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Priority Brief

Cancer Immunology Research

Single Institution Experience of Ipilimumab 3 mg/kg with Sargramostim (GM-CSF) in Metastatic Melanoma

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Abstract

Ipilimumab, 10 mg/kg with sargramostim (GM-CSF; GM), improved overall survival (OS) and safety of patients with advanced melanoma over ipilimumab in a randomized phase II trial. The FDA-approved dose of ipilimumab of 3 mg/kg has not been assessed with GM (IPI-GM). Consecutive patients treated with IPI-GM at a single institution were reviewed. Treatment included ipilimumab every 3 weeks × 4 and GM, 250-μg s.c. injection days 1 to 14 of each ipilimumab cycle. Efficacy, clinical characteristics, toxicities, and blinded radiology review of tumor burden were evaluated. Thirty-two patients were identified with 25 (78%) having immune-related response criteria (irRC) measurable disease and 41% with central nervous system metastases. A total of 88.6% of GM doses were administered. Response rate by irRC and disease control rate at 12 weeks were 20% and 44%, respectively (median follow-up 37 weeks). Immune-related adverse events (irAE) were observed in 10 (31.3%) patients, with 3 (9.4%) grade 3 events. Patients with grade 3 irAEs had prior autoimmunity, advanced age, and poor performance status. The median OS from first dose of ipilimumab was 41 weeks. Ipi-GM treatment is feasible and in this poor-risk advanced melanoma population, efficacy appeared similar but safety appeared improved relative to historical ipilimumab alone. *Cancer Immunol Res; 3(9); 986–91. ©2015 AACR.*

Introduction

Malignant melanoma is an aggressive disease with an annual incidence of greater than 70,000 cases in the United States (1). Ipilimumab is a fully human IgG1 monoclonal antibody that inhibits CTL antigen-4 (CTLA-4). Ipilimumab was shown to induce an overall survival (OS) advantage in patients with melanoma in two randomized phase III studies (2, 3).

Sargramostim (granulocyte-macrophage colony-stimulating factor or GM-CSF) is a cytokine that increases antigen presentation by dendritic cells and increases antitumor activity of T and B lymphocyte populations (4–6). Administration of GM-CSF has been evaluated in multiple tumor types, including melanoma and other cancers (7, 8). The clinical properties of GM-CSF are somewhat controversial as several studies have suggested a potential immunosuppressive role in certain contexts (9). GM-CSF also plays a role in pulmonary and mucosal homeostasis (10, 11), and may modulate some forms of autoimmunity, especially involving the gastrointestinal tract (12).

A randomized multicenter phase II study of ipilimumab, 10 mg/kg with sargramostim, demonstrated improvements in OS and safety profile over ipilimumab alone [Eastern Cooperative Oncology Group (ECOG) study 1608; ref. 13]. Specifically, the incidence of high-grade immune-related adverse events (irAE), including colitis and pneumonitis, was significantly reduced. To date, no experience of ipilimumab at 3 mg/kg (the FDA-approved dose) with sargramostim has been reported.

To assess the feasibility as well as preliminary safety and efficacy of ipilimumab, 3 mg/kg with sargramostim, we conducted a single center, retrospective analysis of 32 patients with metastatic cutaneous melanoma treated with ipilimumab and sargramostim in standard clinical practice. Herein, we report the clinical activity and toxicity observed.

Materials and Methods

Patients and clinical characteristics

Consecutive patients who were not eligible for or declined participation in clinical trials underwent informed consent for treatment with ipilimumab, 3 mg/kg and sargramostim. Clinical data were collected under Institutional Review Board approval. Relevant clinical parameters were collected, including age, gender, ECOG performance status, site(s) of metastatic disease, lines of prior therapy, and number of sargramostim doses administered. Laboratory parameters were collected such as lactate dehydrogenase (LDH) and absolute lymphocyte count (ALC) were collected at baseline and at 7 weeks. Treatment response and safety data were also determined. All data were aggregated following patient deidentification.

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Treatment

Ipilimumab was given as per standard practiceat 3 mg/kg every 3 weeks for 4 doses. Sargramostim was given as an s.c. injection of 250 μg flat dose by the patient or family member at home on days 1 to 14 of each ipilimumab cycle.

Efficacy and toxicity assessment

Efficacy and toxicity were evaluated in all patients who received 1 dose of ipilimumab and sargramostim. Beneficial effects of ipilimumab were categorized as complete response (CR), partial response (PR), or stable disease (SD). Disease control rate was calculated as the percentage of patients without progression at 12 weeks after starting ipilimumab treatment.

Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 and immune-related response criteria (irRC) were applied to determine response in those patients with baseline measurable disease (14–17). OS was calculated by Kaplan–Meier methodology from first dose of ipilimumab to date of death by any cause. Toxicity was assessed through chart review and graded using Common Terminology Criteria for Adverse Events (version 4.0) with attention on irAEs, including dermatitis, colitis, hepatitis, pneumonitis, thyroiditis, and hypophysitis.

Univariate comparisons of OS for baseline LDH, ECOG performance status, tumor mutational status, central nervous system (CNS) metastases and ALC were conducted using Kaplan–Meier estimates; differences were assessed using the log-rank test. LDH was divided as above or below the institutional upper limit of normal; ALC was divided into low (<1,000 cells/μL) or normal (≥1,000 cells/μL). ECOG performance status was classified as fully active versus any restriction (0 vs. 1–2). Covariates of survival were calculated by univariate comparisons for patients who received ≥2 doses of ipilimumab as well as with measurable disease at baseline. Conditional landmark analyses were conducted to compare OS according to 7-week ALC levels (low vs. normal). To minimize the potential for guarantee-time bias, patients who died before 7 weeks or who did not have 7-week ALC data were removed from the analysis. The remaining patients were followed forward in time. Statistical significance was defined as $P < 0.05$.

Results

Patients, clinical characteristics, and drug administration

The clinical characteristics of the 32 patients included in the analysis are shown in Table 1. Patients were predominately male with a median age of 63 years and median ECOG status of 1. The median number of prior therapies was zero and median LDH was 169 U/L (23% elevated). Fifty-six percent of patients had three or more sites of metastatic disease and 41% of patients had CNS metastases. Median number of ipilimumab doses administered was 4. Three patients who were consented for sargramostim were unable to obtain the drug through insurance either due to denial or high patient out-of-pocket cost. These patients were not included in any analysis. Of note, 1,302 of 1,470 (88.6%) planned doses of sargramostim were administered.

Table 1. Patient characteristics

Total study subjects	32	
Age, median (range; y)	63	26–95
Sex		
Male	17	53%
Female	15	47%
ECOG PS pretreatment (median ECOG 1, range 0–2)		
0	14	44%
1	15	47%
2	3	9%
Mutational status		
BRAF	6	19%
NRAS	11	34%
Non-BRAF or -NRAS	15	47%
Pretreatment median LDH (range)	169	112–2,090
Patients with elevated LDH (%)	11	23%
Pretreatment median ALC	1.13	
Prior lines of therapy, *n* (%)		
0	21	66%
1	5	16%
2	3	9%
≥3	3	9%
Median prior lines of therapy	0	
Prior radiation	18	56%
Number of metastatic sites		
1	6	19%
M1b	5	16%
M1c	1	3%
2	8	25%
≥3	18	56%
Brain	13	41%
Median doses of ipilimumab, *n* (range)	4	(1–4)
Total doses of ipilimumab	105	
Doses of GM-CSF[a]	1,302/1,470	88.6%

NOTE: LDH in U/L; ALC (Kcells/μL).

[a]14 doses possible per dose of ipilimumab or 56 for treatment course.

Response analysis

Measurable lesions were present on baseline scans in 24 patients according to RECIST and in 25 patients according to irRC. One patient had a cervical lymph node measuring 1.2 × 1.0 cm alone as the baseline tumor burden; the lesion was nonmeasurable according to RECIST, which requires at least 1.5 cm in short axis for nodes to be measurable, however, was measurable according to irRC because it was ≥0.5 × 0.5 cm. Patients without measurable lesions at baseline had additional tumor burden from nonmeasurable lesions that was deemed significant enough to initiate treatment. These patients were assessed qualitatively and followed until a progression event, and were not included in the best overall response analysis.

Best overall response included 5 patients with PR (5/24, 21%) and 7 patients with SD at 12 weeks (7/24, 29%) by RECIST, and 5 patients with PR (5/25, 20%), and 6 patients with SD (6/25, 24%) by irRC among those with measurable disease at baseline. Overall disease control rate of ≥12 weeks was 12 of 24 patients (50%) by RECIST and 11 of 25 patients (44%) by irRC (Table 2). Median follow-up was 37 weeks. The median time to progression (TTP) was 13.7 weeks and was similar between patients with evaluable (14.0 weeks) and nonevaluable (13.2 weeks) disease. Similarly TTP did not vary significantly by mutational status (BRAF:NRAS: non-BRAF/NRAS) or presence or absence of CNS metastases. Given that treatment was administered in standard practice, the timing of restaging imaging was somewhat variable. In patients with measurable disease by irRC, the first three scans took place at medians of 13.0, 18.0, and 25.7 weeks.

The changes in disease burden from baseline according to RECIST and irRC are shown in Fig. 1A and B. No patients had initial progression followed by a formal tumor response; however, several patients had initial progressive disease with subsequent tumor shrinkage and clinical stability. Patients receiving clinical benefit ranged from 26 to 95 years of age, and were of

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Table 2. Clinical outcomes by RECIST and irRC and toxicities

	RECIST		irRC	
	Patients	**%**	**Patients**	**%**
PD	7/24	50%	9/25	56%
SD	7/24	29%	6/25	24%
PR	5/24	21%	5/25	20%
CR	0/24	0%	0/25	0%
SD + PR	12/24	50%	11/25	44%
	Toxicities			
irAE	**Any grade**	**%**	**G3–4**	**%**
Dermatitis[a]	5	18.5%	1	3.7%
Colitis	2	7.4%	2	7.4%
Thyroiditis	0	0.0%	0	0.0%
Uveitis	0	0.0%	0	0.0%
Pancreatitis	0	0.0%	0	0.0%
Hepatitis	0	0.0%	0	0.0%
Hypophysitis	2	7.4%	0	0.0%
Pneumonitis	1	3.7%	0	0.0%
Total	10	31.3%	3	9.4%

[a]One case of dermatitis was dermatomyositis.

heterogeneous molecular status and included patients with CNS metastases.

The biochemical parameters of patients experiencing clinical benefit included LDH level that was within normal limits in all but 2 patients. All patients experiencing disease control had a rise in ALC from baseline to week 7 (median increase of 430 cells/μL), except one patient who had a decrease of 500 cells/μL and another without a follow-up ALC value at 7 weeks.

OS analysis

The median OS was 41 weeks [95% confidence interval (CI), 30–∞; Fig. 2]. Subsequent treatment within the entire cohort included 6 patients who received anti-programmed death-1 (PD-1) antibodies and 4 patients who received BRAF plus MEK inhibitors. In univariate comparisons of survival according to covariates, only LDH level (normal/elevated) was statistically significantly different between survivors and patients who died (log-rank $P = 0.0001$). Median survival among patients with normal LDH levels was not reached; in patients with elevated levels, the median survival was 16 weeks (95% CI, 1–36). Other factors that did not correlate with survival in the total population included ALC, mutational status and CNS metastases.

The conditional landmark analysis based on ALC at 7 weeks reduced the sample size from 32 patients to 24 patients. There was no difference in OS noted between patients with baseline ALC $\geq$ 1,000 cells/μL ($n = 19$ patients) versus ALC < 1,000 cells/μL ($n = 5$; log-rank $P = 0.71$). Cox proportional hazards model of OS stratified by LDH (normal/elevated) showed that that hazard of

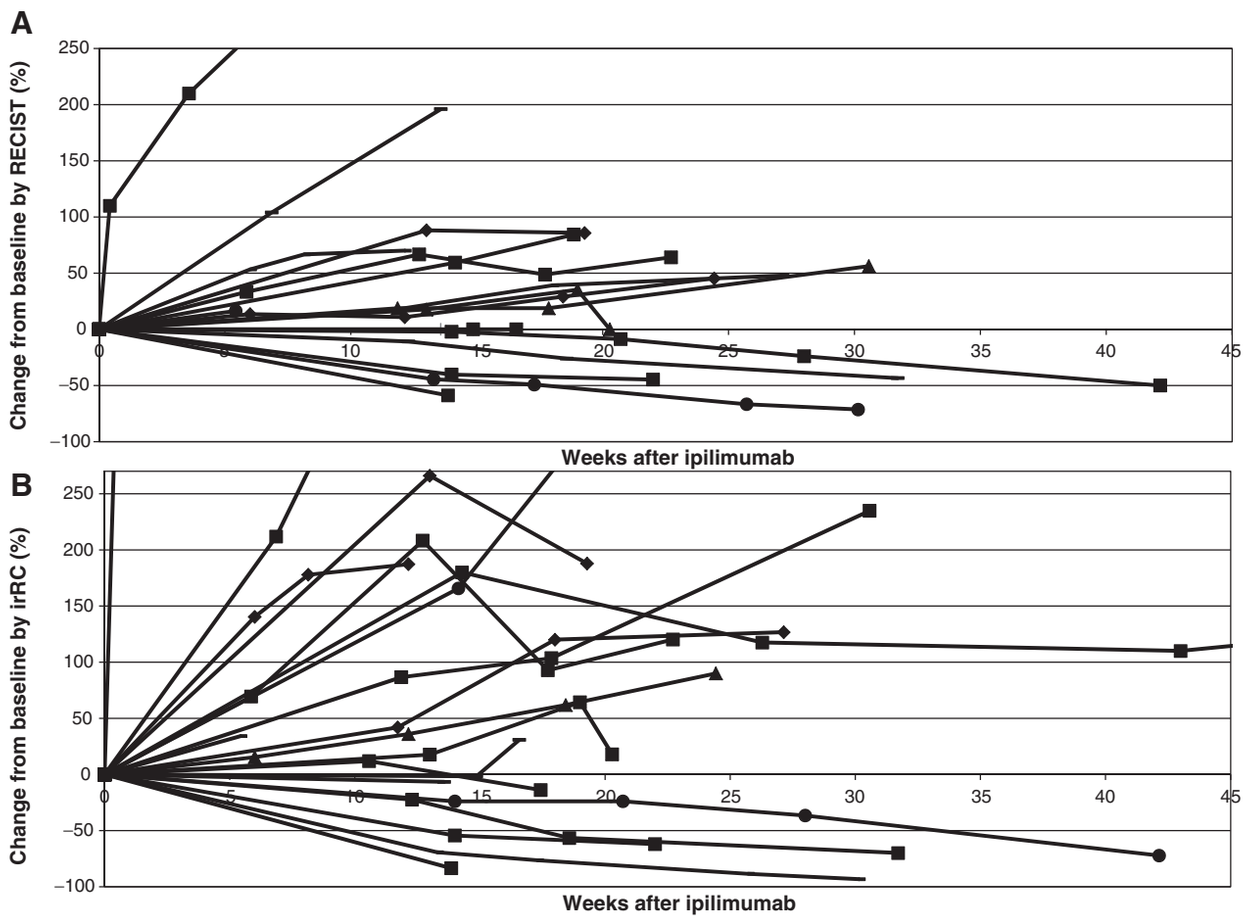

Figure 1.
A and B, change in disease burden for each patient over time by RECIST and irRC.

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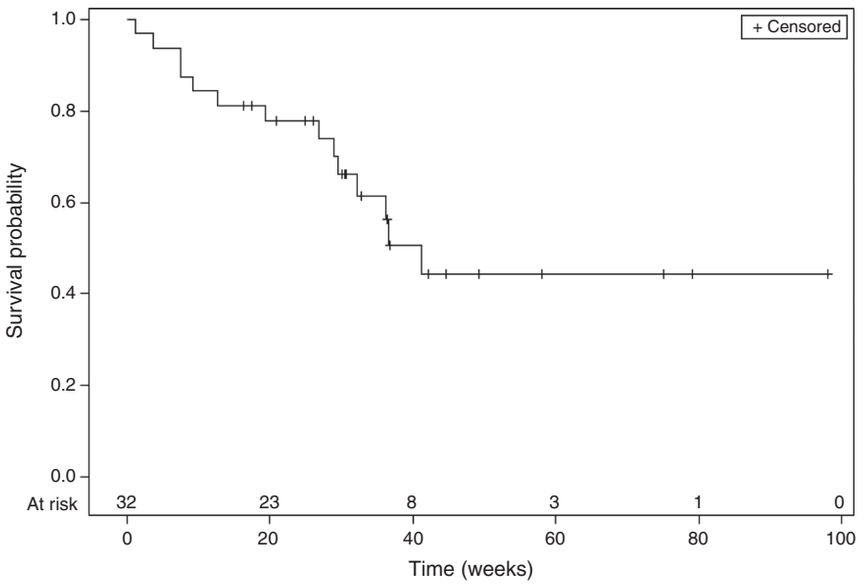

Figure 2.
OS for entire cohort. The median OS for the total cohort was 41 weeks (95% CI, 30–∞).

death for patients with low 7-week ALC was 1.49 times the hazard of patients with normal 7-week ALC. However, the comparison did not reach statistical significance (HR, 1.49; 95% CI, 0.27–8.3; $P = 0.65$).

In the restricted cohort of 25 patients with evaluable disease at baseline, median OS was 37 weeks (95% CI, 19–∞). As with the total cohort, only LDH level (normal vs. elevated) was statistically significantly associated with OS (log-rank $P = 0.0001$). Conditional landmark analysis of survival based on 7-week ALC again did not show a significant relationship (log-rank $P = 0.43$).

Toxicity analysis

The overall incidence of irAE in all patients was 31.3% with 9.4% grade 3 (G3) events and no treatment-related deaths (Table 2). Dermatitis was the most common irAE, affecting five patients. Three G3 irAE were described, including two events of colitis and one event of dermatitis. The three patients who experienced G3 irAEs were complex. One patient had previously discontinued ipilimumab as a single agent due to G3 rash 1 year earlier and upon reinduction with ipilimumab plus sargramostim developed G3 rash again with eventual evolution into dermatomyositis. Two patients developed G3 colitis, including one with a history of collagenous colitis who was on chronic therapy with oral aminosalicylates, and another who was of advanced age (90-year-old). These toxicities were treated using standard management algorithms with intravenous corticosteroids followed by slow tapers of oral steroids.

Discussion

This retrospective study evaluating the feasibility and clinical characteristics of ipilimumab, 3 mg/kg with sargramostim, is the first report of this combination being administered with the currently approved dose of ipilimumab. From a practical standpoint, subcutaneous injection of sargramostim was feasible with 88% of expected doses being administered.

From a clinical perspective, the toxicity and preliminary patient outcomes observed were generally similar with those reported in the randomized phase II study of ipilimumab, 10 mg/kg with sargramostim, compared with ipilimumab alone (ECOG 1608). The best overall response rate (RR) by RECIST and irRC were found to be 21% and 20%, respectively. This is in previous single-agent studies or the approximately 15% reported in ECOG 1608. However, given the small sample size of the population and lack of randomization within this study, the RR reported here does not appear to be a clinically meaningful difference. In the ECOG 1608 study, the RR of ipilimumab with sargramostim was not different compared with ipilimumab alone or from historical ipilimumab controls. Median OS in this study was 41 weeks. The length of follow-up, as well as improved treatment options after ipilimumab plus sargramostim, potentially confound the ability to compare long-term outcomes of patients followed in this study. Notably, however, this was a poor-risk patient population as 41% had active or treated brain metastases, 56% had $\geq$3 sites of metastatic disease and 5 patients who passed away shortly after the first dose of ipilimumab due to disease progression. Subsequent therapy included 12.5% receiving BRAF inhibitor combination therapy, and 19% receiving anti–PD-1 antibodies.

As in the ECOG 1608 study, a more favorable toxicity profile was seen when ipilimumab was administrated with sargramostim compared with historical data. Three (9.4%) high-grade events were observed in this study, which is lower than the rate of high-grade toxicity seen with administration of ipilimumab 3 mg/kg alone. Furthermore, in this study, those patients with high-grade events had high-risk features, including autoimmunity, poor performance status, and advanced age (90 years). Similar patients were generally excluded from the clinical trials evaluating ipilimumab.

Some investigators disputed the benefit in survival seen in ECOG 1608, as no concomitant improvement in progression-free survival (PFS) was observed. In the current series, a clinically similar RR was seen relative to historical ipilimumab alone and the median time to progression was 13 weeks (the median time of

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first restaging). The authors of ECOG 1608 pointed out that improvement in OS without PFS is not unprecedented and that the GM-CSF–containing treatment approach sipuleucel-T similarly showed this pattern (18). PFS estimates were not provided from this study, given the heterogeneity of the patient population (some without baseline measurable disease); however, a median of 23 weeks of treatment was observed, which would compare favorably with historical data of ipilimumab alone.

The ECOG 1608 trial reported a reduction in high-grade toxicity with ipilimumab, 10 mg/kg plus sargramostim, relative to single-agent ipilimumab. This ipilimumab 3-mg/kg-plus-sargramostim experience is consistent with the observation of lower toxicity with the caveats regarding patient selection as described above. As with ECOG 1608, a decrease in the incidence of high-grade colitis and pneumonitis events was observed in this data set. One proposed explanation for the improvement in OS observed in ECOG 1608 was that a greater number of ipilimumab doses may have been possible secondary to the reduction in toxicity facilitated by the addition of sargramostim. The data from this single institutional analysis would support this conclusion as only 3 (9.4%) patients were unable to complete the standard 4 doses of ipilimumab due to toxicity.

Our investigation is limited by several factors. Chart review was used to capture toxicity, and thus may have led to a bias toward under-reporting of lower-grade events. The study sample size of 32 patients is relatively small and statistical comparisons based on the data would be of reduced power. Finally, the patient cohort was heterogeneous, including many with high-risk features (e.g., CNS metastases), which could bias the outcome relative to clinical trial populations. This would seem to further boost the utility of this approach, however, given that such a bias would skew the data toward worse clinical outcomes.

In conclusion, this report represents the first description of ipilimumab, 3 mg/kg administered with sargramostim. In clinical practice, patients are able to tolerate treatment. This retrospective analysis suggests similar efficacy but importantly decreased toxicity relative to historical reports of ipilimumab alone. A randomized clinical trial combining ipilimumab, nivolumab with and without sargramostim is planned (ClinicalTrials.gov Identifier: NCT02339571). Because of the retrospective and nonrandomized nature of this study, definitive statements regarding the role of GM-CSF in combination with immune-checkpoint–blocking antibodies in the clinical management of patients with melanoma are not possible. However, further exploration of GM-CSF in combination with immune-checkpoint–blocking antibodies is warranted.

Disclosure of Potential Conflicts of Interest

M. Nishino is a consultant/advisory board member for Bristol-Myers Squibb. F.S. Hodi reports receiving research support to himself and his institution from Bristol-Myers Squib, Merck, and Genentech, and is a consultant/advisory board member for Bristol-Myers Squibb. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: J.J. Luke, H. Donahue, M. Nishino, F.S. Hodi
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.J. Luke, H. Donahue, M. Nishino, M. Davis, P.A. Ott, F.S. Hodi
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.J. Luke, A. Giobbie-Hurder, P.A. Ott, F.S. Hodi
Writing, review, and/or revision of the manuscript: J.J. Luke, M. Nishino, A. Giobbie-Hurder, M. Davis, N. Bailey, P.A. Ott, F.S. Hodi
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.J. Luke, N. Bailey
Study supervision: J.J. Luke, F.S. Hodi

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