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Tumor-Infiltrating Lymphocyte Therapy or Ipilimumab in Advanced Melanoma

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ABSTRACT

BACKGROUND

Immune checkpoint inhibitors and targeted therapies have dramatically improved outcomes in patients with advanced melanoma, but approximately half these patients will not have a durable benefit. Phase 1–2 trials of adoptive cell therapy with tumor-infiltrating lymphocytes (TILs) have shown promising responses, but data from phase 3 trials are lacking to determine the role of TILs in treating advanced melanoma.

METHODS

In this phase 3, multicenter, open-label trial, we randomly assigned patients with unresectable stage IIIC or IV melanoma in a 1:1 ratio to receive TIL or anti-cytotoxic T-lymphocyte antigen 4 therapy (ipilimumab at 3 mg per kilogram of body weight). Infusion of at least 5×10^9 TILs was preceded by nonmyeloablative, lymphodepleting chemotherapy (cyclophosphamide plus fludarabine) and followed by high-dose interleukin-2. The primary end point was progression-free survival.

RESULTS

A total of 168 patients (86% with disease refractory to anti-programmed death 1 treatment) were assigned to receive TILs (84 patients) or ipilimumab (84 patients). In the intention-to-treat population, median progression-free survival was 7.2 months (95% confidence interval [CI], 4.2 to 13.1) in the TIL group and 3.1 months (95% CI, 3.0 to 4.3) in the ipilimumab group (hazard ratio for progression or death, 0.50; 95% CI, 0.35 to 0.72; $P < 0.001$); 49% (95% CI, 38 to 60) and 21% (95% CI, 13 to 32) of the patients, respectively, had an objective response. Median overall survival was 25.8 months (95% CI, 18.2 to not reached) in the TIL group and 18.9 months (95% CI, 13.8 to 32.6) in the ipilimumab group. Treatment-related adverse events of grade 3 or higher occurred in all patients who received TILs and in 57% of those who received ipilimumab; in the TIL group, these events were mainly chemotherapy-related myelosuppression.

CONCLUSIONS

In patients with advanced melanoma, progression-free survival was significantly longer among those who received TIL therapy than among those who received ipilimumab. (Funded by the Dutch Cancer Society and others; ClinicalTrials.gov number, NCT02278887.)

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PROGRAMMED DEATH 1 (PD-1) PROTEIN blockade with nivolumab or pembrolizumab is a frequently used first-line treatment in patients with metastatic melanoma.¹⁻⁴ Combination immunotherapy with ipilimumab (an anti-cytotoxic T-lymphocyte antigen 4 antibody) and nivolumab induces responses in a higher percentage of patients (58% vs. 45%)⁵ but is associated with a high incidence of severe adverse events and is currently recommended primarily for a subgroup of patients with poor prognostic factors such as a high serum lactate dehydrogenase (LDH) level or liver or brain metastases.

Approximately 50% of melanomas harbor a mutation in *BRAF*; thus, an additional treatment option is combined *BRAF* and MEK inhibition. Although this therapy is associated with a high response, resistance develops in most patients over time.^{6,7} Ipilimumab (with or without nivolumab) has become a second-line treatment option, but objective responses and durable benefits occur in only 15 to 30% of patients.⁸⁻¹² Combination treatment with nivolumab and anti-lymphocyte-activation gene 3 (LAG-3) has also been associated with objective responses in 16% of patients with disease that was refractory to anti-PD-1 therapy, but data on progression-free survival are lacking.¹³ Although these new treatment options have substantially improved the prognosis in patients with metastatic melanoma, approximately 50% still die from the disease within 5 years after the diagnosis of stage IV disease.¹⁴

Adoptive cell therapy with tumor-infiltrating lymphocytes (TILs) is a personalized autologous treatment that involves the ex vivo outgrowth and expansion of tumor-resident T cells and subsequent intravenous adoptive transfer of the cells after preparative lymphodepleting chemotherapy, which is supported by the administration of interleukin-2 to enhance the in vivo expansion of the cells and augment antitumor responses.¹⁵⁻¹⁷ Evidence of clinical activity of TIL therapy in patients with advanced melanoma was reported by Rosenberg and colleagues in the 1990s.¹⁸ Subsequent phase 1-2 trials showed responses in 36% and 70% of patients, with durable complete responses in up to 20% of patients.¹⁹⁻²⁶ More recently, objective responses were observed in 36% of patients who received LN-144 TIL therapy, even among those who had disease progression while receiving anti-PD-1 treatment,

findings that illustrate the potential of this treatment after failure of previous immune checkpoint inhibition.²⁷ Despite these promising results, the role of TILs in the current treatment landscape remains undefined because data on a direct comparison of TILs with standard treatment are lacking. In this multicenter, open-label, phase 3, randomized trial, we compared TILs with ipilimumab as first- or second-line treatment in patients with advanced melanoma.

METHODS

PATIENTS

Patients were eligible for inclusion in the trial if they were 18 to 75 years of age and had histologically confirmed, unresectable or metastatic stage IIIC or IV cutaneous melanoma (hereafter “advanced melanoma”) (as defined in the seventh edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer) with one or more lesions (collectively 2 to 3 cm in diameter) that could be surgically removed for generation of TILs. In addition, patients were required to have residual measurable disease after resection as defined by the following: Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1²⁸; a World Health Organization performance-status score of 0 or 1 (on a scale of 0 to 5, with higher numbers indicating greater disability); and a serum LDH level that was less than or equal to 2 times the upper limit of the normal range. One previous line of systemic treatment for this disease stage, excluding ipilimumab, was allowed. A full overview of eligibility criteria is provided in the Supplementary Methods section in the Supplementary Appendix, available with the full text of this article at [NEJM.org](https://www.nejm.org), and in the trial protocol, also available at [NEJM.org](https://www.nejm.org).

TRIAL DESIGN AND TREATMENT

In this multicenter, open-label, phase 3 trial, patients were randomly assigned in a 1:1 ratio to receive either TILs or ipilimumab. Randomization was stratified according to *BRAF* V600-mutation status, line of treatment, and treatment center. Patients who were assigned to receive TILs underwent a metastasectomy for the retrieval and expansion of TILs, followed by hospital admission for administration of nonmyeloablative, lymphodepleting chemotherapy (cyclophospham-

mide at a dose of 60 mg per kilogram of body weight per day for 2 days intravenously and fludarabine at a dose of 25 mg per square meter of body-surface area per day for 5 days intravenously, single intravenous adoptive transfer of 5×10^9 to 2×10^{11} TILs, and subsequent high-dose interleukin-2 (600,000 IU per kilogram per dose) every 8 hours, for a maximum of 15 doses per protocol (Fig. S1 in the Supplementary Appendix). Patients in the ipilimumab group received 3 mg of ipilimumab per kilogram intravenously every 3 weeks, for a maximum of 4 doses. Administration of ipilimumab could be delayed or discontinued if adverse events occurred, in accordance with the protocol. No dose reductions were allowed.

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival assessed by the investigator with the use of RECIST, version 1.1. Progression-free survival was defined as the time from randomization to first disease progression (either radiologic progression or subsequent anticancer therapy, including systemic therapy, radiotherapy, or surgery) or death. The secondary end points were the following: progression-free survival assessed according to immune-related response criteria²⁹; objective response assessed according to RECIST, version 1.1, and immune-related response criteria; complete response; overall survival; health-related quality of life; and safety.

Health-related quality of life was measured with the use of the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 15 palliative care, a 15-item questionnaire on which higher scores on the global quality-of-life and functioning scales indicate better functioning and higher scores on the symptom scales indicate higher levels of symptom burden.³⁰ Adverse events were evaluated by the treating physician in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Efficacy analyses included all patients who underwent randomization (the intention-to-treat population), and safety analyses included all patients who had received chemotherapy and TIL or at least one dose of ipilimumab. Additional information on end-point assessment is provided in the Supplementary Methods section of the Supplementary Appendix.

TRIAL OVERSIGHT

The trial was designed at one of the two participating clinical sites (the Netherlands Cancer Institute, Amsterdam) and was approved by the Central Committee on Research Involving Human Subjects in the Netherlands and the institutional review board and independent ethics committee at each trial center. The other participating clinical site was the National Center for Cancer Immune Therapy, Copenhagen University Hospital, Herlev, Denmark. The trial was conducted in accordance with the principles of the Declaration of Helsinki, the Harmonized Tripartite Guideline for Good Clinical Practice from the International Council for Harmonisation, and the ethical principles underlying European Union Directive 2001/20/EC. All the patients provided written informed consent and received treatment at one of the two primary clinical sites. An independent data and safety monitoring board reviewed progress and safety.

Data were collected at each participating site, and raw data were seen only by the trial team from each participating site in accordance with the clinical trial agreement; a master data and sample transfer contract was signed by both sites. The data were analyzed at the Netherlands Cancer Institute. Authors who were not employees of the two participating clinical sites did not have access to the raw data. The authors agreed to maintain confidentiality of the data until publication and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. All the authors contributed to drafting the manuscript, provided critical revision, or did both, and all approved the decision to submit the final manuscript for publication. No one who is not an author contributed to writing the manuscript.

GENERATION OF TUMOR-INFILTRATING LYMPHOCYTES

The manufacturing of TILs was based on established techniques.^{19,24,31} TILs were manufactured at each trial center with the use of harmonized standard operating procedures according to the Good Manufacturing Practice guidelines of the European Union and EudraLex volume 4, which is specific to advanced therapy medicinal products. The TILs were classified as advanced therapy medicinal products under European Commission regulation 1394/2007. Further details are

Table 1. Baseline Characteristics of the Patients.*

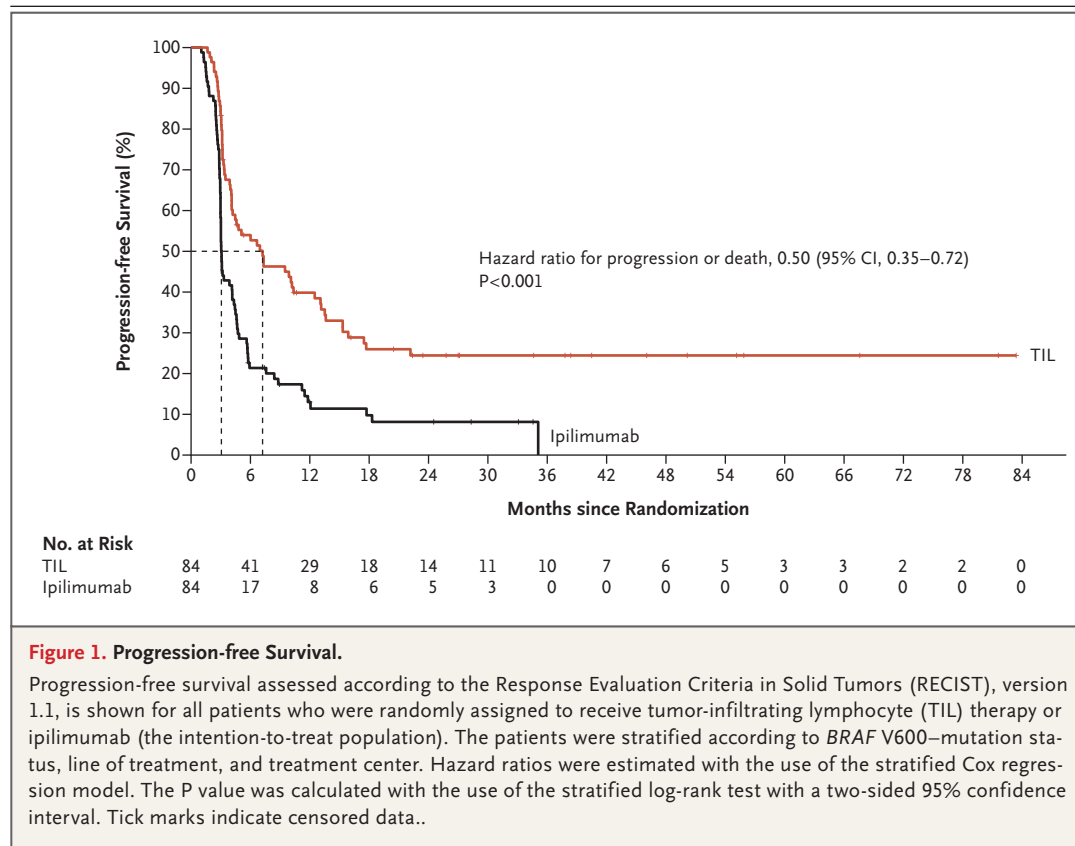
Characteristic	TIL Group (N = 84)	Ipilimumab Group (N = 84)	Total (N = 168)
Sex — no. (%)			
Male	47 (56)	53 (63)	100 (60)
Female	37 (44)	31 (37)	68 (40)
Median age (range) — yr	59 (26–74)	59 (30–77)†	59 (26–77)
WHO performance-status score — no. (%)‡			
0	69 (82)	70 (83)	139 (83)
1	15 (18)	14 (17)	29 (17)
BRAF mutation status — no. (%)			
V600 mutation	37 (44)	36 (43)	73 (43)
Wild-type	47 (56)	48 (57)	95 (57)
Treatment center — no. (%)			
NKI	66 (79)	66 (79)	132 (79)
CCIT-DK	18 (21)	18 (21)	36 (21)
Disease stage at trial entry — no. (%)§			
Unresectable stage IIIC	2 (2)	2 (2)	4 (2)
Stage IV	82 (98)	82 (98)	164 (98)
M1a	13 (15)	18 (21)	31 (18)
M1b	7 (8)	17 (20)	24 (14)
M1c	56 (67)	40 (48)	96 (57)
Liver metastases	20 (24)	9 (11)	29 (17)
M1d	6 (7)	7 (8)	13 (8)
Lactate dehydrogenase level — no. (%)			
≤ULN	67 (80)	70 (83)	137 (82)
1–2 × ULN	17 (20)	14 (17)	31 (18)
Smoking status — no. (%)			
Yes	9 (11)	11 (13)	20 (12)
No	46 (55)	49 (58)	95 (57)
Previous systemic therapy — no. (%)			
Yes	75 (89)	74 (88)	149 (89)
No	9 (11)	10 (12)	19 (11)
Type of previous systemic therapy — no. (%)			
Adjuvant anti-PD-1 therapy	17 (20)	23 (27)	40 (24)
First-line anti-PD-1 therapy	56 (67)	49 (58)	105 (62)
Other	2 (2)	2 (2)	4 (2)

* Data shown are for the intention-to-treat population, which consisted of all patients who underwent randomization. Percentages may not total 100 because of rounding. CCIT-DK denotes National Center for Cancer Immune Therapy, NKI Netherlands Cancer Institute, PD-1 programmed death 1 protein, TIL tumor-infiltrating lymphocyte, and ULN upper limit of the normal range.

† Two patients who were older than 75 years of age were included in the trial because these patients were deemed to be in excellent clinical condition by the principal investigator.

‡ The World Health Organization (WHO) performance-status score is based on a five-step grading system, with 0 indicating no performance restrictions and higher scores indicating increased restrictions.

§ Disease stages are defined according to the seventh edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer.



provided in the Supplementary Methods section of the Supplementary Appendix.

STATISTICAL ANALYSIS

The sample size was calculated on the basis of a comparison of the percentage of patients with progression-free survival at 6 months. On the basis of a study by Hodi et al.,³² it was expected that the percentage of patients with progression-free survival at 6 months in the ipilimumab group would be 20 to 25%. We estimated that at least 80 patients would have to undergo randomization in each group (160 patients in total) for the trial to have 90% power to detect an increase in progression-free survival at 6 months from 20% in the ipilimumab group to 45% in the TIL group (odds ratio, 3.27), using a two-group continuity corrected chi-square test with a two-sided significance level of 0.05. With this level of accrual, an absolute increase from 25 percentage points with ipilimumab to 50 percentage points with TIL therapy (odds ratio, 3.0) in progression-free survival could be detected with 88% power. Considering the possibility that 5 to 10% of the patients randomly assigned to the TIL group

would not receive the intended treatment, the required sample size was calculated to be 168 to 176 patients. Although the trial was powered to compare progression-free survival at 6 months, during the course of the trial it was considered statistically more efficient to analyze the entire progression-free survival curve with the use of survival methods, and this was included in a protocol amendment. Considering that the power calculation reflected a conservative approach, analysis of complete progression-free survival would yield sufficient power.

Progression-free and overall survival curves were constructed with the use of the Kaplan–Meier method, and treatment groups were compared with the use of the stratified (unweighted) log-rank test and the stratified Cox regression model. The trial was considered to be positive if the progression-free survival among patients who received TILs was significantly longer than that among those who received ipilimumab, on the basis of the log-rank test with a two-sided P value below 0.05. In addition, a prespecified per-protocol analysis of the primary end point with the use of a landmark approach was per-

Table 2. Best Response.*

Variable	TIL Group (N=84)	Ipilimumab Group (N=84)
Best response		
Complete response		
No. of patients	17	6
Percentage of patients (95% CI)	20 (12–30)	7 (3–15)
Partial response		
No. of patients	24	12
Percentage of patients (95% CI)	29 (19–40)	14 (8–24)
Stable disease		
No. of patients	16	15
Percentage of patients (95% CI)	19 (11–29)	18 (10–28)
Progressive disease		
No. of patients	24	40
Percentage of patients (95% CI)	29 (19–40)	48 (37–59)
Could not be determined — no. (%)†	3 (4)	11 (13)
Objective response‡		
No. of patients	41	18
Percentage of patients (95% CI)	49 (38–60)	21 (13–32)
Clinical benefit§		
No. of patients	57	33
Percentage of patients (95% CI)	68 (57–78)	39 (29–51)

* The best objective response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and according to investigator review in the intention-to-treat population.

† In 3 of the patients in the TIL group (4%) and 11 of those in the ipilimumab group (13%), the best radiologic response could not be evaluated or was not evaluated because of an event (death or rapid clinical progression that warranted the initiation of subsequent anticancer therapy) before the first response evaluation. One of the 3 patients in the TIL group had target lesions that could not be evaluated during follow-up. In the other 2 patients in the TIL group and all 11 patients in the ipilimumab group, the best radiologic response could not be evaluated because of an event.

‡ Objective response was defined according to RECIST, version 1.1, as a complete response or partial response.

§ Clinical benefit was defined as a complete response, a partial response, or stable disease. Responses are reported with their associated 95% binomial confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used in place of a hypothesis test.

formed, including patients who received the trial treatment without rapid clinical progression within 5 weeks after randomization. As exploratory post hoc analyses, comparisons of progression-free and overall survival across subgroups of interest were performed. Data are presented in a forest plot, and survival curves were constructed with the use of the Kaplan–Meier method.

Responses after TIL and ipilimumab treatment were reported with their associated 95% bino-

mial confidence intervals. Health-related quality-of-life outcomes were evaluated with the use of a generalized-estimating-equations model for longitudinal data.^{33,34} The widths of the confidence intervals for the secondary end points and exploratory post hoc analyses have not been adjusted for multiplicity and cannot be used in place of a hypothesis test. Details are provided in the Statistical Analyses section of the Supplementary Appendix, protocol, and statistical analysis plan.

RESULTS

PATIENTS AND TREATMENT

Between September 2014 and March 2022, a total of 168 patients were randomly assigned to receive either TILs (84 patients) or ipilimumab (84 patients) (the intention-to-treat population) (Fig. S2). Baseline characteristics were balanced between the two treatment groups (Table 1). A total of 149 of 168 patients (89%) had disease progression after receiving previous systemic therapy — mostly adjuvant anti-PD-1 therapy (40 patients [24%]) or first-line anti-PD-1 therapy (105 patients [62%]). Details regarding these systemic therapies are provided in Table S1.

At the time of the data cutoff on June 9, 2022, the overall median follow-up was 33.0 months. A total of 80 patients had received TILs and 82 patients had received at least one infusion of ipilimumab. The reasons for nonreceipt of TILs were patient decision (in 1 patient), late response to previous therapy (in 1 patient), insufficient TIL outgrowth (in 1 patient), and rapid clinical progression (in 1 patient). Patients who received TILs received a median of 40.9×10^9 cells (range, 4.9 to 110.4) and a median of 4 doses of high-dose interleukin-2 (range, 0 to 10). The median duration of hospital admission was 17 days (range, 12 to 38). Two patients did not receive ipilimumab owing to patients' decision or rapidly progressive disease that warranted the immediate initiation of combined BRAF and MEK inhibition. Patients who received ipilimumab received a median of 3 infusions (range, 1 to 4), and 26 of the 42 patients (62%) who discontinued treatment prematurely did so because of adverse events (Table S2).

EFFICACY

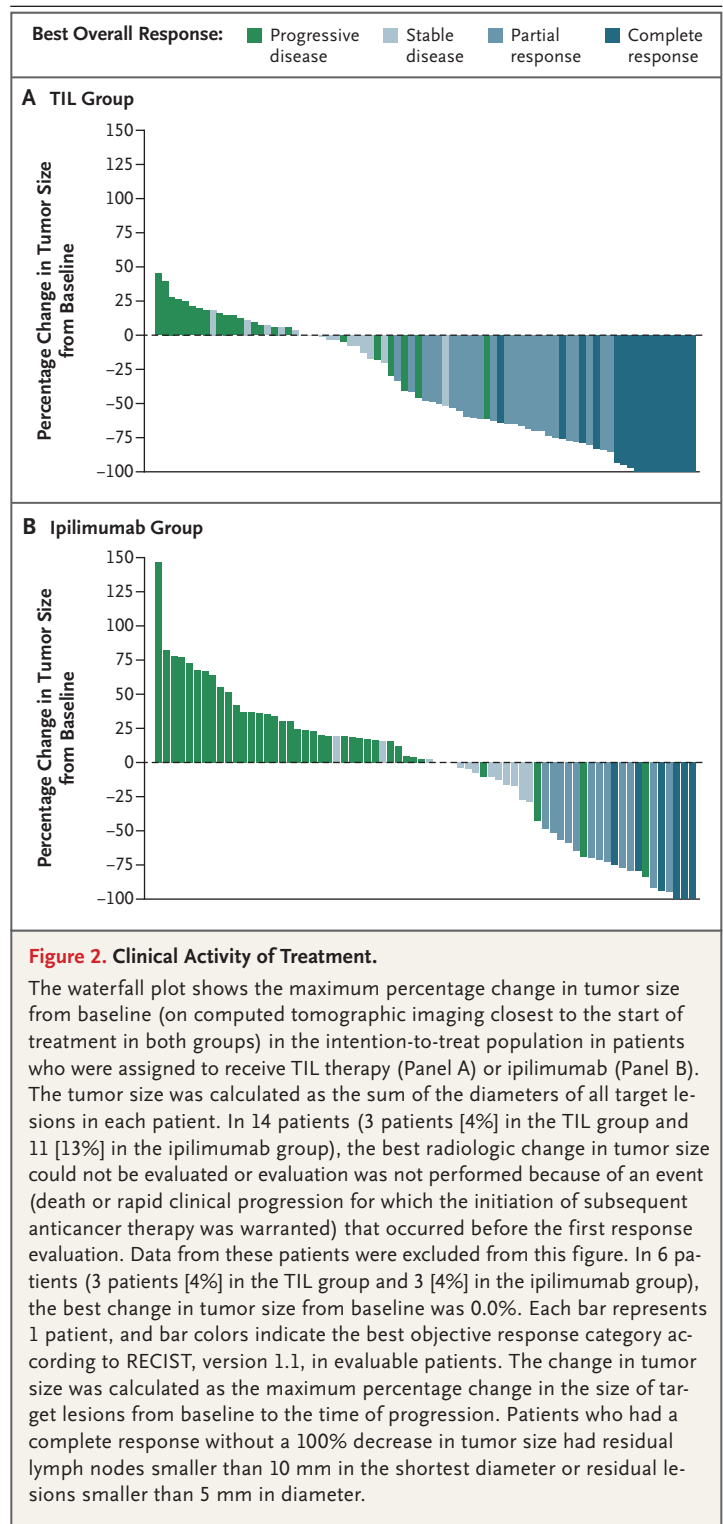
In the intention-to-treat population, TILs were associated with a significant benefit with re-

spect to progression-free survival assessed according to RECIST, version 1.1, with a median progression-free survival of 7.2 months (95% confidence interval [CI], 4.2 to 13.1), as compared with 3.1 months (95% CI, 3.0 to 4.3) with ipilimumab (hazard ratio for progression or death, 0.50; 95% CI, 0.35 to 0.72; $P < 0.001$ by an unweighted stratified log-rank test) (Fig. 1). The percentage of patients with progression-free survival at 6 months was 52.7% (95% CI, 42.9 to 64.7) in the TIL group and 21.4% (95% CI, 14.2 to 32.2) in the ipilimumab group. This benefit of TILs over ipilimumab was confirmed in a pre-specified per-protocol analysis (see the Supplementary Results section in the Supplementary Appendix and Fig. S3). With assessment according to immune-related response criteria, median progression-free survival was 6.0 months (95% CI, 4.6 to 12.0) in the TIL group, as compared with 3.2 months (95% CI, 3.0 to 4.4) in the ipilimumab group (hazard ratio, 0.56; 95% CI, 0.39 to 0.79) (Fig. S4). Results of a post hoc analysis of progression-free survival in key subgroups are shown in Figures S5 and S6.

The percentage of patients with an objective response according to RECIST, version 1.1, was 49% (95% CI, 38 to 60) in the TIL group and 21% (95% CI, 13 to 32) in the ipilimumab group. Complete responses were observed in 20% (95% CI, 12 to 30) of the patients in the TIL group and 7% (95% CI, 3 to 15) of those in the ipilimumab group (Table 2 and Fig. 2), with durable complete responses in both treatment groups (Fig. S7). With assessment according to immune-related response criteria, objective responses were seen in 50% (95% CI, 39 to 61) of patients in the TIL group and 20% (95% CI, 12 to 30) of those in the ipilimumab group. Table S3, which shows an overview of systemic treatments administered after disease progression, indicates that more patients in the TIL group who had not had a response received ipilimumab or the combination of ipilimumab and nivolumab than those in the ipilimumab group who had not had a response.

OVERALL SURVIVAL

Median overall survival among patients in the TIL group was 25.8 months (95% CI, 18.2 to not reached), as compared with 18.9 months (95% CI, 13.8 to 32.6) among those in the ipilimumab group (hazard ratio for death, 0.83; 95% CI, 0.54 to 1.27). The 2-year overall survival was 54.3% (95% CI, 43.9 to 67.2) in the TIL group and



44.1% (95% CI, 33.6 to 57.8) in the ipilimumab group (Fig. S8). Overall survival in key subgroups is shown in Figures S9 through S11.

Table 3. Most Common Treatment-Related Adverse Events.*

Adverse Event	TIL Group (N=80)				Ipilimumab Group (N=82)	
	Chemotherapy		TILs and Interleukin-2		Ipilimumab	
	Any Grade	≥Grade 3	Any Grade	≥Grade 3	Any Grade	≥Grade 3
	<i>number of patients (percent)</i>					
Neutrophil count decreased	80 (100)	80 (100)	—	—	—	—
Platelet count decreased	73 (91)	71 (89)	—	—	—	—
Anemia	73 (91)	16 (20)	—	—	—	—
Nausea	69 (86)	2 (2)	41 (51)	0	30 (37)	2 (2)
Febrile neutropenia	69 (86)	69 (86)	59 (74)	59 (74)	—	—
White-cell count decreased	57 (71)	57 (71)	—	—	—	—
Fatigue	49 (61)	4 (5)	54 (68)	7 (9)	37 (45)	1 (1)
Hypophosphatemia	49 (61)	20 (25)	57 (71)	48 (60)	—	—
Alopecia†	37 (46)	0	—	—	—	—
Diarrhea	36 (45)	2 (2)	36 (45)	2 (2)	37 (45)	12 (15)
Hypocalcemia	36 (45)	1 (1)	29 (36)	0	—	—
Hypoalbuminemia	27 (34)	0	31 (39)	0	—	—
Vomiting	26 (32)	2 (2)	15 (19)	0	11 (13)	1 (1)
Headache	20 (25)	0	19 (24)	0	22 (27)	1 (1)
Hypokalemia	20 (25)	2 (2)	12 (15)	0	—	—
Elevated AST level	18 (22)	4 (5)	26 (32)	8 (10)	18 (22)	7 (9)
Rash	18 (22)	2 (2)	37 (46)	9 (11)	28 (34)	4 (5)
Weight gain	17 (21)	0	28 (35)	0	—	—
Elevated ALT level	14 (18)	7 (9)	25 (31)	8 (10)	22 (27)	8 (10)
Elevated alkaline phosphatase level	14 (18)	3 (4)	17 (21)	3 (4)	12 (15)	4 (5)
Anorexia	13 (16)	1 (1)	—	—	14 (17)	1 (1)
Dizziness	12 (15)	0	—	—	—	—
Increased γ -glutamyltransferase level	11 (14)	6 (8)	12 (15)	6 (8)	—	—
Fever	11 (14)	1 (1)	74 (92)	36 (45)	11 (13)	2 (2)
Dysgeusia	11 (14)	0	—	—	—	—
Hypomagnesemia	11 (14)	0	—	—	—	—
Dyspnea	10 (12)	2 (2)	63 (79)	15 (19)	—	—
Constipation	9 (11)	0	—	—	—	—
Edema limbs	8 (10)	0	23 (29)	0	—	—
Chills	—	—	67 (84)	6 (8)	—	—
Pruritus	—	—	—	—	34 (41)	0
Sinus tachycardia	—	—	40 (50)	1 (1)	—	—
Colitis	—	—	—	—	20 (24)	16 (20)
Abdominal pain	—	—	—	—	19 (23)	1 (1)
Hypotension	—	—	33 (41)	6 (8)	—	—
Malaise	—	—	—	—	13 (16)	0

Table 3. (Continued.)

Adverse Event	TIL Group (N = 80)				Ipilimumab Group (N = 82)	
	Chemotherapy		TILs and Interleukin-2		Ipilimumab	
	Any Grade	≥Grade 3	Any Grade	≥Grade 3	Any Grade	≥Grade 3
	<i>number of patients (percent)</i>					
Creatine kinase level increased	—	—	29 (36)	9 (11)	—	—
Dry mouth	—	—	—	—	9 (11)	0
Pulmonary edema	—	—	26 (32)	1 (1)	—	—
Capillary leak syndrome	—	—	24 (30)	1 (1)	—	—
Hypoxia	—	—	19 (24)	5 (6)	—	—
Hypertension	—	—	15 (19)	11 (14)	—	—
Myalgia	—	—	12 (15)	1 (1)	—	—
Blurred vision	—	—	9 (11)	0	—	—
Skin hypopigmentation	—	—	9 (11)	0	—	—

* Included are the most common treatment-related adverse events of any grade and those of grade 3 or higher, as defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, that occurred in at least 10% of the patients who received chemotherapy and TILs or at least one dose of ipilimumab (the safety analysis population). Dashes indicate that the adverse events did not occur in at least 10% of the patients. All the patients had more than one adverse event. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

† Transient alopecia totalis occurred in all patients in the TIL group after chemotherapy. However, this event was not systematically reported in medical records and thus cannot be reported.

SAFETY

Adverse events that were assessed by the investigators as being related to treatment occurred in all patients in the TIL group and in 96% of those in the ipilimumab group. The most common adverse events of any grade related to TILs and ipilimumab are presented in Table 3. All patients in the TIL group had grade 3 or 4 neutropenia owing to preparative lymphodepleting chemotherapy, with a median duration of neutropenia of 7 days (range, 2 to 58 days). Capillary leak syndrome (of any grade) associated with interleukin-2 occurred in 30% of the patients who received TILs and interleukin-2 (Table 3). In the TIL group, autoimmune toxic effects leading to skin hypopigmentation occurred in 9 patients (11%) (Table 3); uveitis occurred in 6 patients (8%), and hearing impairment occurred in 3 patients (4%) (Table S4).

Treatment-related adverse events of grade 3 or higher occurred in all patients in the TIL group and in 57% of those in the ipilimumab group. Treatment-related serious adverse events occurred in 15% of the patients in the TIL group and 27% of those in the ipilimumab group (Table S5). All treatment-related serious adverse

events are shown in Table S6. New TIL-related adverse events of grade 3 or higher occurred typically during hospital admission (in 99% of cases) and were handled according to protocol on the oncology ward; short-term stabilization in an intensive care unit was warranted in eight patients (10%). One patient in the TIL group died from an arterial thromboembolism on day 22 after treatment; this death was not considered by the investigators to be related to treatment.

HEALTH-RELATED QUALITY OF LIFE

Patients in the TIL group had higher mean scores on the global health-related quality-of-life, physical functioning, and emotional functioning domains after treatment than those in the ipilimumab group (Table 4). Patients in the TIL group reported a lower symptom burden of fatigue, pain, and insomnia than those in the ipilimumab group, with differences still observed at week 60 (Table S8). However, patients in the TIL group reported a higher symptom burden of nausea and vomiting than those in the ipilimumab group, with a mean difference in symptom scores of 1.6 at week 24.

Table 4. Health-Related Quality-of-Life Scores at 6 Months.

Variable	Mean Score		Difference (95% CI)*
	TIL Group	Ipilimumab Group	
Scores on the EORTC QLQ-C15 PAL quality-of-life and functioning scales†			
Global quality of life	77.4	69.6	7.7 (5.1 to 10.4)
Physical functioning	82.0	79.1	2.9 (1.4 to 4.5)
Emotional functioning	85.4	75.7	9.7 (7.5 to 11.9)
Scores on the EORTC QLQ-C15 PAL symptom scales‡			
Fatigue	25.9	33.8	−7.9 (−11.2 to −4.6)
Nausea and vomiting	7.5	5.9	1.6 (0.7 to 2.5)
Pain	14.3	20.7	−6.4 (−9.3 to −3.5)
Dyspnea	10.0	12.4	−2.4 (−5.0 to 0.1)
Insomnia	23.6	28.1	−4.5 (−7.2 to −1.9)
Appetite loss	12.4	13.5	−1.1 (−2.9 to 0.7)
Constipation	6.7	7.1	−0.4 (−1.3 to 0.5)

* The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used in place of a hypothesis test.

† Scores on the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 15 palliative care (EORTC QLQ-C15 PAL) global quality-of-life and functioning scales range from 0 to 100, with higher scores indicating better functioning.

‡ Scores on the EORTC QLQ-C15 PAL symptom scales range from 0 to 100, with higher scores indicating higher levels of symptom burden.

DISCUSSION

This multicenter, phase 3, randomized trial involving patients with advanced melanoma compared TIL T-cell therapy as first- or second-line treatment with ipilimumab, which has previously been used as a second-line option in metastatic melanoma.⁴ Progression-free survival was more than twice as long in the TIL group as in the ipilimumab group, and the hazard of disease progression or death was 50% lower. Separation of the progression-free survival curves occurred within 6 months after randomization, with a 30 percentage-point difference between the groups at 6 months and a continued benefit for patients in the TIL group.

Previous phase 1–2 trials have shown the potential clinical benefit of TILs in patients with metastatic melanoma, although most involved patients who had not received anti-PD-1 therapy.^{19–24,27}

In the current trial, although 86% of the patients had had disease progression after they received previous anti-PD-1 treatment either as adjuvant or first-line agents, 49% of the patients in the TIL group had an objective response, and of these patients, 20% had a complete response. These percentages are higher than those seen in a recent trial of LN-144 TIL therapy,²⁷ possibly because most patients who received LN-144 TIL therapy had had disease progression after multiple previous lines of systemic treatment, including anti-PD-1 therapy, ipilimumab, and — in patients with BRAF V600-mutated melanoma — BRAF and MEK inhibition. In our trial, no major differences in progression-free survival were observed according to the stratification factors of BRAF mutation status, line of treatment, or treatment center.

First-line treatment options for advanced melanoma have rapidly evolved over the past 5 years. In addition to anti-PD-1 therapy, currently approved treatment options are the following: combination therapy with ipilimumab and nivolumab, combined BRAF and MEK inhibitors, and relatlimab (an anti-LAG-3 antibody) plus nivolumab.^{6,14,35} In our trial, nine patients (11%) received TILs as first-line treatment, and no major difference was seen in progression-free survival among patients who had received no previous therapy, those who had received adjuvant therapy, and those who had received previous first-line anti-PD-1 therapy. This finding suggests that TIL therapy can also be effective as first-line treatment; however, patient and disease characteristics (e.g., brain metastases, a high serum LDH level, or poor performance status), potential toxic effects, and the availability of the treatment play important roles in the choice of treatment. Our trial primarily included patients who had received previous adjuvant or first-line anti-PD-1 monotherapy. For these patients, TIL therapy could be a possible first- or second-line treatment option for metastatic disease, as shown in this trial, whereas the data on LN-144 TIL therapy in patients with more refractory disease clearly suggest a broader indication for TILs.

The antitumor activity of ipilimumab monotherapy after failure of anti-PD-1 inhibition is well known, with objective responses in 4 to 56% of patients,^{9–12} results that were confirmed in this trial. In a retrospective, multicenter, cohort trial involving 355 patients with advanced

melanoma that was refractory to anti-PD-1 therapy, 31% of the patients who received a combination of ipilimumab plus nivolumab had an objective response, as compared with 13% of those who received ipilimumab alone.⁹ Similar objective responses were observed in a recent prospective trial involving patients with advanced melanoma that was refractory to anti-PD-1 therapy. That trial showed objective responses in 19 of 69 patients (28%) who received a second-line combination of ipilimumab and nivolumab and in 2 of 23 patients (9%) who received second-line ipilimumab monotherapy.⁸ The estimates of 6-month progression-free survival were 34% (90% CI, 25 to 44) in the combination-treatment group and 13% (90% CI, 4 to 27) in the ipilimumab-monotherapy group. In our trial, the percentage of patients with progression-free survival at 6 months was 52.7% (95% CI, 42.9 to 64.7) in the TIL group and 21.4% (95% CI, 14.2 to 32.2) in the ipilimumab group. The results of these two trials cannot be directly compared, but they suggest a benefit of TILs over the combination of ipilimumab plus nivolumab. The difference between the two ipilimumab groups could be explained by differences in the baseline characteristics of the patients, especially the serum LDH level. In addition to immunotherapies, combined BRAF and MEK inhibition remains a second-line treatment option for patients with BRAF V600-mutated melanoma. Although this treatment has been associated with high objective responses in up to 57% of patients,^{11,36} treatment resistance remains a problem in the majority of patients.

In our trial, treatment-related adverse events were more frequently seen with TILs than with ipilimumab, owing predominantly to chemotherapy, interleukin-2, or both, and these events were in line with those in previous studies.^{19,24} Despite the increased frequency of adverse events, the global health-related quality-of-life scores were higher in patients who received TILs. In this trial, treatment with ipilimumab

resulted in a high incidence of adverse events of grade 3 or higher (57%).

This phase 3, multicenter, open-label, randomized trial involving patients with advanced melanoma (the majority of whom had disease that was refractory to anti-PD-1 therapy) showed that TILs can be successfully generated from resected melanoma metastases in patients with advanced melanoma. Treatment with TILs was associated with significantly longer progression-free survival than treatment with ipilimumab.

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APPENDIX

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REFERENCES

- Hamid O, Robert C, Daud A, et al. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. *Ann Oncol* 2019;30:582-8.
- Robert C, Long GV, Brady B, et al. Five-year outcomes with nivolumab in patients with wild-type BRAF advanced melanoma. *J Clin Oncol* 2020;38:3937-46.
- Robert C, Ribas A, Schachter J, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. *Lancet Oncol* 2019;20:1239-51.
- Michielin O, van Akkooi ACJ, Ascierto PA, Dummer R, Keilholz U. Cutaneous melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2019;30:1884-901.
- Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* 2019;381:1535-46.
- Robert C, Grob JJ, Stroyakovskiy D, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. *N Engl J Med* 2019;381:626-36.
- Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2018;19:603-15.
- Vanderwalde AM, Moon J, Kendra K, et al. S1616: ipilimumab plus nivolumab versus ipilimumab alone in patients with metastatic or unresectable melanoma that did not respond to anti-PD-1 therapy. In: Proceedings and abstracts of the American Association for Cancer Research Annual Meeting 2022. Philadelphia: American Association for Cancer Research, 2022.
- Pires da Silva I, Ahmed T, Reijers ILM, et al. Ipilimumab alone or ipilimumab plus anti-PD-1 therapy in patients with metastatic melanoma resistant to anti-PD-(L)1 monotherapy: a multicentre, retrospective, cohort study. *Lancet Oncol* 2021;22:836-47.
- Zimmer L, Apuri S, Eroglu Z, et al. Ipilimumab alone or in combination with nivolumab after progression on anti-PD-1 therapy in advanced melanoma. *Eur J Cancer* 2017;75:47-55.
- Weichenthal M, Ugurel S, Leiter UM, et al. Salvage therapy after failure from anti-PD-1 single agent treatment: a study by the German ADOReg melanoma registry. *J Clin Oncol* 2019;37:Suppl 15:9505. abstract.
- Friedman CF, Spencer C, Cabanski CR, et al. Ipilimumab alone or in combination with nivolumab in patients with advanced melanoma who have progressed or relapsed on PD-1 blockade: clinical outcomes and translational biomarker analyses. *J Immunother Cancer* 2022;10(1):e003853.
- Ascierto PA, Melero I, Bhatia S, et al. Initial efficacy of anti-lymphocyte activation gene-3 (anti-LAG-3; BMS-986016) in combination with nivolumab (nivo) in pts with melanoma (MEL) previously treated with anti-PD-1/PD-L1 therapy. In: Proceedings and abstracts of the 2017 American Society of Clinical Oncology Annual Meeting. Chicago: American Society of Clinical Oncology, 2017.
- Hodi FS, Sileni VC, Lewis KD, et al. Long-term survival in advanced melanoma for patients treated with nivolumab plus ipilimumab in CheckMate 067. In: Proceedings and abstracts of the 2022 American Society of Clinical Oncology Annual Meeting. Chicago: American Society of Clinical Oncology, 2022.
- June CH, Riddell SR, Schumacher TN. Adoptive cellular therapy: a race to the finish line. *Sci Transl Med* 2015;7:280ps7.
- Malek TR. The biology of interleukin-2. *Annu Rev Immunol* 2008;26:453-79.
- Rosenberg SA, Spiess P, Lafreniere R. A new approach to the adoptive immunotherapy of cancer with tumor-infiltrating lymphocytes. *Science* 1986;233:1318-21.
- Rosenberg SA, Yannelli JR, Yang JC, et al. Treatment of patients with metastatic melanoma with autologous tumor-infiltrating lymphocytes and interleukin 2. *J Natl Cancer Inst* 1994;86:1159-66.
- van den Berg JH, Heemskerk B, van Rooij N, et al. Tumor infiltrating lymphocytes (TIL) therapy in metastatic melanoma: boosting of neoantigen-specific T cell reactivity and long-term follow-up. *J Immunother Cancer* 2020;8(2):e000848.
- Dudley ME, Yang JC, Sherry R, et al. Adoptive cell therapy for patients with metastatic melanoma: evaluation of intensive myeloablative chemoradiation preparative regimens. *J Clin Oncol* 2008;26:5233-9.

21. Rosenberg SA, Yang JC, Sherry RM, et al. Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. *Clin Cancer Res* 2011;17:4550-7.
22. Besser MJ, Shapira-Frommer R, Treves AJ, et al. Clinical responses in a phase II study using adoptive transfer of short-term cultured tumor infiltration lymphocytes in metastatic melanoma patients. *Clin Cancer Res* 2010;16:2646-55.
23. Ellebaek E, Iversen TZ, Junker N, et al. Adoptive cell therapy with autologous tumor infiltrating lymphocytes and low-dose interleukin-2 in metastatic melanoma patients. *J Transl Med* 2012;10:169.
24. Andersen R, Donia M, Ellebaek E, et al. Long-lasting complete responses in patients with metastatic melanoma after adoptive cell therapy with tumor-infiltrating lymphocytes and an attenuated IL2 regimen. *Clin Cancer Res* 2016;22:3734-45.
25. Dudley ME, Wunderlich JR, Yang JC, et al. A phase I study of nonmyeloablative chemotherapy and adoptive transfer of autologous tumor antigen-specific T lymphocytes in patients with metastatic melanoma. *J Immunother* 2002;25:243-51.
26. Pilon-Thomas S, Kuhn L, Ellwanger S, et al. Efficacy of adoptive cell transfer of tumor-infiltrating lymphocytes after lymphopenia induction for metastatic melanoma. *J Immunother* 2012;35:615-20.
27. Sarnaik AA, Hamid O, Khushalani NI, et al. Lifileucel, a tumor-infiltrating lymphocyte therapy, in metastatic melanoma. *J Clin Oncol* 2021;39:2656-66.
28. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228-47.
29. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res* 2009;15:7412-20.
30. Groenvold M, Petersen MA, Aaronson NK, et al. The development of the EORTC QLQ-C15-PAL: a shortened questionnaire for cancer patients in palliative care. *Eur J Cancer* 2006;42:55-64.
31. Tran KQ, Zhou J, Durflinger KH, et al. Minimally cultured tumor-infiltrating lymphocytes display optimal characteristics for adoptive cell therapy. *J Immunother* 2008;31:742-51.
32. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;363:711-23.
33. Hardin JW. Generalized estimating equations. 2nd ed. London: Chapman & Hall, 2003.
34. Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986;73:13-22.
35. Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. *N Engl J Med* 2022;386:24-34.
36. Ackerman A, Klein O, McDermott DF, et al. Outcomes of patients with metastatic melanoma treated with immunotherapy prior to or after BRAF inhibitors. *Cancer* 2014;120:1695-701.

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