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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 $5\times10^9$ 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 1.1[28]; 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, and in the trial protocol, also available at 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 (cyclophospha-

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 $5\times10^9$ to $2\times10^{11}$ 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 criteria[29]; 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.

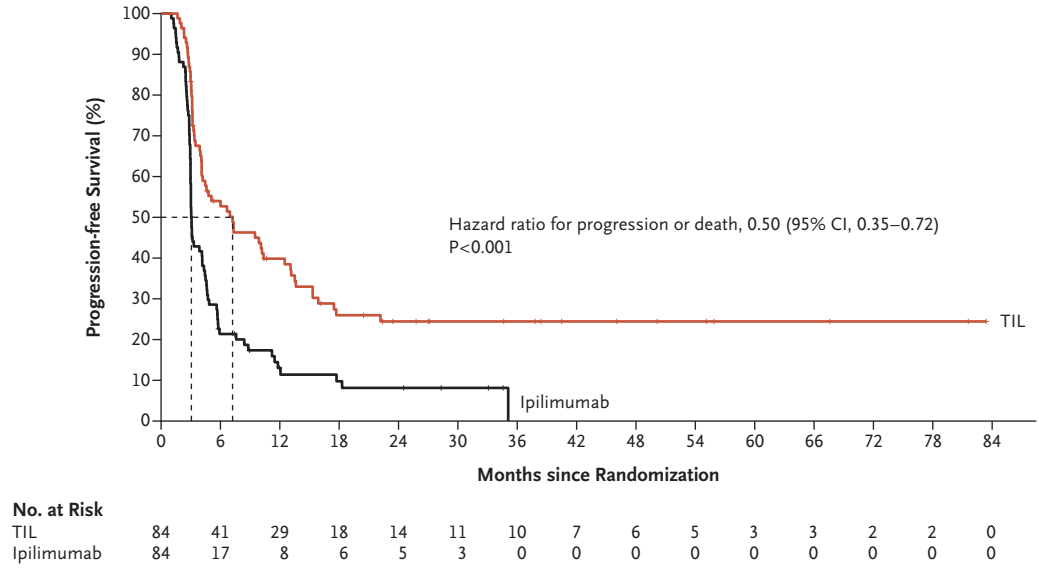


**Figure 1. Progression-free Survival.**

Progression-free survival assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, is shown for all patients who were randomly assigned to receive tumor-infiltrating lymphocyte (TIL) therapy or ipilimumab (the intention-to-treat population). The patients were stratified according to *BRAF* V600–mutation status, line of treatment, and treatment center. Hazard ratios were estimated with the use of the stratified Cox regression model. The P value was calculated with the use of the stratified log-rank test with a two-sided 95% confidence interval. Tick marks indicate censored data..

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% binomial 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 $40.9\times10^9$ 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 prespecified 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.

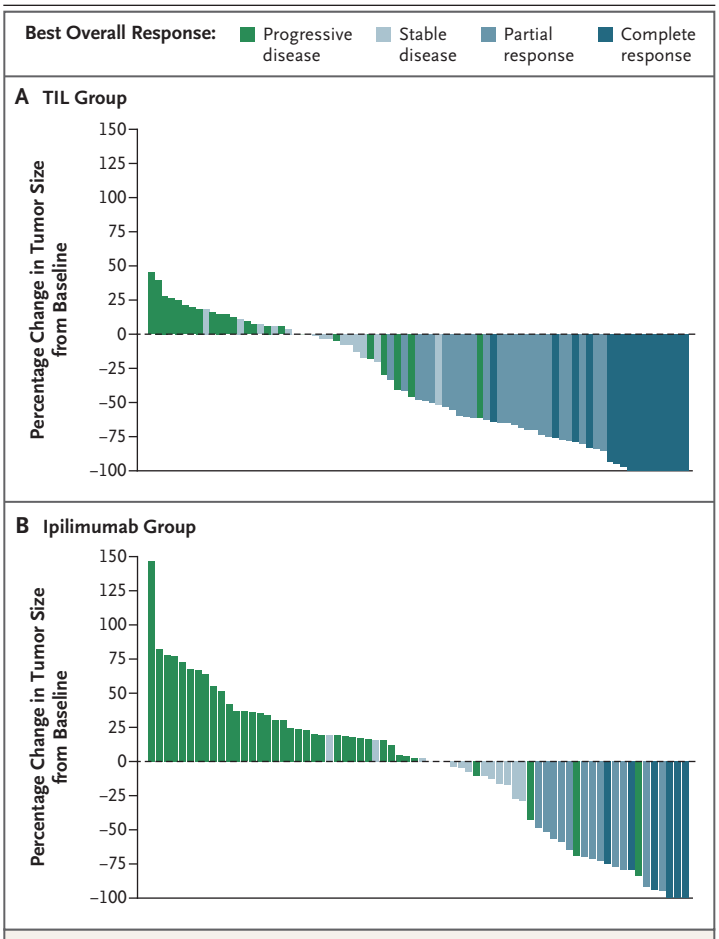


**Figure 2. Clinical Activity of Treatment.**

The waterfall plot shows the maximum percentage change in tumor size from baseline (on computed tomographic imaging closest to the start of treatment in both groups) in the intention-to-treat population in patients who were assigned to receive TIL therapy (Panel A) or ipilimumab (Panel B). The tumor size was calculated as the sum of the diameters of all target lesions in each patient. In 14 patients (3 patients [4%] in the TIL group and 11 [13%] in the ipilimumab group), the best radiologic change in tumor size could not be evaluated or evaluation was not performed because of an event (death or rapid clinical progression for which the initiation of subsequent anticancer therapy was warranted) that occurred before the first response evaluation. Data from these patients were excluded from this figure. In 6 patients (3 patients [4%] in the TIL group and 3 [4%] in the ipilimumab group), the best change in tumor size from baseline was 0.0%. Each bar represents 1 patient, and bar colors indicate the best objective response category according to RECIST, version 1.1, in evaluable patients. The change in tumor size was calculated as the maximum percentage change in the size of target lesions from baseline to the time of progression. Patients who had a complete response without a 100% decrease in tumor size had residual lymph nodes smaller than 10 mm in the shortest diameter or residual lesions smaller than 5 mm in diameter.

### 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 |
| | *number of patients (percent)* | | | | | |
| 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 |
| | *number of patients (percent)* | | | | | |
| 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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