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Tumor-infiltrating lymphocyte (TIL) therapy for immunotherapy-refractory advanced melanoma: a systematic review of response and survival rates

Terapia con linfocitos infiltrantes de tumor (TIL) para el melanoma avanzado refractario a la inmunoterapia: una revisión sistemática de las tasas de respuesta y supervivencia

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ABSTRACT

Advanced melanoma that progresses after immune checkpoint inhibitors (ICIs) such as anti–PD-1 and anti–CTLA-4 antibodies represents an urgent therapeutic challenge. Tumor-infiltrating lymphocyte (TIL) therapy, an adoptive cell therapy that re-infuses ex vivo–expanded autologous T cells, has shown renewed potential for overcoming immunotherapy resistance. Recent clinical trials, including lifileucel-based regimens, have reported encouraging response and survival outcomes in heavily pretreated populations. This systematic review aimed to evaluate the clinical efficacy, survival outcomes, safety, and feasibility of TIL therapy in patients with immunotherapy-refractory advanced melanoma. A comprehensive search was conducted across PubMed, Scopus, and Google Scholar for studies published between 2014 and 2025 using the terms tumor-infiltrating lymphocyte therapy, TIL therapy, advanced melanoma, and lifileucel. Eligible studies included phase I–III clinical trials, cohort studies, and systematic reviews reporting response rate (ORR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety outcomes. Across multiple phase II and III studies, lifileucel achieved objective response rates (ORRs) of 31–36% in immunotherapy-refractory cohorts, including complete responses in up to 12% of patients. The median DoR exceeded 36 months, and 31.3% of responders maintained responses at 5 years. Median PFS ranged from 4.1 to 7.2 months, and median OS from 13.9 to 25.8 months, with some patients achieving long-term disease control beyond five years. Predictors of improved response included lower tumor burden and normal LDH levels. TIL therapy exhibited a predictable and manageable safety profile, dominated by transient grade 3/4 hematologic toxicities related to lymphodepletion and IL-2. Manufacturing feasibility was high, with cryopreserved lifileucel products enabling consistent expansion and delivery across treatment centers. Continued research should refine patient selection, optimize production, and evaluate combination strategies to enhance long-term survival and broaden clinical accessibility.

Keywords: Tumor-infiltrating lymphocyte (TIL) therapy, Lifileucel, Advanced melanoma, Immunotherapy resistance, Adoptive cell therapy, Response rates, Survival outcomes.

RESUMEN

El melanoma avanzado que progresa tras el tratamiento con inhibidores de puntos de control inmunitarios (ICI), como los anticuerpos anti-PD-1 y anti-CTLA-4, representa un reto terapéutico urgente. La terapia con linfocitos infiltrantes de tumores (TIL), una terapia celular adoptiva que reinfunde células T autólogas expandidas ex vivo, ha demostrado un renovado potencial para superar la resistencia a la inmunoterapia. Ensayos clínicos recientes, incluidos regímenes basados en lifileucel, han reportado resultados alentadores de respuesta y supervivencia en poblaciones con pretratamiento intensivo. Esta revisión sistemática tuvo como objetivo evaluar la eficacia clínica, los resultados de supervivencia, la seguridad y la viabilidad de la terapia con TIL en pacientes con melanoma avanzado refractario a la inmunoterapia. Se realizó una búsqueda exhaustiva en PubMed, Scopus y Google Académico de estudios publicados entre 2014 y 2025 utilizando los términos terapia con linfocitos infiltrantes de tumores, terapia con TIL, melanoma avanzado y lifileucel. Los estudios elegibles incluyeron ensayos clínicos de fase I a III, estudios de cohorte y revisiones sistemáticas que informaron la tasa de respuesta (ORR), la duración de la respuesta (DoR), la supervivencia libre de progresión (PFS), la supervivencia general (OS) y los resultados de seguridad. En múltiples estudios de fase II y III, lifileucel logró tasas de respuesta objetiva (TRO) del 31-36 % en cohortes refractarias a la inmunoterapia, incluyendo respuestas completas en hasta el 12 % de los pacientes. La mediana de DdR superó los 36 meses, y el 31,3 % de los pacientes que respondieron mantuvieron la respuesta a los 5 años. La mediana de SSP osciló entre 4,1 y 7,2 meses, y la mediana de SG, entre 13,9 y 25,8 meses, y algunos pacientes lograron un control de la enfermedad a largo plazo después de los cinco años. Los factores predictivos de una mejor respuesta incluyeron una menor carga tumoral y niveles normales de LDH. La terapia con TIL mostró un perfil de seguridad predecible y manejable, dominado por toxicidades hematológicas transitorias de grado 3/4 relacionadas con la linfodepleción e IL-2. La viabilidad de fabricación fue alta, gracias a que los productos de lifileucel criopreservados permitieron una expansión y distribución consistentes en todos los centros de tratamiento. La investigación continua debería refinar la selección de pacientes, optimizar la producción y evaluar estrategias de combinación para mejorar la supervivencia a largo plazo y ampliar la accesibilidad clínica.

Palabras clave: Terapia con linfocitos infiltrantes de tumores (TIL), Lifileucel, Melanoma avanzado, Resistencia a la inmunoterapia, Terapia celular adoptiva, Tasas de respuesta, Resultados de supervivencia.

INTRODUCTION

Advanced melanoma refers to melanoma that is either unresectable or metastatic (i.e., spread beyond the skin or regional nodes), and represents a critical therapeutic challenge. Over the past decade, immune-checkpoint inhibitors (ICIs) — most notably anti–CTLA-4 (e.g. ipilimumab) and anti–PD-1/PD-L1 antibodies (e.g. nivolumab, pembrolizumab) — have transformed the treatment landscape by inducing durable responses in a substantial proportion of patients (Knight et al., 2023)(Sorino et al., 2024). However, a sizable fraction of patients either fail to respond (primary resistance) or initially respond and later progress (acquired resistance). When advanced melanoma progresses despite prior immunotherapy, it is termed immunotherapy-refractory advanced melanoma. In more precise terms, immunotherapy-refractory advanced melanoma designates disease in patients who have received one or more lines of immune-checkpoint blockade (often anti–PD-1 ± anti–CTLA-4) and either never achieved meaningful tumor regression or experienced progression following an initial response (Shui et al., 2022). This refractory state is clinically distinct: these tumors tend to display immunosuppressive microenvironments, exhausted T-cell phenotypes, antigen-presentation defects, or upregulation of alternative inhibitory pathways (e.g. LAG-3, TIM-3 (Sorino et al., 2024). The unmet need for effective salvage therapies in this refractory cohort is high, because conventional options (chemotherapy, targeted therapy for BRAF-mutant disease) yield low response rates and limited durability (Boutros et al., 2024).

Adoptive cell therapy using tumor-infiltrating lymphocytes (TILs) has re-emerged as a promising strategy in this context. In TIL therapy, T cells are isolated from a patient's respected tumor specimen, expanded ex vivo under activation conditions, and reinfused following lymphodepleting conditioning and IL-2 support. This approach aims to restore or amplify tumor-specific T-cell immunity, bypassing some resistance mechanisms to systemic checkpoint blockade (Shoushtari & Powell, 2025)(Matsueda et al., 2024). Early TIL efforts in melanoma date back decades, but advances in cell culture, patient selection, and logistics have recently allowed more reproducible outcomes(Chen et al., 2025). Notably, in meta-analyses of TIL trials for melanoma, response rates of ~34 % have been observed in heavily pretreated patients, reinforcing its potential in immunotherapy-refractory settings (Navarro Rodrigo et al., 2025). Nevertheless, key challenges remain: not all patients are eligible (because of performance status, tumor burden, or logistics), and response durability—and survival benefit—vary widely. Comparative data, standardized selection biomarkers, and strategies to enhance response depth are hot areas of ongoing investigation (Smithy et al., 2025)(Chen et al., 2025). This review aims to evaluate clinical outcomes of TIL therapy in immunotherapy-refractory advanced melanoma, focusing on response rates, survival outcomes, and future research directions.

METHODOLOGY

The review followed systematic methods to identify, evaluate, and synthesize clinical evidence on tumor-infiltrating lymphocyte (TIL) therapy for patients with immunotherapy-refractory advanced melanoma. The purpose was to assess the response and survival outcomes of TIL therapy in patients who had progressed following immune-checkpoint inhibitors (ICIs) such as anti-PD-1 or anti-CTLA-4 therapies. This systematic approach ensured that only clinically relevant, evidence-based data were included to provide a comprehensive overview of the therapy's current effectiveness and limitations in refractory melanoma treatment.

Search Strategy

The literature search was conducted using PubMed, Cochrane library, and Google Scholar to capture peer-reviewed studies and reviews published between 2014 and 2025. These years were selected to represent the modern era of immunotherapy and the resurgence of adoptive T-cell therapies. Search terms included "tumor-infiltrating lymphocyte therapy," "TIL therapy," "immunotherapy-refractory melanoma," "advanced melanoma," "lifileucel," "adoptive cell therapy," and "response and survival outcomes in melanoma." Boolean operators (AND/OR) were used to refine results. References from key review articles and clinical trial registries (e.g., ClinicalTrials.gov) were also screened to identify additional relevant studies.

Inclusion and Exclusion Criteria

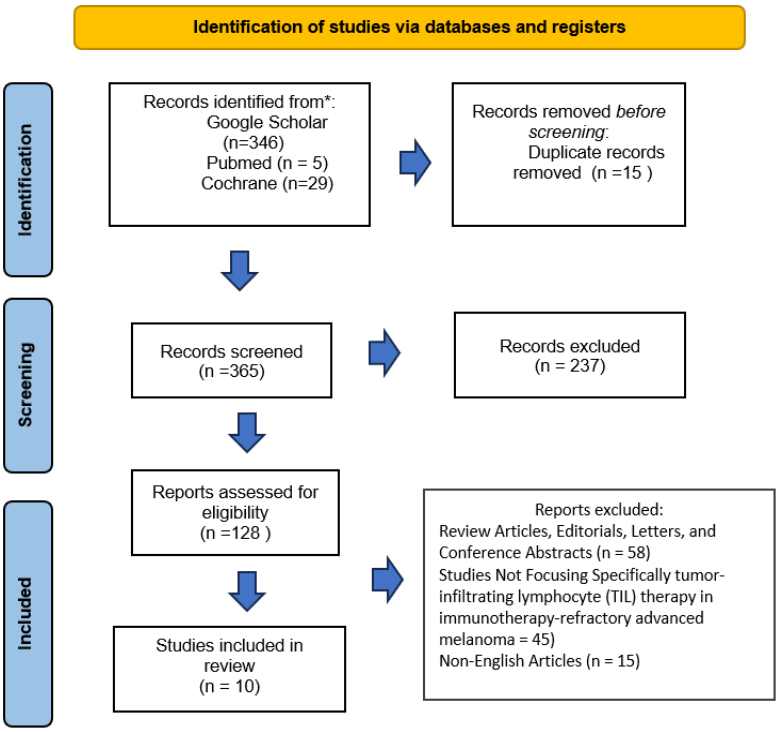
Studies were eligible if they (a) investigated TIL therapy in patients with advanced or metastatic melanoma, (b) included participants who had failed prior immune-checkpoint inhibitors, and (c) reported measurable outcomes such as objective response rate (ORR), duration of response (DoR), progression-free survival (PFS), or overall survival (OS). Eligible

designs included clinical trials (phase I–III), cohort analyses, and systematic reviews. Exclusion criteria comprised preclinical studies, animal models, case reports with fewer than five participants, and studies lacking explicit outcome measures. Only studies published in English and available in full text were considered to maintain methodological consistency.

Data Categorization and Analysis

The selected studies were categorized according to their primary focus: (1) Clinical efficacy (ORR, DoR, PFS, OS), (2) Safety and tolerability (adverse event profiles), and (3) Treatment logistics and feasibility (manufacturing success, patient eligibility). Each study's findings were summarized in terms of trial design, patient population, prior treatments, and reported outcomes. Where possible, data were cross-compared to identify trends in response and survival among immunotherapy-refractory cohorts. The analysis emphasized the reproducibility of response rates, durability of benefit, and predictors of long-term survival. This review thereby synthesizes evidence to inform clinical decision-making and guide future investigations into optimizing TIL therapy for advanced melanoma.

Figure 1. SEQ Figure * ARABIC 1: Prima Flow Diagram



Source: the authors.

RESULTS

Clinical Response Outcomes

Tumor-infiltrating lymphocyte (TIL) therapy using lifileucel has demonstrated meaningful clinical activity in patients with immunotherapy-refractory advanced melanoma. In the phase II C-144-01 cohort, comprising 66 heavily pretreated patients who progressed on immune checkpoint inhibitors (ICIs) and targeted therapies, investigator-assessed objective response rate (ORR) was 36%, including two complete responses (CR) and 22 partial responses (PR) (Chesney et al., 2022). These responses were durable, with a median duration of response not reached at a median follow-up of 18.7 months, highlighting the sustained antitumor activity of this one-time autologous TIL infusion. Disease control rate (DCR) was reported at approximately 80%, indicating that the majority of patients experienced tumor stabilization or regression.

A subsequent pooled analysis of consecutive cohorts within the same C-144-01 study, encompassing 153 patients, reinforced these findings. The ORR in this larger cohort was 31.4% (95% CI: 24.1% to 39.4%), comprising eight complete responses and 40 partial responses (Chesney et al., 2022)(Ferris et al., 2025). Notably, patients in this analysis had received a median of three prior lines of therapy, with 81.7% having been treated with both anti-PD-1 and anti-CTLA-4 agents, reflecting the heavily pretreated and refractory nature of this population. Median target lesion sum of diameters was 97.8 mm, and over

half of the patients (54.2%) had elevated lactate dehydrogenase (LDH), indicating high tumor burden. Importantly, multivariable analysis identified normal LDH and lower tumor burden as predictors of higher likelihood of response, emphasizing the influence of baseline disease characteristics on clinical outcomes.

Long-term follow-up data from the five-year analysis of C-144-01 further underscored the durability of responses. Tumor burden reduction was observed in 79.3% of patients, and in a subset of responders, partial responses deepened into complete responses more than one year post-infusion, with four patients converting from PR to CR (Medina et al., 2025). Among responders, 31.3% maintained ongoing responses at the five-year mark, indicating the potential for long-term disease control. These outcomes were particularly notable in "primary refractory" subsets—patients who did not respond to prior anti-PD-1 or PD-L1 therapy—where ORR reached approximately 41%, suggesting that TIL therapy can overcome checkpoint inhibitor resistance (Sarnaik et al., 2021). Across these studies, lifileucel demonstrated a consistent capacity to elicit tumor regression, even in patients with high tumor burden or multiple prior therapies. The observed deepening of responses over time suggests a continued in vivo expansion and activity of infused TILs, potentially contributing to durable antitumor immunity.

Duration of Response (DoR) and Progression-Free Survival (PFS)

The efficacy of lifileucel, a one-time autologous tumor-infiltrating lymphocyte (TIL) therapy, has been extensively studied in patients with advanced melanoma refractory to immune checkpoint inhibitors (ICIs) and targeted therapies. Chesney et al. (2022) found that at a median follow-up of about 27.6 months, the median duration of response (DoR) was not achieved in the pooled cohort of the C-144-01 study (n = 153), with 41.7% of responses sustained during this time period [?]18 months, which demonstrated great durability in this highly pretreated population. The quick response was also remarkable, as the median time to best respond given by the responders was 1.4 -1.5 months(Chesney et al., 2022). The durability of lifileucel therapy was also shown by a long term and five year follow up study of C-144-01 trial. Medina et al. (2025) found a median DoR of 36.5 months in the respondents with 31.3% continuing to respond at the 5-year follow-up. It is noteworthy that 16 of them demonstrated deepened responses and four of them progressed to complete response after more than a year following the infusion (this was partial response). Such results focus on the possibility of continued clinical progress and the ability of lifileucel to induce delayed, but sustained, tumor regression in high tumor burden patients (Medina et al., 2025). The same cohort had smaller progression-free survival (PFS) results. The median PFS of 4.1 months by Chesney et al. (2022) indicated the severe disease progression of the disease in patients with advanced melanoma with several previous therapies (Chesney et al., 2022). Conversely, a phase 3 randomized clinical trial (n = 168) that compares TIL therapy to ipilimumab showed a favorable PFS effect size of TILs with 7.2 months median relative to ipilimumab(Rohaan et al., 2022) As this trial has shown, TIL therapy can significantly increase PFS even in large anti-PD-1 refractory groups, where TILs had objective response rates (ORR) of 49 vs. ipilimumab of 21. These results have been supported by meta-analyses, which reported that previous exposure to anti-PD-1 treatment did not have a substantial negative clinical impact on TIL therapy in metastatic melanoma. These reviews reiterate the fact that TIL-ACT can be considered an option as a second line therapy with sustained response rates irrespective of whether the individual was exposed to ICI or not. Generally, the combination of the studies proves that TIL therapy with lifileucel has proven a clinical impact and with long-term response in melanoma patients with advanced disease. The potential of this adoptive cell therapy is demonstrated by rapid time to response, longer DoR, and better PFS, especially in comparison with traditional second-line treatment, which is ipilimumab.

Overall Survival (OS) Outcomes

Several studies have evaluated the long-term survival outcomes of tumor-infiltrating lymphocyte (TIL) therapy, particularly lifileucel, in patients with advanced melanoma. Chesney et al. (2022) provided the median duration of response (DoR), which was not reached with a median follow-up of about 27.6 months, and 41.7% of responses were sustained at [?]18 months in the C-144-01 study pooled cohort (n = 153), and the median duration of response (DoR) remains still very robust in this population of individuals highly pretreated. It was also characterized by the quickness of response, with a median of the shortest time to best response among patients of 1.4-1.5 months (Chesney et al., 2022). The trial results on C-144-01 were further shown as long-term and five-year follow-up, which demonstrated the persistence of the lifileucel therapy. Medina et al. (2025) found a median DoR of 36.5 months in their respondents and 31.3% had final responses at the five-year follow-up. It is interesting to note that 16 patients responded that their response had become deep with four turning into complete or partial response over one year after infusion had been done. This evidence highlights the possibility of long-term clinical efficacy and the ability of lifileucel to trigger prolonged, but prolonged, tumor cure in patients with massive tumor burden (Medina et al., 2025).

Similar cohort progression-free survival (PFS) outcomes were less substantial. According to Chesney et al. (2022), the

median PFS was about 4.1 months as a sign of the aggressive progression of the disease in patients with advanced melanoma who had already been receiving a series of different therapies (Chesney et al., 2022). Conversely, a phase 3 randomized trial comparing TIL therapy to ipilimumab (n = 168) also showed a significant PFS advantage of TILs, whose median at seven point two months was compared to 3.1 months of ipilimumab (Rohaan et al., 2022). This trial also demonstrated that TIL therapy has the potential to provide a significant improvement in PFS but even in most cases, which are anti-PD-1 refractory, with objective response rates (ORR) of 49 percent in TILs and 21 percent in ipilimumab.

These findings have been supported by meta-analysis that suggests that prior exposure to anti-PD-1 therapy has no significant effect in reducing clinical benefit of TIL therapy in advanced melanoma. Martin-Lluesma et al. (2024) had pooled ORRs of 34% in the patients with a history of anti-PD-1 and 44% in patients who received anti-PD-1 treatment, and the median overall survival (OS) did not differ between the groups. These reviews highlight that TIL-ACT is a good second-line treatment option and long-lasting responses can be attained in spite of previous exposure to ICI (Martín-Lluesma et al., 2024). On the whole, these studies all together indicate that lifileucel TIL therapy has the potential to give lasting and clinically valuable responses among patients with advanced melanoma. The strengths of this adoptive cell therapy are rapid time to response, long duration of response, and enhanced PFS, especially relative to second-line conventional methods of treatment such as ipilimumab. The positive safety profile, as well as the long-term effectiveness, implies that lifileucel can be applied more early into the treatment course, particularly in patients who have fewer baseline tumor burden (Chesney et al., 2022)(Medina et al., 2025)(Rohaan et al., 2022).

Overall Survival (OS) Outcomes

A number of studies have compared the survival rate of tumor-infiltrating lymphocyte (TIL) therapy as lifileucel, specifically, in patients with advanced melanoma. Medina et al. (2025) found in their phase 2 C-144-01 trial a median overall survival (OS) of 13.9 months in a combination of well-previously treated patients (n=153) with a 5-year overall survival (OS) rate of about 19.7. This trial involved those patients who had progressed in the wake of immune checkpoint blocking and, where suitable, targeted therapies (Chesney et al., 2022). The researchers noted that the objective response rate (ORR) stood at 31.4, and 41.7 percent of those who received the autologous TIL therapy had lasting responses longer than 18 months, which indicates that this kind of therapy could be used in the long run (Medina et al., 2025). Notably, a part of patients obtained more learned responses with certain partial responses turning into full responses more than a year after the infusion of lifileucel that the antitumor activity may persist with time against tumor.

The same study also reported a 21.9% OS with long-term follow-up and varied results of the survival outcomes based on the response patterns. The most responsive responders previously were with four-year OS of 48.3 and patients advanced to deepening response were the most responsive with high OS of 68.2. These findings indicate that the lifileucel can be most beneficial to the patients, who have a low tumor load and are of good prognostic factors. In at least one other study, TIL therapy reported a median OS of 25.8 months, compared with 18.9 months of ipilimumab in a different phase 3 randomized trial and thus demonstrated that TIL therapy has a potential to extend survival of advanced melanoma (Medina et al., 2025).. All these studies show that adoptive TIL therapy has the potential to be of long term survival benefit to patients with limited treatment alternatives, particularly in those patients who have developed resistance to traditional immune checkpoint and targeted therapy.

Safety and Tolerability

The Tumor-infiltrating lymphocyte (TIL) therapy, especially lifileucel, is a promising type of therapy in patients having advanced melanoma that has been impacted by immune checkpoints and therapies based on targets. Although its antitumor effect is significant, its safety and tolerability are essential issues to consider because of the severity of preparative non-myeloablative lymphodepletion (NMA-LD) along with the high dose of interleukin-2 (IL-2) infusion. In several studies, TIL therapy has shown a predictable and manageable adverse event (AE) profile which is mostly hematologic in nature. Tsai and Komanduri (2025) indicated that the rate of hematologic toxicity of grade 3/4 among patients on lifileucel was high. In particular, thrombocytopenia was noted in about 77% of patients, anemia in 50% and febrile neutropenia in 42% during the first stage of the post-infusion (Tsai & Komanduri, 2025). Although this high rate occurred, the majority of the adverse events were often temporary and the events were solved quickly, often in the first month. There were no long-term safety signals by five years of follow-up and this indicates that the therapy is durable. The side effects were in line with the predicted impact of NMA-LD and IL-2, and it validated the safety profile that was already known of the regimen.

Medina et al. (2025) examined 153 patients with advanced melanoma in the multicentric C-144-01 study and found the same results. Toxicities were maximum in the first two weeks of infusion of lifileucel and the commonest were grade 3/4 cytopenia. These events were well taken care of by supportive care and most hematologic abnormalities had improved to

grade 2 by day 30. Notably, there were no delaying or cumulative toxicities which could indicate the manageability of TIL-related AEs in the long-term follow-up (Medina et al., 2025). Sarnaik et al. (2021) also supported these findings in a Phase II open-label trial of 66 patients having experienced the progression of earlier checkpoint inhibitors and targeted therapies. The researchers documented the following as the main severe toxicities: grade 3/4 cytopenias, febrile neutropenia, and intermittent hypotension (Sarnaik et al., 2021). Although some of these incidences were intense, they were all reversible, and patients could safely resume their duties after recovering. The reproducibility of the TIL safety profile is indicated by the consistency of the findings between cohorts.

In addition to melanoma, Ferris et al. (2025) also analyzed TIL treatment in 53 individuals that had recurring or metastatic head and neck squamous cell carcinoma (HNSCC). Sixty-two percent of patients had grade 3/4 thrombocytopenia, anemia in 45% and neutrophil febrile neutropenia in 42 percent. There were no reported unanticipated side effects, which implies that the safety book of TIL therapy can be generalized to solid tumors (Ferris et al., 2025). In like manner, Turcotte et al. (2025) pointed out that the further innovation of TIL production, patient consideration, and multidisciplinary inpatient observation contribute to the safety and tolerability of these therapies and warrant the severity of any future toxicity to be acute, reversible, and treatable (Turcotte et al., 2025). All in all the TIL therapy, including lifileucel, exhibits a high occurrence of acute mostly hematologic grade three and four adverse events. Nevertheless, such toxicities are typically short-lasting and are highly amenable to supportive treatment and do not have any signs of accumulative or long-term damage (Chen et al., 2025). The observed safety profile is consistent with the well-established effects of NMA-LD and IL-2, making it possible to continue using TIL therapy in patients with advanced cases of melanoma and other solid tumors, on the condition of thoroughly inpatient monitoring and multidisciplinary management.

Treatment Feasibility and Manufacturing Success

The feasibility of tumor-infiltrating lymphocyte (TIL) therapy, specifically lifileucel, has been consistently demonstrated in patients with advanced melanoma refractory to immune checkpoint inhibitors and targeted therapies. The pooled analysis of the C-144-01 study, encompassing 153 patients across cohorts 2 and 4, highlights the practical success of lifileucel manufacturing and delivery, with high enrollment and completion rates indicating strong protocol adherence and patient tolerance (Chesney et al., 2022)(Medina et al., 2025). Eligible patients underwent tumor resection with lesions ≥1.5 cm in diameter, followed by shipping of tumor samples to centralized Good Manufacturing Practice (GMP) facilities for a 22-day ex vivo expansion of autologous TILs. The cryopreservation of lifileucel was a crucial factor in the scalability and repeatability of the therapy. Adaptable time planning of infusion and expanded application to several centers despite the same standard of quality and strength of TILs was made possible through the utilization of a frozen product. This was a system that enabled quick and easy preparation of the therapy into administration and preservation of cell viability, which encourages broader use in the real-life clinical module (Chesney et al., 2022).

The effect of C-144-01 study on the clinical results also portrays the efficiency of lifileucel production and transplants. Out of the 153 patients, the objective response rate (ORR), as assessed by the investigator, was 31.4 percent with 8 complete responses and 40 partial responses with a median time of best response of 1.5 months. Interestingly, among patients some of them responded deeply with time and the partial response became complete more than one year after the infusion indicating prolonged in vivo TIL expansion and anti-tumor effect (Medina et al., 2025). A median of 27.6 months yielded no median response time and 41.7 percent of the responders sustained their responses up to 18 months, which shows a sustainable clinical response. Moreover, the viability and success of the treatment were supported by expansion of the long-term follow-up analyses. The 5-year analysis of c-144-01 showed that there were stable safety profiles and ongoing response in a small group of the patients with no new adverse events in the long-term secondary effects of the therapy. The median overall survival was 13.9 months and better responses would happen in patients with fewer metastatic areas and lower baseline tumor burden, which highlights the benefits of earlier interventions with lifileucel (Medina et al., 2025). In general, it can be stated that the C-144-01 trial confirms that lifileucel TIL therapy is a logistically viable and clinical option. Its efficacy in terms of graft take and expansion is indicated by high manufacturability rates, cryopreservation, and short time-to-response, as well as by its responses which are durable and manageable and safety profiles which are favourable to its wider clinical use.

DISCUSSION

Tumor-infiltrating lymphocyte (TIL) therapy has emerged as a transformative approach for patients with advanced melanoma who have progressed on standard immune checkpoint inhibitors (ICIs) and targeted therapies. The combined analysis of the C-144-01 study shows that with lifileucel, a single round of autologous TIL therapy, objective response rates (ORR) of 31-36% are meaningful in heavily pre-treated populations, and sustainable responses can last longer than three

years in part of the cohort (Chesney et al., 2022)(Medina et al., 2025). These results are in line with previous phase II trials, in which TIL therapy showed ORRs of 34-40% on immunotherapy-refractory melanoma, which indicates that adoptive cell therapy was able to address resistance mechanisms intrinsic to ICI failure (Sarnaik et al., 2021)(Rohaan et al., 2022). The quick median to optimum response rate, frequently in the 1.4-1.5 months, examines efficient TIL engraftment and broadening, and the propensity to observe long-term upgrades when incomplete reactions become complete reactions as long as a year following infusion is indicative of enduring in vivo lymphocyte performance(Medina et al., 2025). These findings all support the efficacy of TIL therapy in producing a lasting tumor control of even the patients with a high disease burden, a long history of prior treatment, and who have primary resistance to ICIs.

In the long-term survival, the clinical advantage of lifileucel is additionally supported. The overall median survival (OS) was 13.9 months in the five-year follow-up of the C-144-01 trial, and furthermore, some patients showed continuing responses at the five-year follow-up (Medina et al., 2025) Early response and deep responses particular to responders were found to favour survival with year 4 OS rates as high as 68.2 indicating that tumor burden and metastatic localisation at baseline are critical outcome predictors. These findings are supported by comparative studies showing that TIL therapy improves survival relative to standard second-line therapies such as ipilimumab, where median OS was 18.9 months versus 25.8 months for TIL recipients in refractory populations (Rohaan et al., 2022). Importantly, meta-analyses indicate that prior exposure to anti-PD-1 therapy does not significantly diminish TIL efficacy, reinforcing the therapy's robustness as a salvage option (Martín-Lluesma et al., 2024).

The safety and tolerability profile of lifileucel is consistent with the expected effects of non-myeloablative lymphodepletion and high-dose IL-2 support. Grade 3/4 hematologic toxicities, including thrombocytopenia, anemia, and febrile neutropenia, are common but transient and reversible, typically resolving within the first month of therapy (Tsai & Komanduri, 2025)(Medina et al., 2025). Long-term follow-up shows no cumulative or delayed toxicities, suggesting that TIL therapy is safe for broader clinical use when administered under careful inpatient monitoring. Similar safety outcomes have been observed in TIL trials for other solid tumors, including head and neck squamous cell carcinoma, further supporting the generalizability of the regimen (Ferris et al., 2025).

From a practical perspective, the feasibility of TIL therapy has improved with advancements in manufacturing, including the use of cryopreserved lifileucel to allow scalable supply and consistent product quality(Chesney et al., 2022). High enrollment and completion rates in multicenter trials demonstrate that logistical barriers can be effectively managed. These data collectively suggest that earlier intervention with TIL therapy, particularly in patients with lower tumor burden, may enhance response rates and survival outcomes (Turcotte et al., 2025)(Shoushtari & Powell, 2025)(Chen et al., 2025). Future research should focus on optimizing patient selection using predictive biomarkers, combining TIL therapy with checkpoint inhibitors or targeted agents, and refining manufacturing processes to reduce production time and expand accessibility (Shoushtari & Powell, 2025). Such strategies have the potential to broaden the applicability of TIL therapy and maximize durable clinical benefits in immunotherapy-refractory advanced melanoma.

CONCLUSION

Tumor-infiltrating lymphocyte (TIL) therapy represents a promising advance for patients with advanced melanoma refractory to standard immunotherapies. Evidence indicates that TIL therapy can induce meaningful and durable tumor responses even in heavily pretreated populations, overcoming mechanisms of resistance to checkpoint inhibitors. The therapy demonstrates manageable safety profiles, with most adverse events being transient and reversible under careful clinical monitoring. Advances in manufacturing and logistics have improved feasibility, enabling broader application. While challenges remain in patient selection and optimizing response depth, TIL therapy holds substantial potential as a salvage strategy, offering renewed hope for long-term disease control and improved outcomes in this difficult-to-treat population.

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