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Lifileucel, a Tumor-Infiltrating Lymphocyte Therapy, in Metastatic Melanoma

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abstract

PURPOSE Effective treatment options are limited for patients with advanced (metastatic or unresectable) melanoma who progress after immune checkpoint inhibitors and targeted therapies. Adoptive cell therapy using tumor-infiltrating lymphocytes has demonstrated efficacy in advanced melanoma. Lifileucel is an autologous, centrally manufactured tumor-infiltrating lymphocyte product.

METHODS We conducted a phase II open-label, single-arm, multicenter study in patients with advanced melanoma who had been previously treated with checkpoint inhibitor(s) and BRAF ± MEK targeted agents. Lifileucel was produced from harvested tumor specimens in central Good Manufacturing Practice facilities using a streamlined 22-day process. Patients received a nonmyeloablative lymphodepletion regimen, a single infusion of lifileucel, and up to six doses of high-dose interleukin-2. The primary end point was investigator-assessed objective response rate (ORR) per RECIST, version 1.1.

RESULTS Sixty-six patients received a mean of 3.3 prior therapies (anti–programmed death 1 [PD-1] or programmed death ligand 1 [PD-L1]: 100%; anticytotoxic T-lymphocyte-associated protein-4: 80%; BRAF ± MEK inhibitor: 23%). The ORR was 36% (95% CI, 25 to 49), with two complete responses and 22 partial responses. Disease control rate was 80% (95% CI, 69 to 89). Median duration of response was not reached after 18.7-month median study follow-up (range, 0.2-34.1 months). In the primary refractory to anti–PD-1 or PD-L1 therapy subset, the ORR and disease control rate were 41% (95% CI, 26 to 57) and 81% (95% CI, 66 to 91), respectively. Safety profile was consistent with known adverse events associated with non-myeloablative lymphodepletion and interleukin-2.

CONCLUSION Lifileucel demonstrated durable responses and addresses a major unmet need in patients with metastatic melanoma with limited treatment options after approved therapy, including the primary refractory to anti–PD-1 or PD-L1 therapy subset.

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ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

The treatment of advanced (unresectable or metastatic) melanoma with immune checkpoint inhibitors (ICI) and targeted oncogenic pathway inhibition with BRAF and MEK inhibitors has improved patient outcomes.[1-7] Forty percent to 65% of patients with advanced melanoma have primary resistance to ICI.[8-11] Of those with initial disease control, 30%-40% develop acquired resistance.[8,12] Approximately 15% to 20% of *BRAF* V600 mutation-positive patients fail to respond to targeted therapy initially,[13] and only 22% remain progression-free at 3 years.[14] Although primary resistance is lower in patients treated with programmed death 1 (PD-1) blocking antibody plus anticytotoxic T-lymphocyte–associated protein 4 (CTLA-4) therapy, 36% of patients discontinue therapy because of treatment-emergent adverse events (TEAEs), with 88% developing immune-related adverse events (irAEs), many of these being persistent.[10] Patients progressing after anti–PD-1 therapy, anti–PD-1 plus anti–CTLA-4 therapy, and targeted agents have limited options.[15-17] Only 4%-10% of these patients have objective responses to chemotherapy, with a limited median overall survival (OS) of 7 months.[15,16,18,19] There are no treatment options with approval based on data from patients with advanced melanoma who have progressed after

CONTEXT

Key Objective

This study evaluated the efficacy and safety of lifileucel, a one-time, autologous tumor-infiltrating lymphocyte (TIL) product, in patients with metastatic melanoma who had progressed on standard immune checkpoint inhibitors (ICI) and targeted therapies (if applicable), who otherwise have limited treatment options. Notably, chemotherapy post-ICI shows poor response rates (4%-10%).

Knowledge Generated

Sixty-six patients received lifileucel infusion with $> 1 \times 10^9$ TIL cells. Lifileucel was efficacious with an objective response rate of 36%, and a median duration of response that is not reached at 18.7-month median study follow-up.

Relevance

Lifileucel represents a significant improvement in the treatment of advanced melanoma, particularly in the post-ICI patient population, which is an expanding population. The study contributes to the advancement in TIL therapy through a centrally standardized manufacturing approach for autologous TIL, allowing broader patient access.

one line of ICI therapy (for *BRAF* wild-type tumors), or two lines of therapy (for *BRAF* V600 mutation-positive tumors). In addition, patients recurring with advanced melanoma after adjuvant anti–PD-1 therapy for high-risk disease represent an emerging unmet need.[20-22]

Adoptive cell therapy with tumor-infiltrating lymphocytes (TIL) offers a potential therapeutic option for metastatic melanoma, although it has not been studied extensively in the ICI era.[23-25] TIL are enriched with polyclonal T cells with diverse antigen specificity.[26] Extraction of a fragment of tumor followed by ex vivo expansion removes TIL from the hostile tumor microenvironment and reduces the immunosuppressive effects of intratumoral regulatory T cells. Expansion of TIL ex vivo rejuvenates the cells, yielding billions of such cells to be infused back into the patient. Melanoma is characterized by a high mutational burden[27] and highly individualized neoantigens.[28] A cellular therapy product that can address the broad nature of neoantigens and the unique array from each patient would lead to the possibility of a tailored response. Lifileucel (LN-144) is an autologous TIL therapy that uses tumor-tissue T cells capable of recognizing tumor antigens and being expanded ex vivo while maintaining the heterogeneous repertoire of T cells, using a centralized manufacturing process. We report the safety and efficacy of lifileucel, a one-time cellular therapy, in patients with advanced melanoma who have progressed on ICI and BRAF inhibitors (if *BRAF* V600 mutation-positive).

METHODS

Trial Conduct

The study was approved by the institutional review board at each site and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonization. All patients provided written informed consent. The study was designed and sponsored by Iovance Biotherapeutics, Inc. All authors discussed, analyzed, and interpreted the results, and vouch for the accuracy and completeness of the data analyses and adherence to the Protocol (online only). All authors contributed to this study and the writing of the manuscript. Professional medical writing or editorial assistance was paid for by the sponsor.

Patients and Study Design

The parent study (ClinicalTrials.gov identifier: NCT02360579) consisted of multiple cohorts (Data Supplement, online only). Cohort 2 data are reported here. Patients were enrolled from April 2017 to January 2019 at 26 sites (see the Data Supplement for investigator list).

Patients had unresectable or metastatic melanoma (stage IIIC or IV) with confirmed radiologic progression. Patients must have progressed following one or more prior systemic therapies including a PD-1–blocking antibody and if *BRAF* V600 mutation-positive, a BRAF $\pm$ MEK inhibitor. Key eligibility criteria are detailed in the Data Supplement. Patients with a history of irAEs were eligible, as outlined in the Data Supplement.

At least one resectable lesion (or aggregate of lesions) measuring a minimum of 1.5 cm in diameter postresection was required. Resected tumor was processed in a protocol-specified manner and shipped to a Good Manufacturing Practice facility in the provided tumor procurement kit. The optimized manufacturing conditions involved a centralized 22-day process, resulting in a cryopreserved product (Data Supplement). Lifileucel (LN-144) was shipped to the clinical sites after meeting prespecified release criteria. Patients received a nonmyeloablative lymphodepleting (NMA-LD) regimen with cyclophosphamide (60 mg/kg) once daily for 2 days followed by fludarabine (25 mg/m^2) once daily for 5 days. A single infusion of lifileucel (1×10^9 – 150×10^9 cells) was thawed and administered after approximately 24 hours from the last dose of fludarabine. A

TABLE 1. Patient Demographics and Baseline Characteristics

Characteristic	Cohort 2 (N = 66)
Median age (range), years	55 (20-79)
Sex, No. (%)	
Male	39 (59)
Female	27 (41)
Melanoma stage at study entry	
IIIC	9 (14)
IV	57 (86)
Prior therapies, No. (%)	
Mean No. of prior therapies (SD)	3.3 (1.69)
Anti–PD-1 or PD-L1[a]	66 (100)
Anti–CTLA-4[b]	53 (80)
Anti–PD-1 plus CTLA-4 combination	34 (52)
BRAF± MEK[c]	15/17 (88)
IL-2	7 (11)
Surgery	65 (99)
Radiotherapy	34 (52)
Progressive disease for at least one prior therapy, No. (%)	
Anti–PD-1 or PD-L1[d]	65/66 (99)
Anti–CTLA-4	41/53 (77)
Primary refractory to prior anti–PD-1 or anti–PD-L1, No. (%)	42 (64)
Patients with baseline liver lesions, No. (%)	23 (35)
Patients with baseline brain lesions, No. (%)	7 (11)
Patients with baseline liver and/or brain lesions, No. (%)	28 (42)
Baseline ECOG score, No. (%)	
0	37 (56)
1	29 (44)
BRAF status, No. (%)	
Mutated V600	17 (26)
Wild type	45 (68)
Unknown	3 (5)
Other	1 (2)
Baseline LDH, No. (%)	
≤ ULN	39 (59)
1-2 × ULN	19 (29)
> 2 × ULN	8 (12)
PD-L1 status	
TPS ≥ 5%	24 (36)
TPS < 5%	23 (35)
Missing	19 (29)
Target lesion sum of diameter	
≥ 70 mm, No. (%)	40 (61)
Mean (SD), mm	106 (71)
No. of target and nontarget lesions (at baseline)	
> 3, No. (%)	51 (77)
Mean (SD)	6 (2.7)
Median (range)	5 (2-14)
Median time from stop of anti–PD-1 or PD-L1 to TIL infusion (range), months	4.8 (1.6-56.5)

Abbreviations: CTLA-4, cytotoxic T-lymphocyte–associated protein 4; ECOG, Eastern Cooperative Oncology Group; IL, interleukin; LDH, lactate dehydrogenase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; SD, standard deviation; TIL, tumor-infiltrating lymphocytes; TPS, tumor proportion score; ULN, upper limit of normal.

[a]Includes pembrolizumab, nivolumab, durvalumab, and atezolizumab.

[b]Includes ipilimumab and tremelimumab.

[c]One patient received only BRAF inhibitor. Two patients were enrolled under an earlier protocol version that did not require *BRAF* V600 mutation-positive patients to receive BRAF ± MEK inhibitors. Percentage is calculated based on number of patients who were *BRAF* V600E- or V600K-mutated and received a BRAF inhibitor (dabrafenib or vemurafenib) ± a MEK inhibitor (trametinib or cobimetinib).

[d]One patient discontinued anti–PD-1 therapy because of toxicity and then progressed on interval therapy before enrollment.

short course of bolus interleukin (IL)-2 (600,000 IU/kg) was infused every 8-12 hours for up to six doses, starting within 3-24 hours of completing lifileucel infusion.

End Points and Assessments

The primary objective was to evaluate the efficacy of a single infusion of lifileucel in patients with unresectable or metastatic melanoma using investigator-assessed objective response rate (ORR) by RECIST v1.1.[29] Secondary end points included duration of response (DOR), disease control rate (DCR), OS, and safety. Efficacy assessments started at week 6. Subsequent efficacy, adverse event (AE), and serious AE (SAE) assessment schedules are outlined in the Data Supplement.

Statistical Analysis

The analyses for efficacy and safety were conducted on the full analysis set (FAS), defined as patients from cohort 2 who received lifileucel that met manufacturer's specifications, including a cell dose 1×10^9 – 150×10^9. The planned sample size was 60 based on estimation of ORR using the maximum half-width of the two-sided 95% CI of < 13.2% when ORR is expected to be 20%-50%. This was considered meaningful, assuming that the historical response rate of similar patients after chemotherapy is 10%.[15,30] The FAS consisted of 66 patients because of rapid enrollment.

The ORR was analyzed as a binomial proportion with two-sided 95% CI estimated based on the Clopper-Pearson

TABLE 2. Efficacy Outcomes by Investigator Assessment

Response (RECIST v1.1)	Cohort 2 (N = 66)
ORR, No. (%) (95% CI)	24 (36) (25 to 49)
DCR, No. (%) (95% CI)	53 (80) (69 to 89)
Best overall response, No. (%)	
CR	2 (3)
PR	22 (33)
SD	29 (44)
PD	9 (14)
Nonevaluable	4 (6)
Median DOR, months (range)	Not reached (2.2-26.9+)

NOTE. +, censored.

Abbreviations: CR, complete response; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

exact method. Time-to-event efficacy end points were estimated using the Kaplan-Meier product limit method, and two-sided corresponding 95% CIs were based on log-log transformation. Safety data were reported descriptively. All statistical analyses were conducted using the Statistical Analysis System (SAS) version 9.4.

RESULTS

Patients and Treatment

Seventy-eight patients underwent tumor resection. Sixty-six patients received lifileucel (LN-144) infusion with $> 1 \times 10^9$ but $< 150 \times 10^9$ TIL cells and comprised the FAS. Three patients either did not receive TIL or received $< 1 \times 10^9$ TIL cells, whereas nine patients could not be treated because of other causes (Data Supplement). Table 1 details the demographics and baseline characteristics. Patients had received a mean of 3.3 lines of prior therapies (range, 1-9 lines). All patients had received prior anti–PD-1 or anti–programmed death ligand 1 (PD-L1) therapy, and 53 (80%) had received prior anti–CTLA-4 therapy. Fifty-two percent of the patients had received concurrent CTLA-4 plus PD-1 blockade. Notably, 99% had progressed on prior anti–PD-1 or PD-L1 therapy, and 77% had progressed on prior anti–CTLA-4 therapy. Overall, 42 patients (64%) had a best response of progressive disease to initial anti–PD-1 or PD-L1 therapy (primary refractory subset). Of the 17 patients who were *BRAF* V600 mutation-positive, 88% had received BRAF ± MEK inhibitors. Forty patients (61%) had a baseline target lesion sum of diameters (SOD) ≥ 70 mm, 51 (77%) patients had more than three target and nontarget lesions at baseline, and 27 (41%) had baseline lactate dehydrogenase levels higher than institutional upper limit of normal. Overall, patients had a high tumor burden at

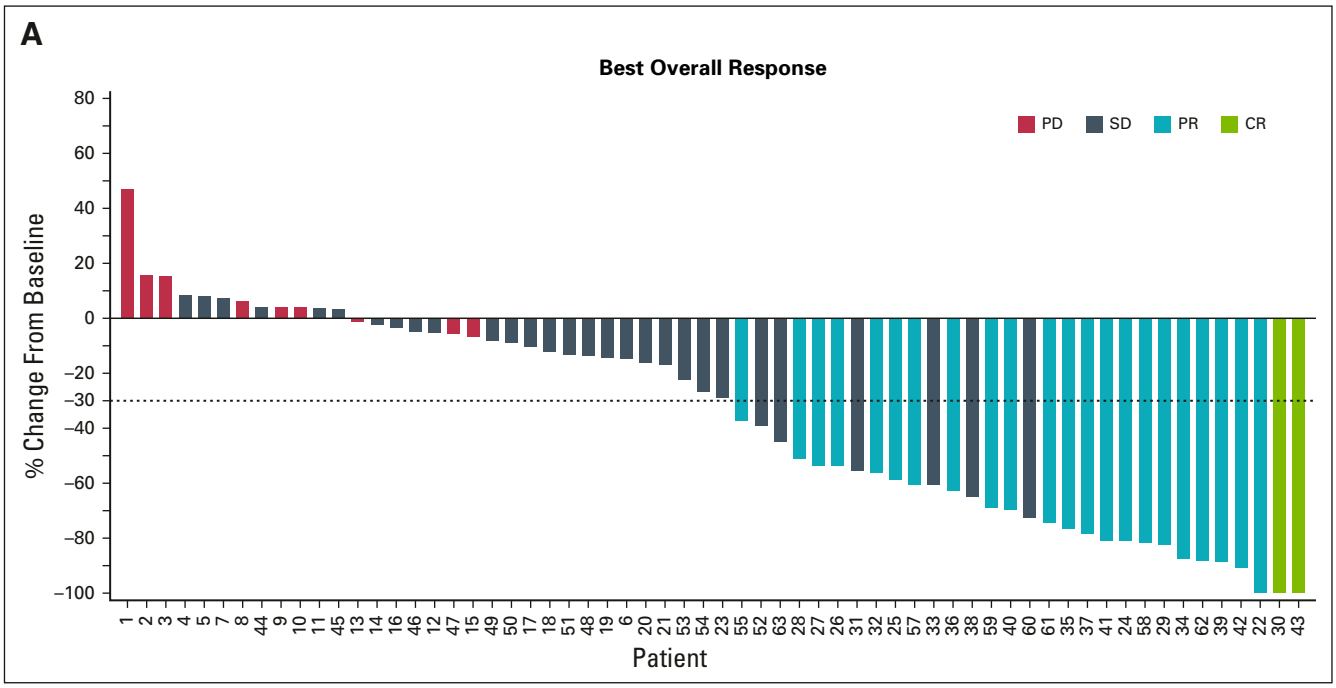

FIG 1. Change in tumor burden of target lesions, response by subgroup, and response assessment in individual patients. (A) Waterfall plot depicting BOR as assessed by investigator and the best change from baseline in the SOD of the target lesions (per RECIST v1.1 criteria) in the FAS. A change of −100% from baseline is presented for CR assessment that includes lymph node lesions that resolved to < 10 mm. The horizontal dashed line indicates a 30% reduction in the tumor burden in the target lesions. Twelve patients had an increase in the SOD of the target lesions, whereas 50 patients had a decrease in the SOD of the target lesions. Thirty patients (two CR, 22 PR, and six SD) had > 30% reduction in the SOD of the target lesions. Three patients had no post-TIL assessments because of early death. One patient had no post-TIL assessment because of start of new anticancer therapy before day 42. (continued on next page)

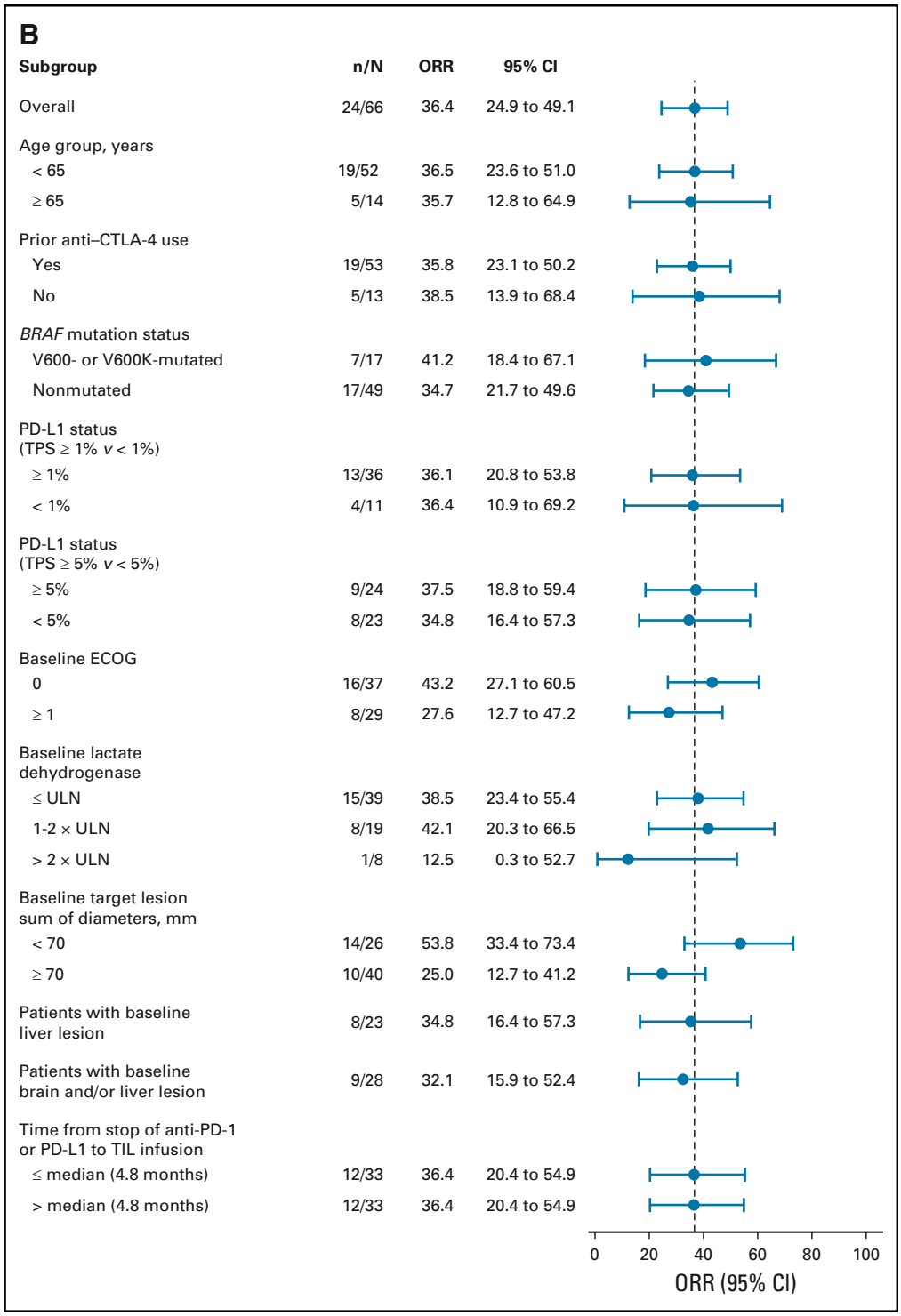

FIG 1. (Continued). (B) Forest plot for ORR (FAS) by subgroup per investigator assessment using the RECIST v1.1 criteria. 95% CI is calculated using the Clopper-Pearson Exact test. (continued on next page).

baseline (mean SOD for the target lesions: 106 mm); 28 patients (42%) had liver and/or brain lesions at baseline.

The harvested tumor was collected from a variety of sites, such as skin, lymph nodes, liver, lung, peritoneum, musculoskeletal sites, breast, and other organs. The median number of cyclophosphamide and fludarabine doses were 2 (range, 1-2) and 5 (range, 2-5), respectively. The mean number of TIL cells infused was 27.3×10^9 (range, 1.2×10^9 to 99.5×10^9). The median number of IL-2 doses administered was 5.5 (range, 1-6).

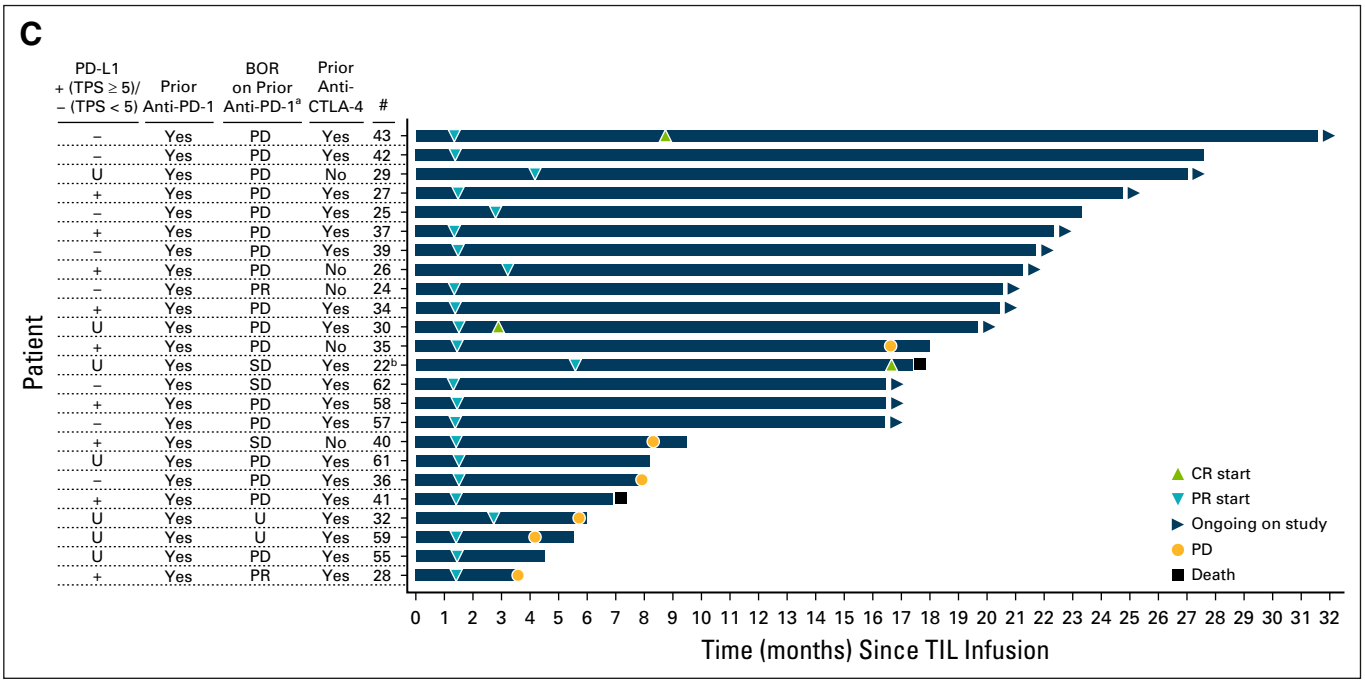

FIG 1. (Continued). (C) Swimmer's plot showing time to first response, duration of response, and time on efficacy assessment in confirmed responders by investigator per RECIST v1.1 criteria. Among 24 responders, 12 (50%) showed ongoing response to lifileucel, six (25%) had progressed, two (8%) had died, three (13%) started a new anticancer therapy, and one patient discontinued assessment because of relocation. [a]BOR is best overall response on prior anti-PD-1 immunotherapy. [b]For patient 22, a CR was not confirmed; therefore, the BOR with lifileucel for this patient was PR. Causes of death: patient 22: possible pulmonary embolism; patient 41: failure to thrive. BOR, best overall response; CR, complete response; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; ORR, objective response rate; PD, progressive disease; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; SOD, sum of diameters; TIL, tumor-infiltrating lymphocytes; TPS, tumor proportion score; U, unknown; ULN, upper limit of normal.

Efficacy

Sixty-six patients received a lifileucel infusion of $\geq 1 \times 10^9$ TIL cells. At the data cutoff of April 23, 2020 (median follow-up of 18.7 months [range, 0.2-34.1 months]), the investigator-assessed ORR was 36% (95% CI, 25 to 49) and the DCR was 80% (95% CI, 69 to 89) (Table 2), with 2 (3%) complete responses (CRs), 22 (33%) partial responses (PRs), and 29 (44%) patients showing stable disease (SD). Sixty-two patients (94%) had a baseline and at least one postbaseline radiologic assessment. Of the four patients in the FAS who did not undergo postbaseline assessment, three had died of disease, and one received an additional line of systemic therapy; all were considered as not evaluable for best overall response. Of the evaluable patients, 50 (81%) had a reduction in tumor burden (Fig 1A). Data Supplement details the percentage change in target SOD from baseline over time in patients who achieved a confirmed response. Response to lifileucel was observed regardless of age, prior anti–CTLA-4 use, *BRAF* mutation status, PD-L1 status as measured by tumor proportion score, baseline Eastern Cooperative Oncology Group performance status, tumor burden (assessed by lactate dehydrogenase elevation above upper limit of normal and target lesion SOD at baseline), presence of liver and/or brain lesions at baseline, and timing of prior PD-1 therapy (Fig 1B).

Median time from lifileucel infusion to best response was 1.4 months (range, 1.3-8.7 months). Time to response for individual patients is illustrated in Figure 1C; 19 of 24 patients achieved response by the time of first planned assessment (6 weeks after lifileucel infusion). Only 25% of patients had progressed after achieving a response. The median DOR has not been reached (95% CI, 11.8 months to not reached) (Fig 2A) with a 1-year DOR of 69% (95% CI, 46 to 84). The median OS was 17.4 months (95% CI, 11.0 to not reached; Fig 2B). Of the patients who had SD and PR or CR, 38% and 92% patients, respectively, had an OS $\geq$ 1 year. Progression-free survival for the FAS is shown in the Data Supplement, and duration of SD in individual patients is outlined in the Data Supplement.

An efficacy analysis was performed for the primary-refractory subset (42 patients primary refractory to anti–PD-1 or PD-L1 therapy). The ORR was 41% (95% CI, 26 to 57), with 2 CRs (5%) and 15 PRs (36%), and the DCR was 81% (95% CI, 66 to 91). Seventeen (41%) of these patients had SD, and five (12%) had progressive disease; three patients were nonevaluable. Median DOR was not reached for this subpopulation.

Thirty-four (52%) patients received anti–PD-1 plus anti–CTLA-4 combination therapy, either as frontline (n = 15, 23%), or after failing frontline therapy (n = 19, 29%). The

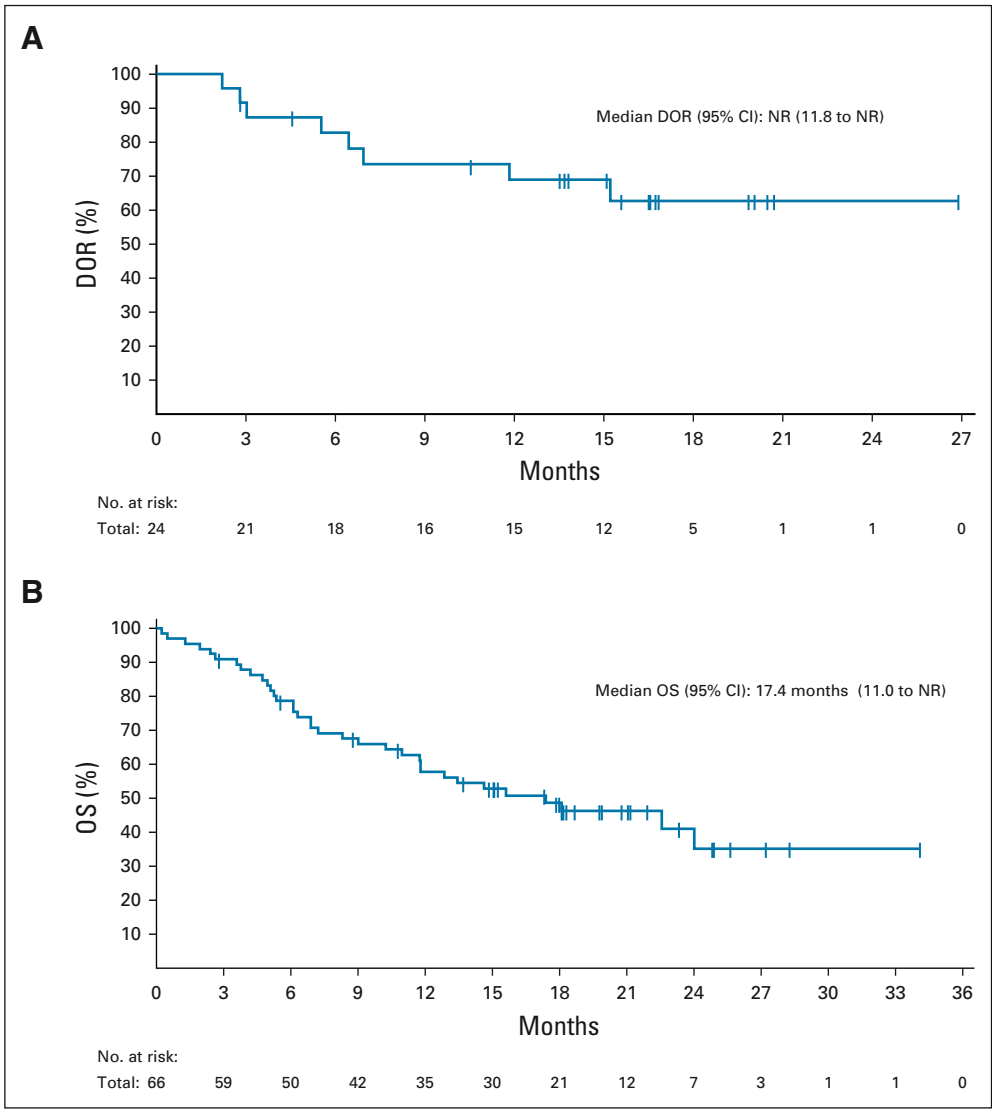

FIG 2. (A) The Kaplan-Meier curve for DOR in confirmed responders who achieved a PR or better. The DOR is measured from the time point at which the initial measurement criteria are met for a PR or CR, whichever occurred first, until the first date that PD or death occurred. (B) The Kaplan-Meier curve for OS in the full analysis set. OS was defined as the time (in months) from the start date of lifileucel infusion to death because of any cause. Patients who were alive at the time of data cutoff had their event times censored on the last date of their known survival status. The median OS was 17.4 months (95% CI, 11.0 to NR), with 1-year OS of 58% (95% CI, 45 to 69). CR, complete response; DOR, duration of response; NR, not reached; OS, overall survival; PD, progressive disease; PR, partial response.

ORRs for lifileucel in these two subsets were 33% (5/15) and 32% (6/19), respectively. The ORRs for lifileucel in patients with primary resistance (n = 17) or acquired resistance (n = 11) to anti–PD-1 plus anti–CTLA-4 combination therapy were 35% (6/17) and 27% (3/11), respectively. Details of these patients who responded to lifileucel are outlined in the Data Supplement.

Exploratory analyses of product-specific characteristics, including levels of phenotypic markers of T-cell lineage, memory subset, youth, activation or exhaustion, or trafficking (Data Supplement), did not demonstrate association with response. Tumor burden reductions were seen across the continuum of cell doses (Data Supplement).

Safety

All patients experienced at least one TEAE, with the most common (≥ 30%) grade 3 or 4 TEAEs being thrombocytopenia (82%), anemia (56%), febrile neutropenia (55%), neutropenia (39%), hypophosphatemia (35%), leukopenia (35%), and lymphopenia (32%) (Table 3), consistent with the toxicity profile of NMA-LD and IL-2. Fatal TEAEs occurred in two patients—1 death was because of intra-abdominal tumor

TABLE 3. TEAEs Occurring in ≥ 20% of Patients

	Cohort 2 (N = 66)		
Preferred Term, No. (%)	**Any Grade**	**Grade 3 or 4**	**Grade 5**
No. of patients reporting at least one TEAE	66 (100)	64 (97)	2 (3)[a]
Thrombocytopenia	59 (89)	54 (82)	0
Chills	53 (80)	4 (6)	0
Anemia	45 (68)	37 (56)	0
Pyrexia	39 (59)	11 (17)	0
Neutropenia[b]	37 (56)	26 (39)	0
Febrile neutropenia	36 (55)	36 (55)	0
Hypophosphatemia	30 (46)	23 (35)	0
Leukopenia[b]	28 (42)	23 (35)	0
Fatigue	26 (39)	1 (2)	0
Hypotension	24 (36)	7 (11)	0
Lymphopenia[b]	23 (35)	21 (32)	0
Tachycardia	23 (35)	1 (2)	0
Alopecia	19 (29)	0	0
Increased AST	19 (29)	0	0
Decreased appetite	19 (29)	1 (2)	0
Diarrhea	19 (29)	1 (2)	0
Hypokalemia	17 (26)	2 (3)	0
Hypoxia	17 (26)	10 (15)	0
Peripheral edema	17 (26)	1 (2)	0
Rash	17 (26)	3 (5)	0
Hypocalcemia	16 (24)	3 (5)	0
Hypomagnesemia	16 (24)	0	0
Increased weight	16 (24)	1 (2)	0
Increased ALT	15 (23)	2 (3)	0
Nausea	15 (23)	0	0
Increased blood alkaline phosphatase	14 (21)	2 (3)	0
Dyspnea	14 (21)	3 (5)	0
Hypoalbuminemia	14 (21)	3 (5)	0
Maculopapular rash	14 (21)	6 (9)	0
Vomiting	14 (21)	0	0
Constipation	13 (20)	0	0
Pruritus	13 (20)	0	0

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event; TIL, tumor-infiltrating lymphocytes.

[a]One death was because of intra-abdominal hemorrhage reported as possibly related to TIL, and one was because of acute respiratory failure assessed as not related to TIL by the investigator.

[b]All patients had grade 4 laboratory abnormality per the Common Terminology Criteria for Adverse Events v4.03 for leukopenia, neutropenia, and lymphopenia during the treatment-emergent period. Only clinically significant laboratory abnormalities per investigators were reported as AEs.

hemorrhage reported as possibly related to TIL, and one was because of acute respiratory failure assessed as not related to TIL by the investigator. The incidence of TEAEs, including grade 3 or 4 TEAEs, decreased rapidly over time (Fig 3) with no lifileucel-related SAEs reported after 6 months, and no recurrence of irAEs related to prior ICI. Tumor harvest AEs related to surgery are outlined in the Data Supplement.

DISCUSSION

Treatment options for patients with advanced melanoma who progress after treatment with ICI and BRAF ± MEK inhibitors are limited. Cytotoxic chemotherapy has shown poor response rates,[15,16,18,19] with a limited median OS of 7 months.[15] Many of the patients in our study had exhausted all approved therapy (mean lines of prior therapy, 3.3). The encouraging antitumor activity of lifileucel observed in our study addresses a major unmet need in patients with advanced melanoma after progression on ICI, and targeted agents if indicated.

Lifileucel, a one-time cellular therapy, represents a significant improvement in the treatment of advanced melanoma, particularly the current post-ICI patient population. First, lifileucel demonstrated an ORR of 36%, meeting the study primary end point in a patient population that had failed frontline anti–PD-1 therapy, the current standard of care. This is noteworthy because prior TIL therapy studies were conducted in the pre-ICI era, or enrolled a very small population of patients who had received prior anti–PD-1 therapy.[23-25,31] A previous cohort 2 analysis has demonstrated a high concordance rate of 89.4% between the Independent Review Committee–assessed and investigator-assessed ORR.[32] Second, at a median 18.7-month follow-up, the median DOR has not been reached, emphasizing the durability of lifileucel responses in a heavily pretreated post-ICI patient population with a high baseline tumor burden. Third, the efficacy of lifileucel was equivalent agnostic of PD-L1 status, *BRAF* mutation status, or prior anti–CTLA-4 therapy. Lifileucel was efficacious in the subset of patients who were primarily refractory to anti–PD-1/PD-L1 therapy, demonstrating an ORR of 41% and a DCR of 81% in this subgroup. Furthermore, lifileucel demonstrated similar ORR in patients who received anti–PD-1 plus anti–CTLA-4 combination as a frontline therapy (33%) or after failing frontline therapy (32%).

TIL recognize multiple tumor-specific neoantigens,[33] which may be required for response in solid tumors with high mutational burden. Removal from the hostile microenvironment and ex vivo expansion enable TIL to evade a broad array of immunosuppressive mechanisms. Indeed, both downregulation of PD-1 expression and restored functionality were reported for ex vivo expanded TIL.[34,35] By

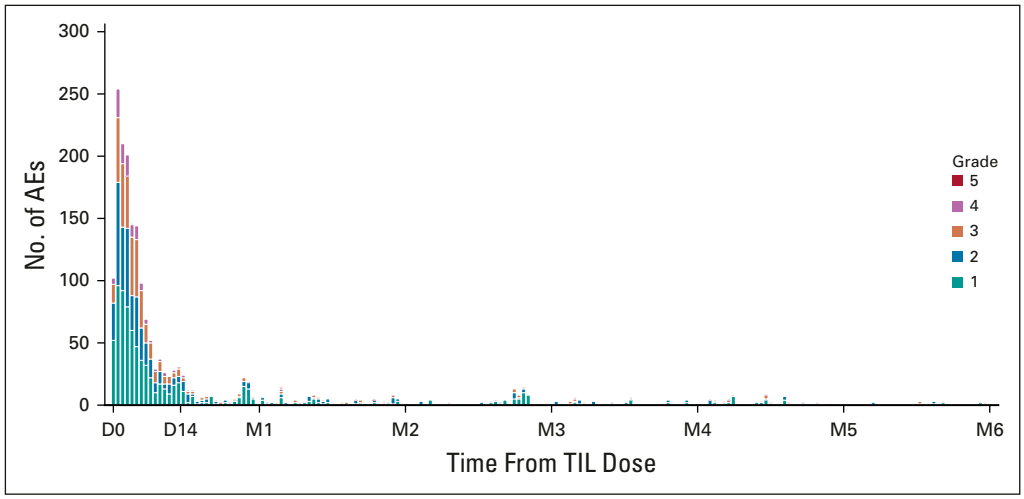

FIG 3. AEs over time. The distribution of onset of AEs starting from lifileucel infusion until 6 months postinfusion is shown. A TEAE was defined as any AE with onset after start of lifileucel through day 30 postinfusion. All occurrences of AEs were counted if a patient experienced a new onset of the same AE at different timepoints. If multiple records were reported on the electronic case report form because of toxicity grade decrease of the same AE that had not resolved, then the event was counted once with the highest grade reported. Overall, 24 AEs were reported post month 6 until data cutoff date, which are not shown in the histogram. No SAEs related to lifileucel were reported post month 6. AE, adverse event; D, day; M, month; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TIL, tumor-infiltrating lymphocytes.

contrast, ICI target only a limited number of pathways in situ. Additionally, in vitro culture results in large-scale expansion of TIL, potentially increasing the number of tumor-specific T cells available for tumor targeting after adoptive transfer. The T cells comprising the TIL product are recovered directly from the tumor tissue, a site enriched for T-cell clones that are able to recognize patient-specific tumor antigens.[36,37] As a result, a polyclonal product is obtained that has the potential to target multiple relevant antigens, addressing (1) the ability to identify the unique spectrum of patient-specific tumor antigens[38]; (2) the heterogeneous nature of solid tumors[39]; and (3) immune escape through antigen loss.[40] Finally, substantial fractions of TIL-derived T cells were shown to persist for at least 6 weeks,[41] consistent with the memory phenotype of the majority of the T cells comprising the product.[35] These varied mechanisms and TIL properties likely contribute to the antitumor efficacy of lifileucel.

The tumors were harvested with minimal surgical morbidity, although 58% were extranodal or nonskin/subcutaneous lesions. A small subset of enrolled patients (12%) could not be treated because of progression, death, or other causes.

TEAEs occurred during or immediately after NMA-LD or IL-2 administration and were generally transient, with no new lifileucel-associated SAEs reported after 6 months. Although patients were hospitalized for NMA-LD and IL-2 administration, lifileucel is a one-time cellular therapy with durable responses, as demonstrated by an ongoing response in 50% of responders at a median follow-up of 18.7 months. In addition, the safety profile indicates that lifileucel is a viable option for patients who are not eligible for ICI because of prior significant irAEs, as it is not associated with recrudescence of irAEs.

Single-center studies conducted at NCI[23,31] have been important in laying the groundwork for TIL therapy in patients with advanced melanoma but were limited to a few centers with dedicated on-site cell therapy facilities. Although lifileucel centralized manufacturing required shipping of the tumor samples, TIL could be manufactured in 96% of patients. The present multicenter study constitutes a significant advance by successfully demonstrating the feasibility of a centrally standardized manufacturing approach for TIL therapy, which allows for broadened patient access, whereas cryopreservation of lifileucel provides flexibility in treatment scheduling in the real-world clinical setting.

In summary, lifileucel, a first-in-class centrally manufactured autologous TIL cell therapy, was efficacious and demonstrated durable responses in heavily pretreated patients and represents a potential new standard of care for patients with advanced melanoma following failure of ICI and targeted therapy. Patients with advanced melanoma who have failed anti–PD-1 therapy (and BRAF ± MEK inhibitors if *BRAF* V600 mutation-positive), irrespective of baseline tumor characteristics, should be considered for the one-time lifileucel therapy as second-line therapy (third-line if *BRAF* V600 mutation positive) if they have performance status and organ function adequate for administration of lymphodepleting chemotherapy and a shortened course of IL-2. The US Food and Drug

Administration has granted lifileucel a Regenerative Medicine Advanced Therapy designation, Orphan Drug designation, and a Fast Track designation for advanced melanoma. Based on these encouraging results, an additional cohort has been fully enrolled, using Independent Review Committee–assessed ORR for registration purposes. Given the favorable risk-benefit profile of lifileucel, its role earlier in the disease course and in combination with ICI is being investigated in melanoma, as well as additional studies in other metastatic solid malignancies.

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Lifileucel, a Tumor-Infiltrating Lymphocyte Therapy, in Metastatic Melanoma

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