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ORIGINAL REPORT

Randomized, Placebo-Controlled, Phase III Trial of Yeast-Derived Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) Versus Peptide Vaccination Versus GM-CSF Plus Peptide Vaccination Versus Placebo in Patients With No Evidence of Disease After Complete Surgical Resection of Locally Advanced and/or Stage IV Melanoma: A Trial of the Eastern Cooperative Oncology Group–American College of Radiology Imaging Network Cancer Research Group (E4697)

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ABSTRACT

Purpose
We conducted a double-blind, placebo-controlled trial to evaluate the effect of granulocyte-macrophage colony-stimulating factor (GM-CSF) and peptide vaccination (PV) on relapse-free survival (RFS) and overall survival (OS) in patients with resected high-risk melanoma.

Patients and Methods
Patients with completely resected stage IV or high-risk stage III melanoma were grouped by human leukocyte antigen (HLA) -A2 status. HLA-A2–positive patients were randomly assigned to receive GM-CSF, PV, both, or placebo; HLA-A2–negative patients, GM-CSF or placebo. Treatment lasted for 1 year or until recurrence. Efficacy analyses were conducted in the intent-to-treat population.

Results
A total of 815 patients were enrolled. There were no significant improvements in OS (stratified log-rank $P = .528$; hazard ratio, 0.94; 95% repeated CI, 0.77 to 1.15) or RFS ($P = .131$; hazard ratio, 0.88; 95% CI, 0.74 to 1.04) in the patients assigned to GM-CSF (n = 408) versus those assigned to placebo (n = 407). The median OS times with GM-CSF versus placebo treatments were 69.6 months (95% CI, 53.4 to 83.5 months) versus 59.3 months (95% CI, 44.4 to 77.3 months); the 5-year OS probability rates were 52.3% (95% CI, 47.3% to 57.1%) versus 49.4% (95% CI, 44.3% to 54.3%), respectively. The median RFS times with GM-CSF versus placebo were 11.4 months (95% CI, 9.4 to 14.8 months) versus 8.8 months (95% CI, 7.5 to 11.2 months); the 5-year RFS probability rates were 31.2% (95% CI, 26.7% to 35.9%) versus 27.0% (95% CI, 22.7% to 31.5%), respectively. Exploratory analyses showed a trend toward improved OS in GM-CSF–treated patients with resected visceral metastases. When survival in HLA-A2–positive patients who received PV versus placebo was compared, RFS and OS were not significantly different. Treatment-related grade 3 or greater adverse events were similar between GM-CSF and placebo groups.

Conclusion
Neither adjuvant GM-CSF nor PV significantly improved RFS or OS in patients with high-risk resected melanoma. Exploratory analyses suggest that GM-CSF may be beneficial in patients with resected visceral metastases; this observation requires prospective validation.

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INTRODUCTION

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a well-tolerated cytokine with activities that suggest a possible role in cancer immunotherapy.[1] It increases the number of monocytes/macrophages in patients with cancer [2] and, in vitro, enhances their ability to lyse tumor cells.[3] GM-CSF has a clear role in the growth and maturation of dendritic cells.[4] It may also have antiangiogenic activity.[5]

Early clinical trials support the possible benefit of GM-CSF as adjuvant therapy for melanoma. Spitler et al[6] reported longer overall survival (OS) of 48 patients with stage III to IV melanoma treated for 1 year with adjuvant GM-CSF compared with historical controls (median OS, 37.5 *v* 12.2 months; 2-year survival, 64% *v* 15%). A subsequent single-arm trial in 98 patients with stage II, III, or IV melanoma evaluated GM-CSF for 3 years and demonstrated 5-year melanoma-specific survival rates of 67% and 40% among patients with resected stage III and IV disease, respectively.[7] A retrospective study of 317 patients with resected stage III melanoma reported a median melanoma-specific survival of 102 months for patients treated with GM-CSF versus 99 months for patients under observation only and respective 10-year survival rates of 49% versus 39% ($P = .08$).[8] Subset analysis showed that OS was statistically significantly improved in patients with stage IIIC disease. Forty-two patients with stage IIIB to IIIC or IV disease who were enrolled on a biomarker study and treated with GM-CSF had a median OS of 65 months.[9]

Administration of cytokines, including GM-CSF, with melanoma vaccines has shown augmented immunologic responses and clinically significant antitumor responses in some studies.[10-12] A multicenter, randomized, phase II study (E1696) evaluated the effect of systemically administered GM-CSF or interferon-alfa-2b (IFN-α-2b) on responses to a multiepitope peptide vaccine, composed of the same peptides used in this trial, in patients with active metastatic melanoma. The ability to mount an immune response to at least one vaccinating peptide was predictive of improved survival.[13] There were positive but nonsignificant trends toward enhancement of the immune response with both GM-CSF and IFN-α-2b.

We conducted a multicenter, intergroup, randomized, placebo-controlled, phase III trial to evaluate the ability of GM-CSF and/or multiepitope peptide vaccination (PV) to improve relapse-free survival (RFS) and OS in patients with completely resected high-risk stage III to IV melanoma.

PATIENTS AND METHODS

Patient Eligibility

Patients gave informed consent after approval by the human investigations committee. Patients were randomly assigned within 16 weeks of complete resection of high-risk melanoma, defined as locoregional recurrence after prior adjuvant IFN-α-2b or relapse from the biochemotherapy arm of study S0008[14]; local recurrence after adequate resection of the primary tumor; clinically evident satellite or in-transit disease; stage III disease with gross extracapsular extension; recurrence in a previously resected nodal basin; four or greater involved lymph nodes or matted lymph nodes if ineligible for study S0008; ulcerated primary melanoma and any involved lymph nodes; or completely resected stage IV disease. Patients with cutaneous, uveal, or mucosal primaries were eligible. Other eligibility criteria are in the Data Supplement.

Random Assignment and Treatment

Because the PVs used in this trial are only immunologically recognized in the context of human leukocyte antigen (HLA)-A2, patients were separated into HLA-A2–positive (serologically defined) and HLA-A2–negative groups (Fig 1, CONSORT diagram; Fig 2). HLA-A2–positive patients were randomly assigned to receive GM-CSF plus PV, GM-CSF placebo plus PV, GM-CSF plus peptide placebo, or GM-CSF placebo plus peptide placebo. HLA-A2–negative patients were randomly assigned to receive GM-CSF or placebo. Random assignment was conducted centrally by using permuted blocks within strata, defined by the following: HLA-A2 status (positive or negative), site of metastases (nonvisceral *v* visceral *v* both sites *v* none), and number of metastatic lesions (0, 1, 2 to 3, ≥ 4).

GM-CSF (sargramostim) 250 μg/d and GM-CSF placebo were administered subcutaneously on day 1 through 14 of each 28-day cycle. The multiepitope vaccine was composed of tyrosinase 368-376(370D), gp100 209-217(210M), and MART-1(27-35) peptides. Peptides and respective peptide placebos were emulsified in Montanide ISA-51 (Seppic, Puteaux, France) and administered separately via two subcutaneous injections into three different sites on days 1 and 15 of cycle 1 and day 1 of subsequent cycles. During the study, the Montanide preparation was changed to one with no animal products. Patients received 13 cycles of treatment unless they experienced disease progression or unacceptable toxicity. Patients with resectable recurrences before completion of 12 months of treatment were encouraged to resume treatment for an additional 6 months or until a total of 12 months of treatment, whichever was longest. All patients were observed for RFS and OS for 15 years from the date of registration.

End Points

The primary objective was to compare RFS and OS between GM-CSF and placebo in the entire population. The main secondary objective was to compare RFS of peptide vaccine (PV-positive) and placebo (PV-negative) groups in HLA-A2–positive patients. OS was defined as time from random assignment to death as a result of any cause. RFS was defined as time from random assignment to first disease recurrence or death. Adverse events (AEs) were coded and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 2.

Statistical Analysis

A total of 800 patients and 400 deaths were required for 80% power to detect a 33% increase in the median OS of patients treated with GM-CSF versus placebo (projected survival, 53.2 *v* 40 months, respectively), by stratified log-rank test with a two-sided type I error of .05. Interim analyses of OS, detailed in the Data Supplement, were performed semi-annually; they began when approximately 25% of the planned full information became available and continued until criteria for early stopping were met or full information was reached. The September 2009 interim analysis showed an improvement in RFS (hazard ratio [HR], 0.82; 95% CI, 0.69 to 0.98; $P = .03$) but not OS (HR, 0.94; 95% CI, 0.75 to 1.16; $P = .55$). These data were submitted as an abstract to the 46th Annual Meeting of the American Society of Clinical Oncology in 2010. By the time of presentation, a repeat analysis showed that the difference in RFS was no longer significant.[15] At the time of OS monitoring, interim analysis was also conducted for RFS to compare PV versus placebo groups in HLA-A2–positive patients.

All OS and RFS analyses were based on the intent-to-treat population regardless of eligibility status. OS and RFS distributions were estimated by using the Kaplan-Meier method, with 95% CIs calculated with Greenwood's formula. Stratified log-rank tests were used to compare distributions of OS and RFS between groups. Stratified Cox proportional hazard models were conducted to estimate HRs for the treatment effect for OS and RFS. The Jennison-Turnbull repeated CI was calculated for the OS comparison between GM-CSF and placebo and the RFS comparison between PV and placebo. Proportional hazards assumption was examined by the Schoenfeld residuals method.

As an exploratory analysis, effects of GM-CSF and PV on OS and RFS were evaluated in subgroups of patients on the basis of prespecified factors: HLA-A2 status, visceral or nonvisceral metastases, and number of metastases. Because the staging system was undergoing revision at the time the study was

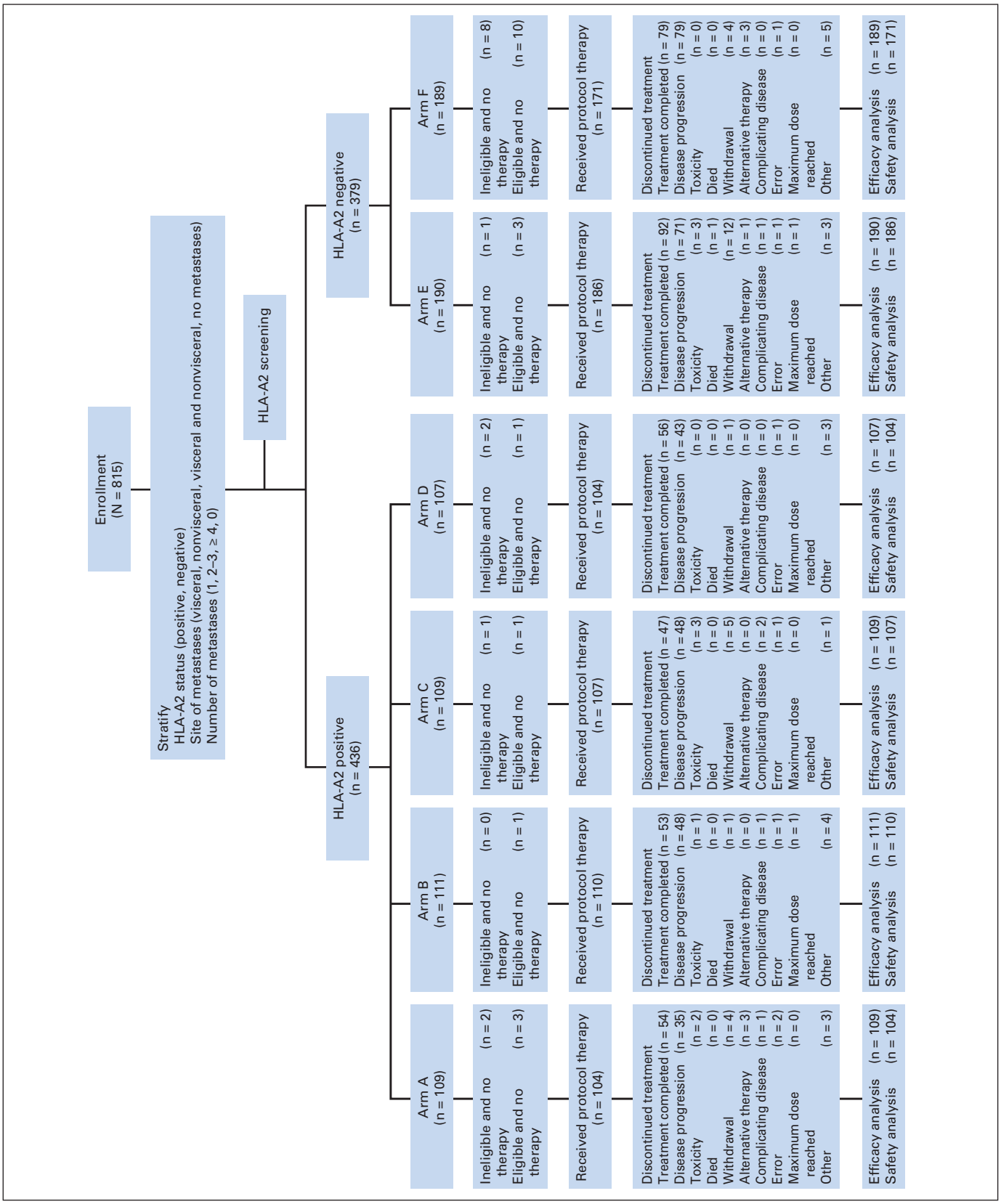

Fig 1. CONSORT diagram. HLA, human leukocyte antigen.

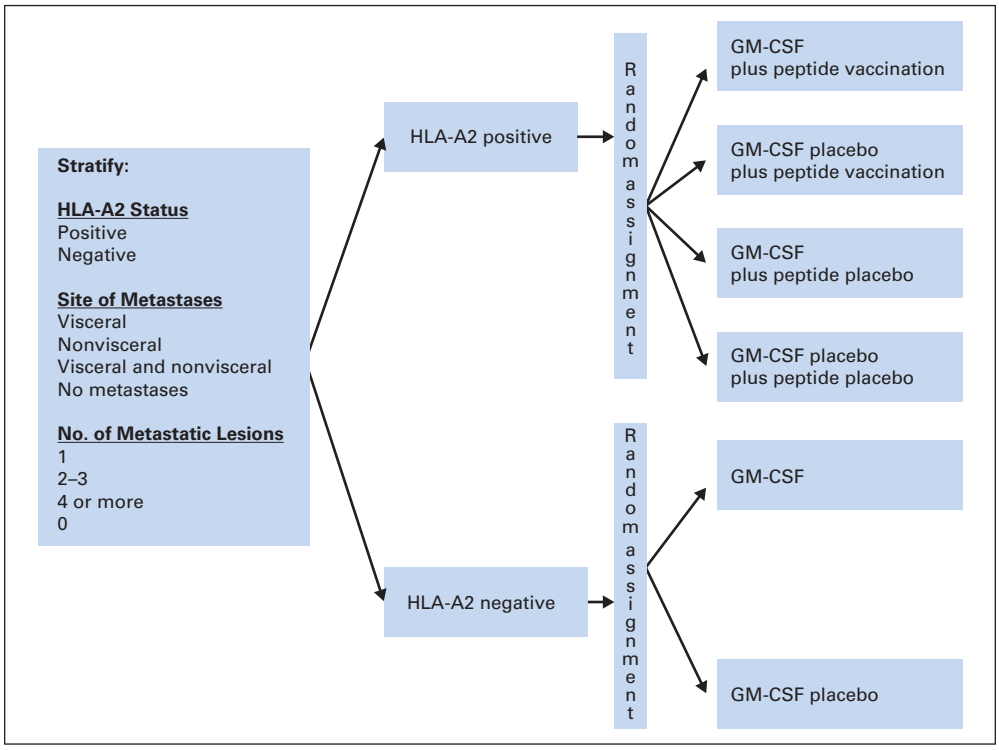

Fig 2. Study schema. GM-CSF, granulocyte-macrophage colony-stimulating factor; HLA, human leukocyte antigen.

written, stage was not a prespecified stratification factor. When the seventh edition of the American Joint Committee on Cancer Staging Manual was published in 2010, patients were centrally staged. Because the analysis of prespecified stratification factors suggested that the effects might differ on the basis of whether resected disease was visceral or nonvisceral, the effects of GM-CSF and PV were examined separately on patients with stage III-M1a and stage M1b or M1c disease. The significance of the predictive value of these factors was tested by including a treatment-by-factor interaction term in the Cox proportional hazards models. No adjustment was made for multiple comparisons for subgroup analysis because of the exploratory nature of these analyses. Analyses of AEs were conducted in the 782 patients who received at least one dose of protocol therapy (n = 777 patients reported treatment data). The incidence of grade 3 or higher AEs was summarized and compared between arms by using Fisher's exact tests.

All reported *P* values were for two-sided tests. The nominal two-sided significance levels were less than .001 (corresponding upper boundary value, 2.05) for the OS comparison between GM-CSF and placebo and less than .001 (corresponding upper boundary value, 2.02) for the RFS comparison between PV and placebo. For all other analyses, the two-sided significance level was .05.

Blood samples for correlative studies were collected and shipped to the Eastern Cooperative Oncology Group Central Immunology Laboratory, University of Pittsburgh (Pittsburgh, PA); these results will be reported separately.

RESULTS

Baseline and Treatment Characteristics

This study accrued 815 patients between December 29, 1999, and October 31, 2006; 436 (53.5%) were HLA-A2 positive and 379 (46.5%) were HLA-A2 negative. Table 1 displays on-study patient demographics and disease characteristics. Thirty patients had primary mucosal melanoma and 11 had primary uveal melanoma. Treatment arms were well balanced regarding known prognostic factors. At study entry, 38.6% of patients had stage IV disease; 26.5% had two or more metastatic sites resected; 33.7% had prior adjuvant immunotherapy, and 11.9% had prior radiotherapy.

Of 815 patients, 75 were ineligible and 33 did not start protocol therapy (detailed in Data Supplement). Most of the reasons for ineligibility involved interpretation of the complex eligibility requirements. One was a pathologic misdiagnosis, which is not a rare occurrence in melanoma. Treatment data were reported for 777 of 782 treated patients (for treatment characteristics, see the Data Supplement). The median number of treatment cycles completed was 12 (range, 1 to 19 cycles). Approximately half of the patients (381 of 777; similar across arms) completed all 13 cycles of protocol therapy. Administration of protocol therapy was similar in all arms. Treatment beyond 13 cycles was allowed for patients with resected recurrences; 47 patients received more than 13 cycles; two completed 19 cycles.

Relapse was the main reason in all arms for treatment discontinuation before completion. Nine patients stopped protocol treatment because of toxicity. Other reasons, including deaths (unrelated to treatment or disease) and patient withdrawal, were similar in all arms. Figure 1 displays the CONSORT diagram for the study as of October 8, 2012.

OS and RFS by GM-CSF in Intent-to-Treat Population

As of October 8, 2012, 443 of 815 patients had died. A total of 327 (73.8%) died as a result of melanoma; 33 (7.5%), as a result of other causes; and 83 (18.7%), as a result of unspecified causes (Data Supplement). The median follow-up time was 82.1 months (range, 0 to 144.2 months) for the 372 surviving patients.

The median OS was 10.3 months longer in patients who received GM-CSF than in those who received GM-CSF placebo (69.6 *v* 59.3

Table 1. Patient Demographics and Disease Characteristics in All Patients

Variable	Arm A No.	A %	B No.	B %	C No.	C %	D No.	D %	E No.	E %	F No.	F %	Total No.	Total %
No. of patients (N = 815)	109		110		109		107		190		189		815	
Age, years														
Mean (SD)	60.1 (13.3)		56.4 (14.2)		58.2 (13.0)		58.8 (13.6)		59.2 (13.7)		57.6 (12.9)		58.4 (13.4)	
Median (range)	60 (27-83)		56 (22-82)		57 (23-87)		58 (23-82)		60 (19-88)		57 (19-87)		58 (19-88)	
Sex (n = 814)														
Male	61	56.0	66	59.0	64	59.0	68	64.0	112	59.3	112	59.0	483	59.3
Female	48	44.0	45	40.5	45	41.3	39	36.5	77	40.7	77	40.7	331	40.7
Ethnicity														
White	102	93.6	103	92.8	105	96.3	97	90.7	172	90.5	167	88.4	746	91.5
Other	3	2.8	2	1.8	1	0.9	3	2.8	3	1.6	7	3.7	19	2.3
Pre-NCI*	4	3.7	6	5.4	3	2.8	7	6.5	15	7.9	15	7.9	50	6.1
ECOG performance status (n = 811)														
0	91	85.1	95	86.4	89	81.7	80	74.8	149	78.8	154	81.5	658	81.1
1	16	15.0	15	13.6	20	18.3	27	25.2	40	21.2	35	18.5	153	18.9
T of primary tumor: Breslow, mm (n = 616)														
≤ 0.75	6	7.1	11	13.3	5	6.0	4	4.9	14	9.8	8	5.8	48	7.8
0.76-1.50	22	25.9	11	13.3	17	20.2	25	30.5	26	18.2	31	22.5	132	21.4
1.51-4.0	38	44.7	34	41.0	45	53.6	37	45.1	72	50.4	72	52.2	298	48.4
≥ 4.1	19	22.4	27	32.5	17	20.2	16	19.5	31	21.7	27	19.6	137	22.2
N: nodal involvement of primary tumor (n = 670)														
No regional node	64	70.3	61	70.1	61	68.5	53	62.4	107	66.9	103	65.2	449	67.0
1 Regional node with diameter ≤ 3 cm	16	17.6	18	20.7	18	20.2	25	29.4	36	22.5	44	27.9	157	23.4
1 Node with diameter > 3 cm	6	6.6	4	4.6	6	6.7	4	4.7	10	6.3	8	5.1	38	5.7
Multiple nodes	5	5.5	4	4.6	4	4.5	3	3.5	7	4.4	3	1.9	26	3.9
M: metastatic involvement of primary tumor (n = 703)														
No distant mets	87	93.6	84	90.3	83	89.3	79	88.8	151	89.4	155	93.4	639	90.9
Skin or subcutaneous	2	2.2	8	8.6	6	6.5	6	6.7	13	7.7	6	3.6	41	5.8
Visceral	4	4.3	1	1.1	4	4.3	4	4.5	5	3.0	5	3.0	23	3.3
Depth of invasion (Clark) of primary tumor (n = 591)														
Above basal lamina	2	2.4	1	1.3	3	3.6	0	0.0	3	2.2	2	1.5	11	1.9
Extension into papillary dermis	3	3.7	7	8.8	7	8.4	8	10.0	4	3.0	7	5.3	36	6.1
Interface papillary-reticular dermis	19	23.2	18	22.5	11	13.3	18	23.1	28	20.7	21	15.8	115	19.5
Reticular dermis	44	53.7	43	53.8	50	60.2	42	53.9	77	57.0	88	66.2	344	58.2
Subcutaneous fat	14	17.1	11	13.8	12	14.5	10	12.8	23	17.0	15	11.3	85	14.4
Disease stage at study entry (n = 766)														
IIIA	2	1.94	1	0.93	0	0	1	0.97	0	0	1	0.56	5	0.7
IIIB	29	28.2	31	29.0	32	33.0	32	31.1	48	27.1	44	24.6	216	28.2
IIIC	32	31.1	37	34.6	30	30.9	31	30.1	57	32.2	62	34.6	249	32.5
M1a	17	16.5	9	8.4	9	9.3	14	13.6	35	19.8	24	13.4	108	14.1
M1b	14	13.6	17	15.9	15	15.5	12	11.7	23	13.0	29	16.2	110	14.4
M1c	9	8.7	12	11.2	11	11.3	13	12.6	14	7.9	19	10.6	78	10.2
III	63	61.2	69	64.5	62	63.9	64	62.1	105	59.3	107	59.8	470	61.4
IV	40	38.8	38	35.5	35	36.1	39	37.9	72	40.7	72	40.2	296	38.6
Primary tumor site (n = 717)														
Head and neck	16	17.2	15	15.5	23	23.5	17	18.1	33	19.9	27	16.0	131	18.3
Upper limb	14	15.1	15	15.5	18	18.4	15	16.0	29	17.5	31	18.3	122	17.0
Lower limb	27	29.0	17	17.5	20	20.4	22	23.4	27	16.3	33	19.5	146	20.4
Subungual	1	1.1	0	0.0	1	1.0	2	2.1	1	0.6	0	0.0	5	0.7
Trunk	31	33.3	41	42.3	24	24.5	30	31.9	55	33.1	55	32.5	236	32.9
Anogenital	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.6	1	0.1
Eye	0	0.0	1	1.0	1	1.0	1	1.1	3	1.8	5	3.0	11	1.5
Mucosal	2	2.2	4	4.1	8	8.2	3	3.2	9	5.4	3	1.8	29	4.1
Other	2	2.2	4	4.1	3	3.1	4	4.3	9	5.4	14	8.3	36	5.0

(continued on following page)

Table 1. Patient Demographics and Disease Characteristics in All Patients (continued)

Variable	Arm A No.	A %	B No.	B %	C No.	C %	D No.	D %	E No.	E %	F No.	F %	Total No.	Total %
No. of positive nodes at primary presentation (n = 693)														
0	65	69.2	57	64.0	65	69.9	55	63.2	111	67.3	108	65.5	461	66.5
1-3	23	24.5	26	29.2	25	26.9	26	29.9	43	26.1	46	27.9	189	27.3
≥ 4	6	6.4	6	6.7	3	3.2	6	6.9	11	6.7	11	6.7	43	6.2
Pigmentation histology of primary tumor (n = 508)														
Amelanotic	7	10.0	6	8.2	6	9.5	10	14.9	17	14.9	19	15.7	65	12.8
Melanotic	63	90.0	67	91.8	57	90.5	57	85.1	97	85.1	102	84.3	443	87.2
Ulceration histology of primary tumor (n = 578)														
No	42	55.3	56	70.0	40	52.0	49	63.6	69	51.5	84	62.7	340	58.8
Yes	34	44.7	24	30.0	37	48.1	28	36.4	65	48.5	50	37.3	238	41.2
Lymphoid infiltration of primary tumor (n = 474)														
Absent	47	70.2	37	57.8	40	63.5	42	58.3	63	63.0	75	69.4	304	64.1
Sparse focal infiltrate	18	26.9	20	31.3	19	30.2	23	31.9	22	22.0	26	24.1	128	27.0
Dense or prominent	2	3.0	7	10.9	4	6.4	7	9.7	15	15.0	7	6.5	42	8.9
Current evidence of disease (n = 704)														
No	90	98.9	93	97.9	90	98.9	88	98.9	164	98.2	169	99.4	694	98.6
Yes	1	1.1	2	2.1	1	1.1	1	1.1	3	1.8	1	0.6	9	1.3
Matted lymph nodes (n = 630)														
No	75	96.2	75	89.3	83	97.7	77	97.5	148	95.5	144	96.6	602	95.6
Yes	3	3.9	9	10.7	2	2.4	2	2.5	7	4.5	5	3.4	28	4.4
Previous therapy														
Immunotherapy (n = 697)	35	38.5	42	43.8	39	42.9	36	40.9	56	33.7	67	40.6	275	39.5
Chemotherapy (n = 696)	0	0.0	2	2.1	5	5.5	2	2.3	3	1.8	11	6.7	23	3.3
Radiation therapy (n = 698)	6	6.6	17	17.7	13	14.3	10	11.2	27	16.3	24	14.6	97	13.9
Surgical treatment for melanoma														
Initial biopsy (n = 668)	80	91.0	77	84.6	79	91.0	75	87.0	140	89.7	132	83.0	583	87.3
Resection of primary (n = 674)	79	88.8	80	86.0	77	88.5	74	86.1	144	90.6	135	84.4	589	87.4
Lymphatic mapping (n = 650)	22	27.5	31	34.1	22	25.9	25	30.5	48	30.8	56	35.9	204	31.4
Sentinel lymph node biopsy (n = 671)	45	53.6	40	43.5	39	43.3	43	50.6	80	50.0	87	54.4	334	49.8
Resection of local skin recurrence (n = 676)	24	27.3	28	30.1	21	24.7	24	27.6	31	19.1	35	21.7	163	24.1
Resection of regional recurrence (n = 672)	25	28.4	26	28.3	19	22.1	21	24.4	30	18.4	38	24.2	159	23.7
Sentinel lymph node dissection (n = 672)	20	22.7	23	25.0	17	19.3	24	27.6	46	28.9	44	27.9	174	25.9
Regional lymph node dissection (n = 687)	52	57.8	58	61.7	56	62.2	46	53.5	105	63.6	99	61.1	416	60.6
Resection of nonvisceral distant recurrence (n = 673)	18	20.5	23	25.0	16	18.6	23	27.1	39	24.1	31	19.4	150	22.3
Resection of visceral distant recurrence (n = 683)	16	17.8	17	18.1	18	20.7	11	12.8	21	12.9	34	20.9	117	17.1
Other current/prior malignancy (n = 697)														
No	80	87.9	75	79.0	80	87.9	80	88.9	139	83.7	144	87.8	598	85.8
Yes	11	12.1	20	21.1	11	12.1	10	11.0	27	16.3	20	12.2	99	14.2
History of disease														
Cardiovascular/pulmonary (n = 808)	57	53.3	62	56.4	51	46.8	54	50.5	97	51.6	108	57.8	429	53.1
Immunologic dysfunction (n = 795)	1	1.0	6	5.5	4	3.7	2	1.9	4	2.1	6	3.3	23	2.9
Neurologic/psychiatric (n = 801)	30	28.6	32	29.1	29	26.9	30	28.6	50	26.6	50	27.0	221	27.6
Cancer other than melanoma (n = 801)	14	13.1	19	17.3	9	8.5	11	10.5	23	12.2	16	8.7	92	11.5
Renal: history of dysfunction (n = 800)	12	11.4	2	1.8	7	6.5	6	5.7	13	6.9	11	6.0	51	6.4
Hepatic: history of dysfunction (n = 799)	6	5.7	4	3.7	4	3.7	4	3.9	4	2.1	7	3.8	29	3.6
Gastrointestinal (n = 804)	30	28.3	28	25.5	34	31.2	29	27.6	51	27.0	49	26.5	221	27.5
Endocrinologic (n = 797)	81	77.1	91	83.5	88	82.2	87	82.9	144	77.0	162	88.0	144	18.1
Genitourinary (n = 800)	29	27.6	20	18.2	14	13.1	20	19.1	38	20.2	35	18.9	156	19.5
Dermatologic (n = 800)	30	28.6	21	19.1	23	21.5	23	21.9	42	22.3	22	11.9	161	20.1
Musculoskeletal (n = 800)	30	28.6	39	35.5	32	29.9	23	21.9	52	27.7	55	29.7	231	28.9
Stratification factors used for random assignment														
HLA-A2														
Positive	109	100.0	111	100.0	109	100.0	107	100.0	0	0.0	0	0.0	436	53.5
Negative	0	0.0	0	0.0	0	0.0	0	0.0	190	100.0	189	100.0	379	46.5

(continued on following page)

Table 1. Patient Demographics and Disease Characteristics in All Patients (continued)

Variable	Arm A No.	Arm A %	Arm B No.	Arm B %	Arm C No.	Arm C %	Arm D No.	Arm D %	Arm E No.	Arm E %	Arm F No.	Arm F %	Total No.	Total %
Site of metastases														
Visceral	18	16.5	17	15.3	19	17.4	19	17.8	31	16.3	37	19.6	141	17.3
Nonvisceral	75	68.8	79	71.2	73	67.0	75	70.1	136	71.6	131	69.3	569	69.8
Visceral and nonvisceral	2	1.8	4	3.6	2	1.8	3	2.8	2	1.1	2	1.1	15	1.8
No	14	12.8	11	9.9	15	13.8	10	9.4	21	11.1	19	10.1	90	11.0
No. of metastatic lesions														
1	67	61.5	71	64.0	70	64.2	69	64.5	121	63.7	124	65.6	522	64.1
2-3	20	18.4	18	16.2	18	16.5	20	18.7	30	15.8	34	18.0	140	17.2
≥ 4	7	6.4	7	6.3	6	5.5	7	6.5	14	7.4	11	5.8	52	6.4
0	15	13.8	15	13.5	15	13.8	11	10.3	25	13.2	20	10.6	101	12.4

NOTE. $P = .02$ for history of dermatologic disease by Fisher's exact test; $P > .05$ for all other binary or categoric variables by Fisher's exact test; $P > .05$ for age by analysis of variance test. Arms: A, GM-CSF plus PV; B, GM-CSF placebo plus PV; C, GM-CSF plus PV placebo; D, GM-CSF placebo and PV placebo; E, GM-CSF; F, GM-CSF placebo.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; GM-CSF, granulocyte-macrophage colony-stimulating factor; HLA, human leukocyte antigen; NCI, National Cancer Institute; PV, peptide vaccination; SD, standard deviation.
*Prior to the requirement for reporting the ethnicity of participants.

months; 17.4% improvement). This was less than the projected absolute increase of 13.3 months and the relative improvement of 33% required for significance (HR, 0.94; 95% repeated CI, 0.77 to 1.15; stratified log-rank $P = .528$; Table 2; Fig 3A; Data Supplement). The 5-year OS probability was 52.3% (95% CI, 47.3% to 57.1%) in GM-CSF–treated patients and 49.4% (95% CI, 44.3% to 54.3%) in GM-CSF placebo–treated patients.

Five hundred sixty-seven patients experienced disease recurrence, and 24 died without recurrence (Data Supplement), for a total of 591 RFS events among the 815 patients. The median RFS

Table 2. Median Time and 5-Year Rate of OS and RFS

Group	OS No. of Events/ No. of Patients	OS Median (range) Time, Months	OS 5-Year Rate, % (95% CI)	OS *P**	RFS No. of Events/ No. of Patients	RFS Median (range) Time, Months	RFS 5-Year Rate, % (95% CI)	RFS *P**
GM-CSF				.53				.13
No	222/407	59.3 (44.4-77.3)	49.4 (44.3 to 54.3)		296/407	8.8 (7.5-11.2)	27.0 (22.7 to 31.5)	
Yes	221/408	69.6 (53.4-83.5)	52.3 (47.3 to 57.1)		295/408	11.4 (9.4-14.8)	31.2 (26.7 to 35.9)	
PV				.60				.71
No	115/216	63.3 (49.2-105.0)	51.4 (44.4 to 58.0)		156/216	9.8 (7.7-15.5)	29.7 (23.4 to 36.0)	
Yes	114/220	68.6 (47.0-92.3)	53.7 (46.7 to 60.2)		151/220	11.5 (8.7-20.4)	32.9 (26.6 to 39.3)	
Treatment arm								
HLA-A2 positive				.88				.91
A	55/109	72.1 (41.3-NR)	55.5 (45.4 to 64.5)		76/109	12.8 (9.0-22.0)	32.4 (23.6 to 41.5)	
B	59/111	63.7 (36.3-NR)	51.9 (42.0 to 61.0)	.44†	75/111	10.0 (5.8-25.4)	33.2 (24.4 to 42.2)	.59†
C	59/109	69.3 (34.8-115.4)	51.1 (41.2 to 60.1)	.43†	79/109	10.0 (7.4-20.9)	31.3 (22.8 to 40.2)	.78†
D	56/107	62.2 (39.1-105.0)	51.6 (41.4 to 60.9)	.77†	77/107	9.8 (5.9-19.0)	28.0 (19.7 to 36.9)	.43†
HLA-A2 negative				.69				.13
E	107/190	69.9 (45.2-82.7)	51.2 (43.8 to 58.2)		140/190	11.0 (8.6-18.2)	30.6 (24.1 to 37.3)	
F	107/189	51.4 (37.3-79.9)	46.7 (39.3 to 53.8)		144/189	8.4 (6.2-9.7)	22.9 (17.1 to 29.2)	
No PV				.84				.47
Arms E + F	214/379	57.9 (44.4-76.4)	49.0 (43.8 to 54.0)		284/379	9.2 (8.4-11.4)	26.7 (22.3 to 31.3)	
Arms C + D	115/216	63.3 (49.2-105.0)	51.4 (44.4 to 58.0)		156/216	9.8 (7.7-15.5)	29.7 (23.7 to 36.0)	
Arm C *v* E				.97				.90
Arm D *v* F				.68				.36

NOTE. Arms: A, GM-CSF plus PV; B, GM-CSF placebo plus PV; C, GM-CSF plus PV placebo; D, GM-CSF placebo and PV placebo; E, GM-CSF; F, GM-CSF placebo.
Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; HLA, human leukocyte antigen; NR, not reached; OS, overall survival; PV, peptide vaccination; RFS, relapse-free survival.
**P* values were from a stratified log-rank test. The stratification factors for the GM-CSF comparison were HLA-A2 status, site of metastases, and number of metastatic lesions. For the peptide vaccine comparison, the stratification factors were GM-CSF, site of metastases, and number of metastatic lesions. For all other comparisons, the stratification factors were site of metastases and number of metastatic lesions.
†*P* values were for pairwise comparisons between arms B, C, D, and A (reference group) in HLA-A2–positive patients.

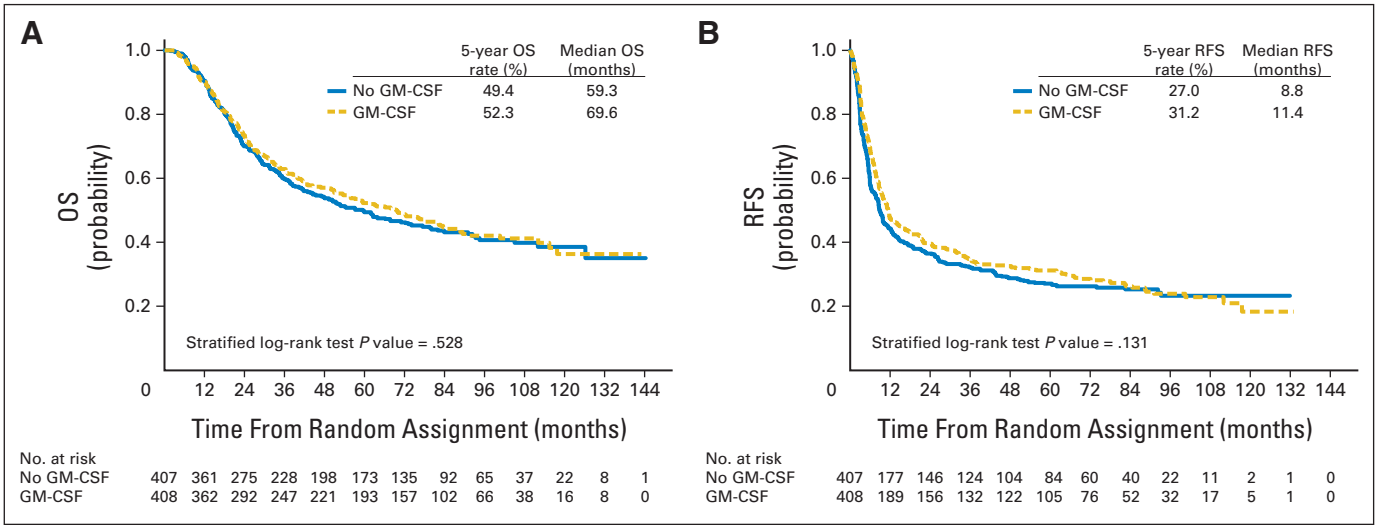

Fig 3. Kaplan-Meier plot of (A) overall survival (OS) and (B) relapse-free survival (RFS) by granulocyte-macrophage colony-stimulating factor (GM-CSF).

was 11.4 months (95% CI, 9.4 to 14.8 months) in GM-CSF–treated patients and 8.8 months (95% CI, 7.5 to 11.2 months) in GM-CSF placebo–treated patients: an increase of 2.6 months, or 30% (HR, 0.88; 95% CI, 0.74 to 1.04; stratified log-rank $P = .131$; Table 2; Fig 3B; Data Supplement). The 5-year RFS probability was 31.2% (95% CI, 26.7% to 35.9%) in GM-CSF–treated patients and was 27.0% (95% CI, 22.7% to 31.5%) in GM-CSF placebo–treated patients.

OS and RFS With PV in HLA-A2–Positive Patients

Of 436 HLA-A2–positive patients, 220 were randomly assigned to receive PV (n = 109, with GM-CSF; n = 111, without), and 216 received PV placebo (n = 109, with GM-CSF; n = 107, without).

There were a total of 229 deaths (Data Supplement). The median OS time was 68.6 months (95% CI, 47.0 to 92.3 months) in patients who received PV and 63.3 months (95% CI, 49.2 to 105.0 months) in PV placebo–treated patients (HR, 0.93; 95% CI 0.71 to 1.21; $P = .598$; Table 2; Fig 4A; Data Supplement).

There were 307 RFS events (n = 316 events with full information) in the 436 HLA-A2–positive patients (Data Supplement). The median RFS time was 11.5 months (95% CI, 8.7 to 20.4 months) for PV-treated patients and 9.8 months (95% CI, 7.7 to 15.5 months) for PV placebo–treated patients (HR, 0.96; 95% repeated CI, 0.74 to 1.23; $P = .708$; Table 2; Fig 4B; Data Supplement.

Effect of HLA Status on OS and RFS in All Patients

Neither OS nor RFS was significantly different between HLA-A2–positive and –negative patients, regardless of treatment (median OS, 68.6 *v* 57.9 months, respectively [$P = .519$; Data Supplement]; median RFS, 11.3 *v* 9.2 months, respectively [$P = .285$; Data Supplement]).

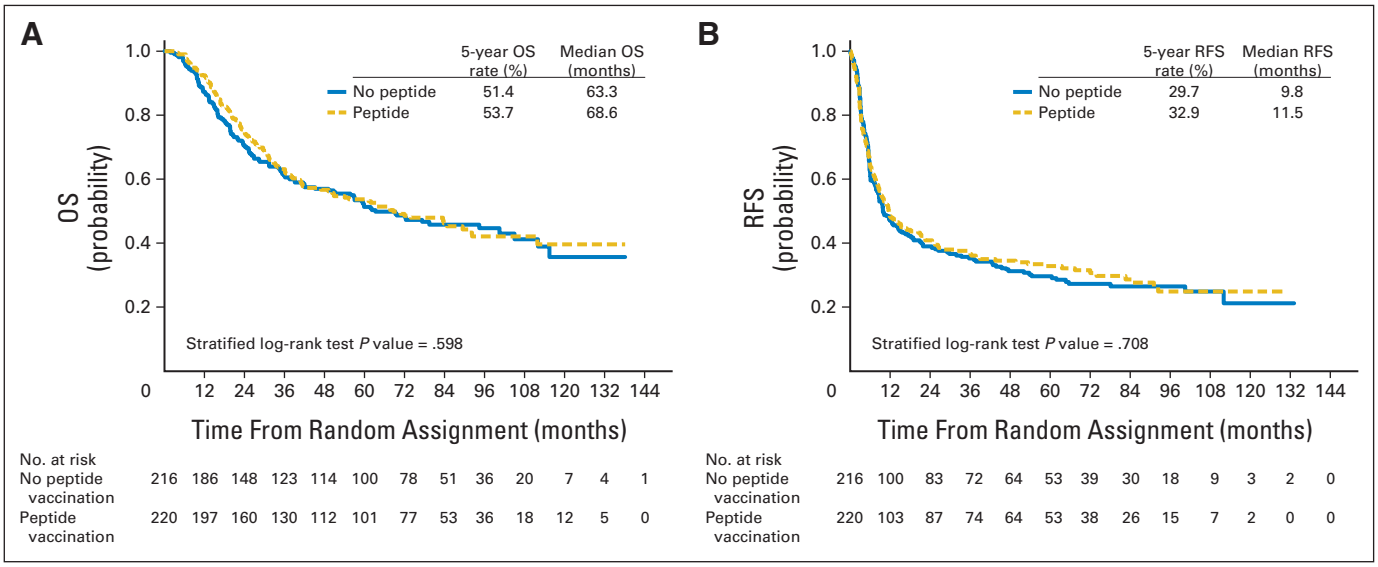

Fig 4. Kaplan-Meier plot of (A) overall survival (OS) and (B) relapse-free survival (RFS) by peptide vaccination in human leukocyte antigen A2–positive patients.

Effect of Systemic GM-CSF on Clinical Response to PV

The median OS for HLA-A2–positive patients who received GM-CSF plus PV was 72.1 months compared with 63.7, 69.3, and 62.2 months for peptide alone, GM-CSF alone, and placebo, respectively (Data Supplement). This difference was not statistically significant ($P = .881$).

Exploratory Subgroup Analyses of OS and RFS

The analysis of treatment effects by the three stratification factors (HLA-A2 status, site of metastases, and number of metastatic lesions) suggested a possible interaction between treatment with GM-CSF and whether the resected metastases were visceral or nonvisceral.

After publication of the seventh edition of the American Joint Committee on Cancer Staging Manual in 2010, 766 patients were centrally staged according to that system. In an exploratory manner not prespecified in the protocol, the effect of GM-CSF was evaluated by stage of disease at study entry. No effect of GM-CSF on RFS or OS was observed in patients with stage IIIA, IIIB, or IIIC/M1a disease (data not shown). For patients with resected, stage M1b or M1c tumors (with visceral metastases), the median RFS time was 10.2 months for those treated with GM-CSF versus 5.8 months for those treated with GM-CSF placebo ($P = .261$); the median OS was 72.4 months versus 37.3 months, respectively ($P < .001$; Data Supplement).

For the comparison between PV and placebo in HLA-A2–positive patients, the effect observed in this unplanned analysis showed a different trend: there was no difference in RFS or OS for patients with stage IIIA or IIIB disease (data not shown), but patients with stage IIIC/M1a disease who received PV versus placebo had better RFS (median, 15.2 *v* 9.7 months; $P = .040$) and OS (median, 91.1 *v* 39.1 months; $P = .128$). Among patients with stage M1b or M1c disease, however, PV versus placebo was associated with worse RFS (median, 5.5 *v* 20.9 months; $P = .018$) and OS (median, 32.8 *v* 72.4 months; $P = .288$; Data Supplement).

AEs

AEs were reported for 782 patients who received at least one dose of protocol therapy. Overall, the incidence of treatment-related grade 3 or higher AEs was similar in patients who received GM-CSF (12.3%) and those who did not (9.9%; $P = .306$) and in those who received PV (13.6%) and those who did not (11.4%; Table 3). Overall, the most common grade 3 or higher AEs were injection-site reactions (17 [2.2%] of 782) and headache (16 [2.0%] of 782; Data Supplement). A total of four grade 5 AEs (ie, deaths) occurred during treatment on the study, none of which was considered related to protocol treatment (Data Supplement).

Second Malignancies

Seventy-three patients developed a second primary cancer during the study period. Fifty-five patients had one second primary cancer, and 18 had multiple new cancers, which resulted in a total of 118 new cancer events. Most second primary cancers were melanoma (n = 12) and nonmelanoma (n = 58) skin cancers (Data Supplement). There were no instances of myeloid leukemia, but one patient developed acute lymphocytic leukemia.

DISCUSSION

This is the first randomized trial of adjuvant GM-CSF in patients with resected, stage III and IV melanoma. The median OS was 10.3 months longer (69.6 *v* 59.3 months, representing a 17.4% improvement) in patients who received GM-CSF than in patients who received GM-CSF placebo; this result was less than the hypothesized increase in OS (absolute increase, 13.3 months; relative improvement, 33%) sought in the trial. The RFS times were 11.4 months for GM-CSF versus 8.8 months for placebo. These results are not statistically significant but leave open the question of whether GM-CSF may have smaller benefits. Other possible contributors to this lack of significant benefit

Table 3. Comparison of Incidence of Grade 3 or Higher Adverse Events in Treated Patients

Group	Treatment-Related AEs				All AEs		
	No. of Patients	No. of Grade ≥ 3 AEs	Incidence, % (95% CI)	*P**	No. of Grade ≥ 3 AEs	Incidence, % (95% CI)	*P**
GM-CSF				.306			.064
No	385	38	9.9 (7.1 to 13.3)		79	20.5 (16.6 to 24.9)	
Yes	397	49	12.3 (9.3 to 16.0)		104	26.2 (21.9 to 30.8)	
PV				.558			.827
No	211	24	11.4 (7.4 to 16.4)		55	26.1 (20.3 to 32.5)	
Yes	214	29	13.6 (9.3 to 18.9)		58	27.1 (21.3 to 33.6)	
Treatment arm				.452			.633
HLA-A2 positive							
A	104	12	11.5 (6.1 to 19.3)		30	28.8 (20.4 to 38.6)	
B	110	17	15.4 (9.3 to 23.6)		25	22.7 (15.3 to 31.7)	
C	107	15	14.0 (8.1 to 22.1)		23	21.5 (14.1 to 30.5)	
D	104	9	8.6 (4.0 to 15.8)		25	24.0 (16.2 to 33.4)	
HLA-A2 negative				.149			.022
E	186	22	11.8 (7.6 to 17.4)		51	27.4 (21.1 to 34.4)	
F	171	12	7.0 (3.7 to 11.9)		29	17.0 (11.7 to 23.4)	

NOTE. Arms: A, GM-CSF plus PV; B, GM-CSF placebo plus PV; C, GM-CSF plus PV placebo; D, GM-CSF placebo and PV placebo; E, GM-CSF; F, GM-CSF placebo.
Abbreviations: AE, adverse event; GM-CSF, granulocyte-macrophage colony-stimulating factor; HLA, human leukocyte antigen; PV, peptide vaccination.
*Fisher's exact test was used for all comparisons. $P > .05$ for pairwise comparisons between arms A, B, C, and arm D (reference group) in HLA-A2–positive patients.

include lack of efficacy, pre-existing immune status of patients, immunologic response to GM-CSF, development of neutralizing antibodies to GM-CSF, effects of GM-CSF on suppressor elements (such as myeloid-derived suppressor cells), and possible suboptimal dose and/or duration of treatment.[6,7,9] The greater effect on OS than on RFS seen in other studies[6-8] was not seen in this study.

In HLA-A2–positive patients, the median RFS was 1.7 months longer in patients who received PV versus PV placebo (11.5 *v* 9.8 months; 17.3% improvement), which was less than the expected improvement (3 months; 33% improvement) and not statistically significant. Possible reasons for this include baseline immune status of the patients, limited response of patients to PV, lack of relevance of any immune response to PV, adjuvant selection, and vaccine administration issues.

Among HLA-A2–positive patients, the median OS and RFS were longer in patients receiving both GM-CSF and PV than in patients in the other three arms, but the differences were not significant. The study does not support the hypothesis that systemically administered GM-CSF enhances the efficacy of PV, as administered in this trial. This is consistent with the findings from trial E1696 conducted in patients with active disease.[13]

Analysis of results by prespecified stratification factors suggested differential effects of both GM-CSF and PV according to the sites of metastases (visceral *v* nonvisceral). These results are hypothesis generating and may be explained by differences in immune status of patients with visceral metastases that persist past resection, effect of resection itself, and possible differential effects of immunomodulatory agents on visceral-versus-nonvisceral tumor microenvironments that contribute to the prevention of additional growth of unrecognized micrometastases.

There was no difference in the natural history of HLA-A2–positive and –negative patients, nor in treatment effect of GM-CSF between the two HLA types. Others, however, found that patients with the HLA-Cw*06 allele had better RFS and OS after IFN treatment than those with other alleles,[16] and data suggest an effect of HLA-A2 status on the benefit of adjuvant IFN.[17] Thus, there may be interactions between HLA type and response to other immunotherapeutic agents, or interactions with other HLA types and GM-CSF.

Safety data analysis confirms that GM-CSF and PV are well tolerated and safe. The most common AEs were injection-site reactions and headache.

Although, overall, this study did not support the hypothesis that adjuvant GM-CSF could make a significant impact on RFS or OS of the study population, trials that test GM-CSF in patients with resected visceral melanoma metastases are worthy of consideration. Such studies may target a patient population unable, unlikely, or unwilling to tolerate current immunotherapeutic adjuvant agents (eg, IFN, cytotoxic T-cell lymphocyte-4 blockade) on the basis of a borderline performance status or other comorbid conditions, such as symptomatic lung disease, inflammatory bowel disease, or significant autoimmune diseases.

GM-CSF may find its greatest use in melanoma in combination with other agents. Recent data strongly suggest that the addition of GM-CSF at the dose used in our study to ipilimumab 10 mg/kg, with maintenance dosing (higher dose and longer treatment than that approved for metastatic melanoma), may improve both efficacy and safety in patients with metastatic disease. This suggestion led to an ongoing trial (EA6141) that will definitively test this hypothesis.[18] If successful, this regimen may be tested in the adjuvant setting.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized, Placebo-Controlled, Phase III Trial of Yeast-Derived Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) Versus Peptide Vaccination Versus GM-CSF Plus Peptide Vaccination Versus Placebo in Patients With No Evidence of Disease After Complete Surgical Resection of Locally Advanced and/or Stage IV Melanoma: A Trial of the Eastern Cooperative Oncology Group–American College of Radiology Imaging Network Cancer Research Group (E4697)

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