residuals method.
*: repeated CI, adjusting for previous interim analyses

Table S5: Multivariable stratified Cox models for OS

Variables	Level	HR	95% CI		P-value
GM-CSF (n=810)	Yes vs. No	0.93	0.76	1.13	0.456
(stratified on HLA-A2, site and number of metastases)					
Peptide (n=433)	Yes vs. No	0.97	0.74	1.27	0.814
(stratified on GM-CSF, site and number of					
Treatment in HLA-A2 positive patients (n=433)	B vs. A	1.18	0.80	1.73	0.395
(stratified on site and number of metastases)	C vs. A	1.11	0.76	1.63	0.582
	D vs. A	1.08	0.73	1.58	0.714
Treatment in HLA-A2 negative patients (n=377)	F vs. E	1.09	0.82	1.45	0.545
(stratified on site and number of metastases)					
HLA-A2 in patients without peptide (n=593)	Positive vs.	0.96	0.76	1.22	0.768
(stratified on GM-CSF, site and number of metastases)					

Note:
1) HR>1 indicated an increased hazard for death (i.e., worse survival).
2) PH assumption was met for all models by Schoenfeld residuals method.
3) Adjusted covariates were same in all models, which included age, gender, ECOG PS, ulceration at primary site, depth of invasion of primary disease (Clark level), number of positive nodes, disease stage at study entry, and prior immunotherapy.
4) Four patients had missing value for ECOG PS and 1 patient had missing value for gender, these patients were excluded from the multivariable Cox models for OS.

Table S6: Univariate Stratified Cox Regression Analysis for RFS

Variables	Level	HR	95% CI		P-value
GM-CSF (n=815) (stratified on HLA-A2, site and number of metastases)	Yes vs. No	0.88	0.75	1.04	0.132
Peptide (n=436) (stratified on GM-CSF, site and number of	Yes vs. No	0.96	0.76 0.74	1.20 1.23*	0.708
Treatment in HLA-A2 positive patients (n=436) (stratified on site and number of metastases)	B vs. A C vs. A D vs. A	1.09 1.05 1.12	0.79 0.76 0.81	1.50 1.46 1.56	0.609 0.747 0.475
Treatment in HLA-A2 negative patients (n=379) (stratified on site and number of metastases)	F vs. E	1.20	0.95	1.53	0.130
HLA-A2 in patients without peptide (n=595) (stratified on GM-CSF, site and number of metastases)	Positive vs.	0.93	0.76	1.13	0.458

Note:
1) HR>1 indicated an increased hazard for disease recurrence or death (i.e., worse RFS).
2) PH assumption was met for all models by Schoenfeld residuals method.
*: repeated CI, adjusting for previous interim analyses

Table S7: Multivariable stratified Cox models for RFS

Variables	Level	HR	95% CI		P-value
GM-CSF (n=810) (stratified on HLA-A2, site and number of metastases)	Yes vs. No	0.88	0.74	1.04	0.129
Peptide (n=433) (stratified on GM-CSF, site and number of	Yes vs. No	0.95	0.75	1.20	0.649
Treatment in HLA-A2 positive patients (n=433) (stratified on site and number of metastases)	B vs. A C vs. A D vs. A	1.12 1.10 1.14	0.81 0.79 0.81	1.56 1.52 1.59	0.491 0.578 0.448
Treatment in HLA-A2 negative patients (n=377) (stratified on site and number of metastases)	F vs. E	1.19	0.93	1.53	0.163
HLA-A2 in patients without peptide (n=593) (stratified on GM-CSF, site and number of metastases)	Positive vs.	0.93	0.76	1.14	0.482

Note:
1) HR>1 indicated an increased hazard for disease recurrence or death (i.e., worse RFS).
2) PH assumption was met for all models by Schoenfeld residuals method.
3) Adjusted covariates were same in all models, which included age, gender, ECOG PS, ulceration at primary site, depth of invasion of primary disease (Clark level), number of positive nodes, disease stage at study entry, and prior immunotherapy.
4) Four patients had missing value for ECOG PS and 1 patient had missing value for gender, the 5 patients were excluded from the multivariable Cox models for RFS.

Table S8: Incidence of Grade 3-5 Adverse Events in Treated Patients (n=782) regardless of treatment attribution

AEs type	Treatment Arm																	
	A (n=104)			B (n=110)			C (n=107)			D (n=104)			E(n=186)			F(n=171)		
	Grade			Grade			Grade			Grade			Grade			Grade		
	3	4	5	3	4	5	3	4	5	3	4	5	3	4	5	3	4	5
	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)
Allergic reaction	1	-	-	1	-	-	1	-	-	1	-	-	1	-	-	-	-	-
Inner ear/hearing	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-
Hearing-other	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hemoglobin	-	-	-	-	-	-	-	-	-	3	-	-	-	-	-	1	-	-
Leukocytes	-	-	-	-	-	-	2	-	-	1	-	-	-	-	-	-	-	-
Neutrophils	2	-	-	2	-	-	-	2	-	3	1	-	2	3	-	1	1	-
Supraventricular arrhythmias	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-
Arrhythmia-other	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	1	-
Cardiac-ischemia	2	2	-	-	1	-	-	1	-	-	-	-	-	-	-	-	-	-
Cardiac troponin I	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Edema	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hypertension	1	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-
Pericardial effusion/pericarditis	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-
Phlebitis	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-
Thrombosis/embolism	1	-	-	-	-	-	-	1	-	-	-	-	1	-	-	1	1	-
Cardiac-other	-	-	-	-	-	-	-	-	-	-	-	-	1	1	-	-	-	-
Fatigue	1	-	-	1	-	-	3	-	-	1	-	-	4	-	-	4	-	-
Weight gain	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-
Weight loss	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	1	-	-
Constitutional	-	-	-	-	-	1	-	-	-	-	-	1	-	-	-	-	1	-
PTT	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PT	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	2	-	-
Flushing	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Injection site reaction	2	-	-	9	-	-	2	-	-	2	-	-	1	-	-	1	-	-
Pruritus	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-
Rash/desquamation	1	1	-	1	-	-	1	-	-	-	-	-	2	-	-	-	-	-
Urticaria	1	-	-	1	-	-	-	-	-	-	-	-	1	-	-	-	-	-
Wound - infectious	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-
Skin-other	-	-	-	-	-	-	1	-	-	1	-	-	-	-	-	-	-	-
Hot flashes	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-
SIADH	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-
Anorexia	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-
Ascites	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-
Colitis	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-
Constipation	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-
Dehydration	-	-	-	1	-	-	-	-	-	-	-	-	1	-	-	-	-	-
Dyspepsia	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-
Nausea	1	-	-	2	-	-	-	-	-	-	-	-	1	-	-	1	-	-
Pancreatitis	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vomiting	1	-	-	2	1	-	-	-	-	1	-	-	-	-	-	1	-	-
Diarrhea w/o prior colostomy	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	2	-	-
GI-other	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	1	-
CNS hemorrhage	-	-	-	-	-	-	-	-	-	1	-	-	-	-	1	-	-	-
Hematuria	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-
Melena/GI bleeding	-	-	-	-	-	-	-	-	-	2	-	-	-	1	-	-	-	-
Bilirubin	-	-	-	1	-	-	2	-	-	2	1	-	2	-	-	2	-	-

AEs type	Treatment Arm																	
	A (n=104)			B (n=110)			C (n=107)			D (n=104)			E(n=186)			F(n=171)		
	Grade			Grade			Grade			Grade			Grade			Grade		
	3	4	5	3	4	5	3	4	5	3	4	5	3	4	5	3	4	5
	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)
SGOT	-	-	-	-	-	-	1	-	-	-	-	-	2	-	-	1	-	-
SGPT	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-
Infection w/ grade 3 or 4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-
Infection w/ unknown ANC	-	-	-	2	-	-	-	-	-	-	-	-	2	-	-	2	-	-
Infection w/o neutropenia	-	1	-	1	-	-	-	-	-	-	-	-	3	-	-	1	-	-
Infection-other	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-
Lymphatics	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lymphatics-other	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-
Acidosis	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hyperglycemia	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-
Hypokalemia	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	1	-	-
Metabolic-other	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Arthritis	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Muscle weakness	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-
Joint, muscle, bone-other	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ataxia	-	-	-	-	-	-	-	-	-	1	-	-	1	-	-	-	-	-
Cerebrovascular ischemia	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-
Confusion	1	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-
Dizziness/lightheadedness	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hallucinations	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-
Insomnia	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-
Anxiety/agitation	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-
Depression	-	-	-	-	-	-	1	-	-	-	-	-	2	-	-	-	-	-
Neuropathy-cranial	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	1	-	-
Neuropathy-motor	1	-	-	-	1	-	-	-	-	-	-	-	2	1	-	2	-	-
Neuropathy-sensory	-	-	-	-	1	-	-	-	-	-	-	-	1	-	-	-	-	-
Seizure	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	1	-	-
Speech impairment	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-
Syncope	1	-	-	-	-	-	1	-	-	-	-	-	3	-	-	-	-	-
Neurologic-other	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Glaucoma	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ocular-other	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-
Abdominal pain	-	-	-	1	-	-	1	-	-	2	-	-	1	-	-	1	-	-
Arthralgia	-	-	-	1	-	-	5	-	-	-	-	-	2	-	-	-	-	-
Bone pain	-	-	-	-	-	-	-	-	-	1	-	-	4	1	-	2	-	-
Chest pain	-	-	-	-	1	-	1	-	-	-	-	-	4	-	-	2	-	-
Headache	4	-	-	1	1	-	-	-	-	2	-	-	8	-	-	-	-	-
Myalgia	1	-	-	2	-	-	2	1	-	1	-	-	1	-	-	1	-	-
Neuropathic pain	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-
Pleuritic pain	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pain-other	2	-	-	2	-	-	1	1	-	-	-	-	3	-	-	3	-	-
Cough	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-
Dyspnea	1	1	-	1	1	-	-	-	-	-	-	-	4	1	-	2	-	-
Hypoxia	1	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-
Pleural effusion	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-
Pulmonary-other	-	1	-	1	-	-	1	-	-	-	-	-	1	-	-	1	-	-
Bladder spasms	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Creatinine	-	-	-	-	-	-	-	-	-	1	-	-	-	1	-	1	-	-
WORST DEGREE	**23**	**6**	**1**	**21**	**3**	**1**	**18**	**5**	**-**	**22**	**2**	**1**	**40**	**10**	**1**	**24**	**5**	**-**

Table S9: Deaths While on Treatment Reported by AdEERS

Treatment Arm	AEs Type	Description
A	Neurologic-other	Patient died on last day of cycle 4. Nervous system disorders -Other, specify: brain aneurysm, which was attributed to congenital arterial aneurysm (attribution code was definite) and aspirin (attribution code was possible). Attribution code for protocol therapy was unlikely, and attribution code for melanoma was unlikely based on NCI assessment.
E	CNS hemorrhage	Patient died on day 15 in cycle 7. Massive hemorrhage in left cerebellar hemisphere, probably due to melanoma metastasis, and one possible reason is h/o hypertension. Attribution code for protocol therapy was unlikely and attribution code for melanoma was probable based on NCI assessment.
B	Constitutional	Patient died on last day of cycle 2 due to melanoma metastases (attribution code was definite). General disorders and administration site conditions - Other, specify: extensive recurrent metastatic melanoma of liver and spleen. Attribution code for protocol therapy was unlikely.
D	Constitutional	Patient died on day 19 in cycle 2 due to progressive disease. General disorders and administration site conditions - Other, specify: Death - Disease Progression NOS (2 mets, visceral + non-visceral). Attribution code for protocol therapy was unrelated based on NCI assessment.
A	Dyspnea	Patient died on day 20 in cycle 5. General disorders and administration site conditions –other, specify progressive disease. Attribution code for protocol therapy was unlikely, and attribution code for melanoma was definite based on NCI assessment.
D	Constitutional	Patient died in cycle 2. General disorders and administration site conditions –other, specify progressive disease. Attribution code for protocol therapy was unlikely, and attribution code for melanoma was probable based on NCI assessment.
F	Death NOS	Patient died in cycle 7 from melanoma and h/o depression (attribution code was possible for both). Attribution code for protocol therapy was unrelated based on NCI assessment.
E	Constitutional	Patient died in cycle 2. General disorders and administration site conditions –other, specify progressive disease. Attribution code for protocol therapy was unrelated, and attribution code for melanoma was definite based on NCI

		assessment.

Note: Four of the 8 patients were considered grade 5 adverse events in the ECOG study data base. The other 4 cases were not recorded in the ECOG data base as of Oct 8, 2012.

Table S10: Number and Site of Second Primary Cancer

Site of second primary cancer	Arm A (n=109)	Arm B (n=111)	Arm C (n=109)	Arm D (n=107)	Arm E (n=190)	Arm F (n=189)	Total (n=815)
Breast	0	0	2	1	0	2	5
Colon	1	1	0	0	0	0	2
Rectum	0	0	0	0	1	0	1
Gastric	1	0	0	0	0	0	1
Pancreas	0	0	0	1	0	1	2
Esophagus	0	0	0	0	2	0	2
Brain tumor	0	0	0	0	1	0	1
Non-Hodgkins lymphoma	0	0	0	0	1	0	1
Acute lymphocytic leukemia-ALL	0	0	0	0	1	0	1
Small cell lung	0	0	0	0	1	0	1
Non-small cell lung	1	0	0	0	0	0	1
Melanoma	1	0	2	2	2	5	12
Basel cell carcinoma	2	6	2	4	7	7	28
Skin cancer, not melanoma	2	1	5	3	2	17	30
Ovarian	0	1	0	0	0	0	1
Renal cell	0	0	0	0	1	2	3
Bladder, urinary track	0	0	0	0	0	1	1
Prostate	1	2	1	1	3	1	9
Unknown site	1	0	3	0	10	2	16
Total	10	11	15	12	32	38	118

Note: A total of 73 patients developed second primary cancer during the study period, 55 of them had one second primary cancer and 18 patients had multiple new cancers.

Figure S1A: OS by HLA-02 Status in All Patients (n=815)

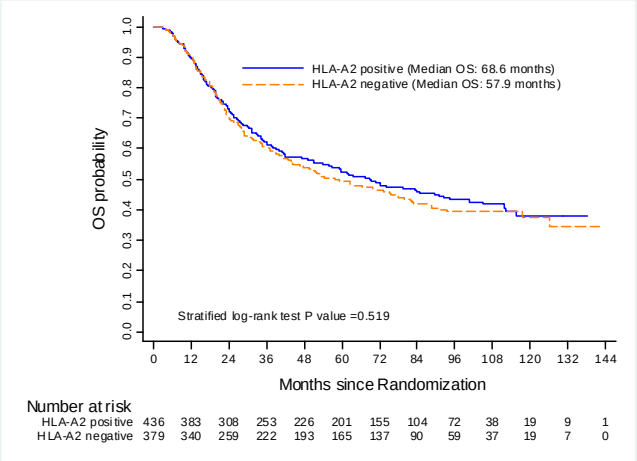


Figure S1B: RFS by HLA-A2 Status in All Patients (n=815)

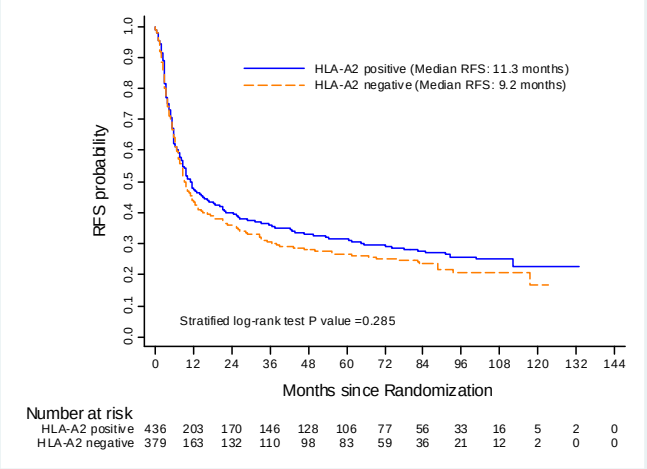
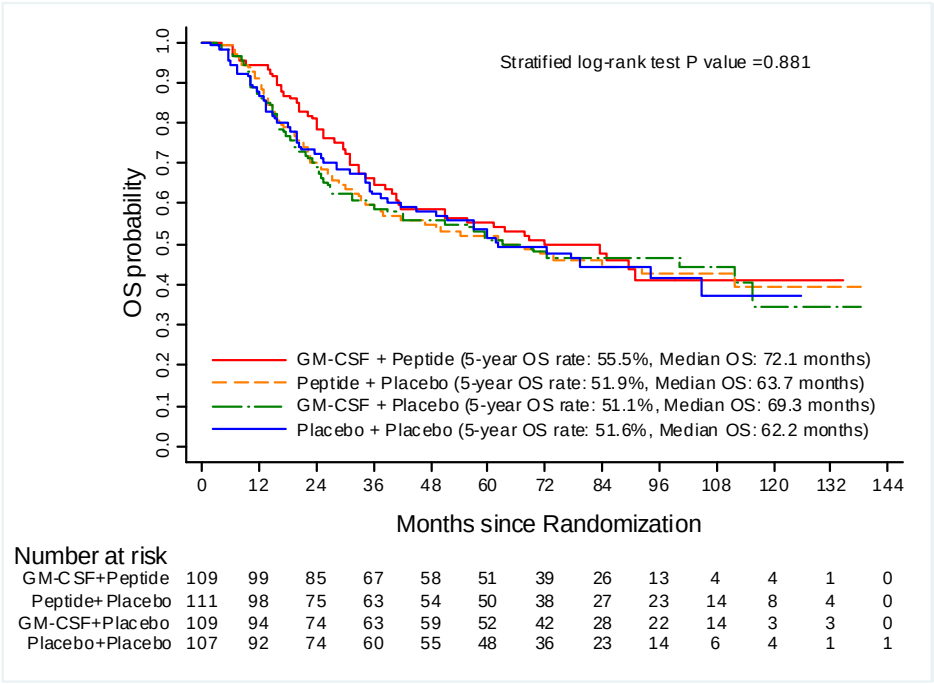


Figure S2: Effect of Systemic GM-CSF in combination with peptide vaccination on OS in HLA-A2+ Patients (n=436)



Number at risk

GM-CSF+Peptide	109	99	85	67	58	51	39	26	13	4	4	1	0
Peptide+Placebo	111	98	75	63	54	50	38	27	23	14	8	4	0
GM-CSF+Placebo	109	94	74	63	59	52	42	28	22	14	3	3	0
Placebo+Placebo	107	92	74	60	55	48	36	23	14	6	4	1	1

Figure S3A: OS by GM-CSF vs Placebo in patients with stage M1b/M1c disease at study entry

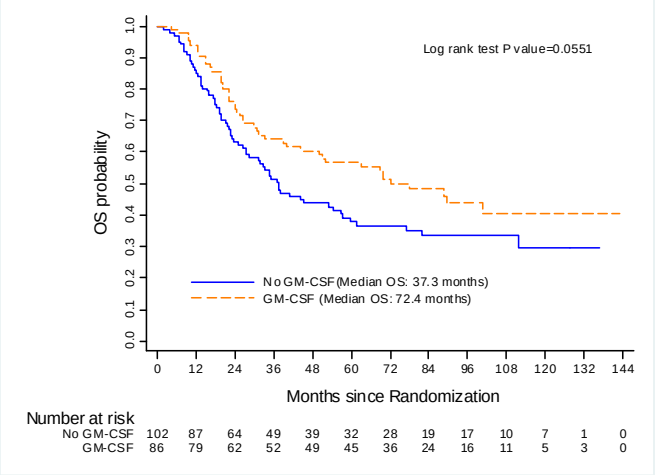


Figure S3B: OS by GM-CSF in patients with stage IV disease at study entry

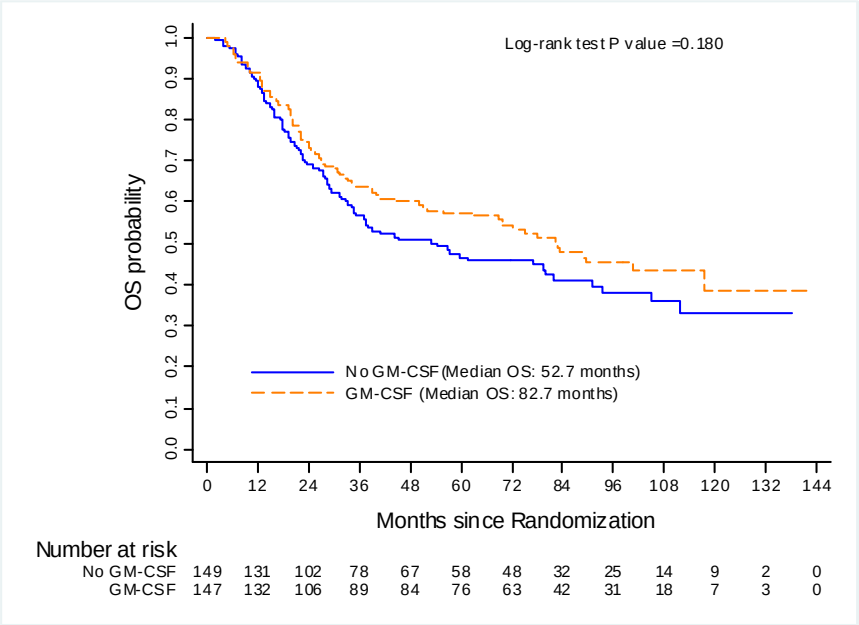


Figure S4A: RFS by peptide vaccine in HLA-A2+ patients with stage M1b/M1c disease at study entry

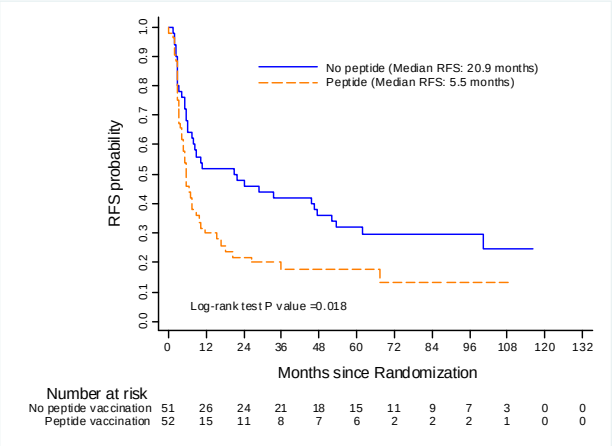


Figure S4B: OS by peptide vaccine in patients with stage M1b/M1c disease at study entry