Tumor-Infiltrating Lymphocyte Cell Therapy for the Treatment of Advanced Melanoma: From Patient Identification to Posttreatment Management

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Authors' disclosures of conflicts of interest are found at the end of this article.

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https://doi.org/10.6004/jadpro.2025.16.7.8

Abstract

Adoptive cell therapy with tumor-infiltrating lymphocytes (TILs) was recently approved for patients with advanced melanoma (metastatic or unresectable) previously treated with immune checkpoint inhibitors and BRAF/MEK targeted therapies (where appropriate). Tumor-infiltrating lymphocytes isolated from patient-derived tumor tissues enter the tumor microenvironment and recognize tumor-specific antigens, leading to the destruction of tumor cells. The multistep TIL cell therapy journey is led by a multidisciplinary health care team. Patients selected for TIL cell therapy undergo tumor tissue procurement for TIL generation, followed by preparative lymphodepletion before receiving a single-dose infusion of TIL and a short course of high-dose interleukin-2. Successful implementation of TIL cell therapy requires well-established procedures and workflows to select and screen patients, procure tumor tissue, administer TIL cell therapy, and monitor patients during treatment and after discharge. The advanced practice provider plays a central role in a patient's TIL treatment journey by planning and coordinating care across the health-care system, educating patients and staff, and providing direct and supportive patient care. Here, we review the treatment landscape for advanced melanoma and clinical data supporting TIL cell therapy. We also provide guidance related to patient selection, tumor tissue procurement, TIL cell therapy regimen, safety monitoring, symptom management, and post-discharge follow-up.

J Adv Pract Oncol 2025

Melanoma is the fifth most common cancer type in the United States, representing approximately 5% of new cancer cases. In 2024, 100,640 estimated new cases of melanoma and 8,290 melanoma-related deaths were reported (National Cancer Institute, 2024). Melanoma is most frequently diagnosed in patients aged 55 to 74 years, with a median age at diagnosis of 66 years. Approximately 15% of melanoma diagnoses are made at an advanced stage (regional or distant metastasis). Although the 5-year survival rate for localized melanoma (stage 0–IIC) is > 99%, the rate for advanced stage (regional or distant metastasis) melanoma is 35% to 74% (American Cancer Society, 2023; National Cancer Institute, 2023).

The first-line standard-of-care treatment for advanced melanoma includes single-agent or combination immune checkpoint inhibitors (ICIs) and, if a patient's tumor harbors a *BRAF* mutation, BRAF/MEK-targeted therapy (Seth et al., 2023). Pembrolizumab (Keytruda) and nivolumab (Opdivo) are single-agent ICIs known as anti–programmed cell death protein-1 (PD-1)/programmed cell death protein ligand 1 (PD-L1) therapies (Bristol-Myers Squibb Company, 2023; Merck & Co., Inc., 2023). Nivolumab plus ipilimumab (Yervoy; cytotoxic T lymphocyte antigen-4 [CTLA-4]) and nivolumab plus relatlimab (Opdualag; lymphocyte activation gene-3 inhibitor) are combination ICI therapies (Bristol-Myers Squibb, 2022; Bristol-Myers Squibb, 2023). For *BRAF* V600E/K-mutant disease, combination targeted therapies include dabrafenib (Tafinlar; BRAF inhibitor) plus trametinib (Mekinist; MEK inhibitor), vemurafenib (Zelboraf; BRAF inhibitor) plus cobimetinib (Cotellic; MEK inhibitor), and encorafenib (Braftovi; BRAF inhibitor) plus binimetinib (Mektovi; MEK inhibitor; Array BioPharma Inc., 2018, Array BioPharma Inc., 2020; Genentech USA, 2020, Genentech USA, Inc., 2023; Novartis Pharmaceuticals, 2022; Novartis Pharmaceuticals Corporation, 2022).

Advanced melanoma presents a treatment challenge due to its high mutational burden and tumor cells' ability to evade the immune system (Villani et al., 2022). Despite advances in metastatic melanoma treatment with the emergence of ICIs and targeted therapies, 47% to 55% of patients have refractory disease (Lim et al., 2023; Savoia et al., 2020), and 25% to 30% are likely to relapse (De Risi et al., 2022). Thus, additional therapeutic approaches are needed for patients whose disease has relapsed or is resistant to these therapies (Lopes et al., 2022). Recommended first-line treatment with either single-agent or combination ICI therapies resulted in objective response rates (ORRs) of 33% to 58%, with a median progression-free survival (PFS) of 5 to 12 months (Bristol-Myers Squibb, 2022; Robert et al., 2019a; Seth et al., 2023; Tawbi et al., 2022; Wolchok et al., 2022). Although BRAF/MEK inhibitors resulted in ORRs of 64% to 70% with a median PFS of 11 to 15 months, only a subset of advanced melanomas carry a *BRAF* V600 mutation (Ascierto et al., 2021; Cheng et al., 2018; Dummer et al., 2022; Robert et al., 2019b). Retreatment with single-agent or combination ICI regimens in patients previously treated with anti–PD-1 therapies yielded ORRs of 9% to 31% (Ascierto et al., 2023; Chapman et al., 2021; Olson et al., 2021; Pires da Silva et al., 2021; VanderWalde et al., 2023).

TUMOR-INFILTRATING LYMPHOCYTE CELL THERAPY

Adoptive cell therapies are immune cell therapies in which tumor-reactive T cells are used to combat cancer (Kumar et al., 2021). Tumor-infiltrating lymphocyte (TIL) cell therapy is a type of adoptive cell therapy that involves the infusion of autologous TILs isolated from patient-derived tumor tissue (Zhao et al., 2022). Naturally occurring TILs are composed primarily of polyclonal effector memory T cells that infiltrate the solid tumor microenvironment, can recognize multiple tumor-specific antigens, and mediate cell death (Antohe et al., 2019; Kazemi et al., 2022). In clinical studies, TIL cell therapy exhibited efficacy in the treatment of various solid tumors, including melanoma (Chesney et al., 2022; Rohaan et al., 2022; Zhao et al., 2022).

Research on TIL cell therapy began at the National Cancer Institute in the 1980s (Rosenberg et al., 1988; Topalian et al., 1988); initial studies demonstrated encouraging activity in patients with metastatic melanoma, and subsequent studies optimized the TIL cell therapy regimen (Dudley et al., 2005; Goff et al., 2016; Mehta et al., 2018; Rosenberg et al., 2011; Rosenberg et al., 1994). Recent trials have evaluated TIL cell therapy in the second-line setting and beyond in patients with advanced

melanoma (Zhao et al., 2022). A phase III study (ClinicalTrials.gov identifier: NCT02278887) designed by the Netherlands Cancer Institute evaluated the efficacy and safety of first- or second-line TIL cell therapy vs. ipilimumab in patients with advanced melanoma (Rohaan et al., 2022). Patients in the study who received TIL cell therapy had a significantly longer median PFS (7.2 months) than those who received ipilimumab (3.1 months). The ORR was also higher with TIL cell therapy vs. ipilimumab (49% vs. 21%, respectively). During lymphodepletion, all patients experienced grade ≥ 3 neutropenia, and most also experienced grade ≥ 3 thrombocytopenia (89%), febrile neutropenia (86%), and leukopenia (71%). The most common grade ≥ 3 AEs during TIL and interleukin-2 (IL-2) administration were febrile neutropenia (74%), hypophosphatemia (60%), and fever (45%). Capillary leak syndrome related to IL-2 administration occurred in 30% of patients (Rohaan et al., 2022).

Lifileucel in Advanced Melanoma (Unresectable or Metastatic)

Lifileucel (Amtagvi) is a tumor-derived autologous T cell immunotherapy approved by the US Food and Drug Administration for the treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if *BRAF* V600E/K positive, a BRAF inhibitor with or without a MEK inhibitor (Iovance Biotherapeutics, 2024). The safety and efficacy of lifileucel were evaluated in a phase II study (ClinicalTrials.gov identifier: NCT02360579) in patients with unresectable or metastatic melanoma treated with ≥ 1 prior systemic therapy (Chesney et al., 2022; Sarnaik et al., 2021). The approval of lifileucel was based on an analysis of 73 patients in this study who received lifileucel at the recommended dosing range of 7.5×10^9 to 72×10^9 viable cells (Iovance Biotherapeutics, 2024). The ORR in this population was 31.5% (95% confidence interval = 21.1%–43.4%). The median duration of response was not reached at a median follow-up of 18.6 months; 56.5%, 47.8%, and 43.5% of responders maintained response for at least 6, 9, and 12 months, respectively (Iovance Biotherapeutics, 2024).

In pooled safety analyses of 156 patients, the most common grade 3 to 4 AEs in patients treated with lifileucel (based on investigator assessment) were laboratory abnormalities, namely, thrombocytopenia (78.2%), neutropenia (69.2%), and anemia (58.3%; Iovance Biotherapeutics, 2024); these were consistent with the known safety profiles of lymphodepletion therapy and IL-2 administration. The incidence of infusion-related reactions (6.4%), anaphylactic reactions (1.3%), and cytokine release syndrome (3.2%) were low. Grade ≥ 3 neurologic AEs included encephalopathy (5.8%) and headache (0.6%). Serious AEs leading to death were severe infections (sepsis, septic shock, pneumonia, and encephalitis; $n = 4$), internal organ hemorrhage ($n = 2$), renal failure ($n = 2$), acute respiratory failure ($n = 1$), cardiac arrhythmia ($n = 1$), ascites and liver injury ($n = 1$), and bone marrow failure ($n = 1$; Iovance Biotherapeutics, 2024). Treatment-emergent AEs mainly occurred during the first 2 weeks after lifileucel infusion and rapidly declined thereafter (Chesney et al., 2022).

TIL Product Manufacturing

Manufacturing the TIL product can take up to 5 weeks from receipt of tumor tissue at the manufacturing facility to delivery of the final TIL product (Gastman et al., 2020); for lifileucel, the median time from tumor tissue procurement to TIL infusion was 33 days (Iovance Biotherapeutics, 2024). Tumor tissue procurement involves surgical resection of a tumor tissue fragment ≥ 1.5 cm in diameter. Tumor tissue fragments are incubated in an IL-2–enriched culture medium that promotes the death of remaining tumor cells while supporting the viability of TIL (Hopewell et al., 2019; Sarnaik et al., 2021). Tumor-infiltrating lymphocytes are cocultured and expanded with feeder cells, monoclonal antibodies, and cytokines to yield billions of viable cells. The final TIL product is tested by flow cytometry for expression of lymphocyte-specific markers (e.g., CD45, CD3, CD4, and CD8; Hopewell et al., 2019). Cryopreservation of the final TIL product provides logistical flexibility for shipping, delivery, and patient scheduling for infusion (Sarnaik et al., 2021).

TIL CELL THERAPY JOURNEY

Role of the Advanced Practice Provider

Advanced practice providers (APPs) are integral members of the oncology care team. As the primary organizers of TIL cell therapy, APPs navigate all

aspects of the treatment journey, including patient selection, tumor harvest, treatment regimen, and follow-up care. The APP may also train inpatient staff on drug administration, AE management, and discharge instructions. As such, APPs are critical in the coordination of patient care as well as monitoring, managing, and documenting AEs.

Patient Selection and Workup

Given the need for multidisciplinary care, including toxicity management, patients are referred by their treating oncologist to an Authorized Treatment Center for TIL cell therapy. The patient's ability to access an Authorized Treatment Center for TIL cell therapy should be determined. For patients living at a considerable distance from an Authorized Treatment Center, APPs can coordinate care with the local oncologist as clinically indicated.

During initial screening, the patient's case should be reviewed by a multidisciplinary team that includes clinical specialists from medical oncology, surgery, and cellular therapy, APPs, and medical social workers to determine the patient's suitability for TIL cell therapy.

Careful planning is required for the safe and timely execution of all necessary steps from tumor tissue procurement surgery to TIL infusion. As TIL product manufacturing takes several weeks (for lifileucel, the median time from tumor tissue procurement to the end of the manufacturing process was 23 days), TIL cell therapy may not be the best option for patients with rapidly progressing disease (Gastman et al., 2020). Patients with slowly progressing soft tissue tumors and those with a shorter duration of prior anti–PD-1 therapy are best suited to receive TIL cell therapy (Betof Warner et al., 2023; Larkin et al., 2021).

Patients must be medically fit based on an Eastern Cooperative Oncology Group performance status of ≤ 1 without clinically relevant comorbidities, such as irreversible cardiac dysfunction, impaired pulmonary function, autoimmune disorders requiring immunosuppression, or active or uncontrolled infections (Table 1; Gastman et al., 2020; Mullinax et al., 2022). Patients should have adequate organ function, including renal (creatinine clearance), cardiac (echocardiogram to assess left ventricular ejection fraction), and pulmonary (pulmonary function tests to assess pulmonary reserve) function (Table 2). Blood cell and platelet counts should be assessed to rule out bone marrow dyscrasias or other abnormalities and determine the patient's ability to tolerate lymphodepletion. The APP may perform physical examinations during patient workup and order diagnostic tests as needed. Patients should also complete evaluation by medical social workers who can provide them and their caregivers with information and resources to assist patients with the emotional, financial, and psychosocial aspects of their disease and treatment.

Before TIL cell therapy initiation, the APP should assess whether prior treatment- or immune-related AEs have sufficiently resolved and ensure the discontinuation of corticosteroid treatment except replacement therapy at physiologic doses in patients with adrenal insufficiency.

Tumor Tissue Procurement

The appropriate anatomic site for tumor resection is determined via imaging studies by a multidisciplinary team of physicians, surgeons, and APPs from both oncology and surgery (Figure 1; Mullinax et al., 2022). Skin, soft tissue, and superficial lymph nodes are preferred sites of resection because they are more accessible, minimize morbidity, and can usually be done in an outpatient setting. If resection at these sites is not possible, peripheral sites and smaller nodules within visceral organs (e.g., liver, lungs) can be considered. Gastrointestinal tissues and other mucosal lesions (e.g., vagina, nasopharynx) should be avoided when possible due to the risk of contamination of tumor samples with gut bacteria or yeast. Sites that were irradiated within 3 months prior to tissue harvest should be avoided due to the likelihood of decreased TIL activity from radiation exposure (Crompton et al., 2018). Ulcerated tumors should be avoided due to the risk of microbial contamination.

Bridging Therapy

Administration of bridging therapy between tumor resection and lymphodepletion can reduce the likelihood of disease progression during TIL manufacturing (Betof Warner et al., 2023). For patients with *BRAF*-mutant disease, BRAF/MEK inhibitors may be used as bridging therapy due to high response rates (> 60%; Betof Warner et al., 2023; Goff & Rosenberg, 2019). A single chemotherapy

Table 1. Patient Selection Considerations for TIL Cell Therapy in Advanced Melanoma (Unresectable or Metastatic)

Conditions that support administration of TIL cell therapy	Conditions that may not support TIL cell therapy
• Age ≥ 18 years • Unresectable or metastatic melanoma (Stage IIIC, IIID, or IV per AJCC 8th edition criteria) • Melanoma progression, no response for ≥ 6 months, or intolerance due to toxicity following ≥ 1 line of prior systemic therapy • ECOG performance status of 0 or 1 and an estimated life expectancy of ≥ 3 months • At least 1 resectable lesion (or aggregate of lesions) with an estimated minimum diameter of 1.5 cm for TIL generation • Resolution of toxicities from prior therapies to grade ≤ 1 or controlled by medication except for vitiligo or alopecia • No evidence of colitis by sigmoidoscopy if patients have signs or symptoms of colitis • Hematologic parameters: » ANC ≥ 1,000 cells/mm^3 » Hemoglobin ≥ 9.0 g/dL » Platelet count ≥ 100,000 cells/mm^3 • Adequate organ function with the following laboratory values: » Serum ALT and AST ≤ 3 × ULN; participants with liver metastasis may have ALT and AST ≤ 5 × ULN » Total bilirubin ≤ 2 mg/dL; participants with Gilbert's syndrome may have total bilirubin ≤ 3 mg/dL » Estimated CrCl ≥ 40 mL/min using the Cockcroft-Gault formula • Seronegative status for anti-HIV, anti-hepatitis C, and syphilis antibodies, and anti-hepatitis B antigen	• Symptomatic untreated brain metastases • Rapidly progressing disease • History of organ allograft excluding kidney transplant or prior cell transfer therapy • Requirement of systemic corticosteroid therapy of prednisone > 10 mg/d or another steroid equivalent dose • Active uveitis requiring active treatment • Active medical illness including uncontrolled active systemic infections and major cardiovascular, respiratory, or immune disorders • Primary or acquired immunodeficiency syndrome (e.g., SCID or AIDS) • Ongoing grade 2–4 toxicity from prior immunotherapy (excluding endocrine disorder or vitiligo) • Clinical evidence of an ongoing malignancy except for adequately treated carcinoma in situ of the breast, cervix, or bladder, localized prostate cancer, and non-melanoma skin cancer • History of hypersensitivity to lymphodepletion, any component of the TIL infusion, or IL-2 • Grade ≥ 2 hemorrhage within 2 weeks before tumor resection • Receipt of a live or attenuated vaccine within 28 days before initiating lymphodepletion • Left ventricular ejection fraction < 45% or NYHA functional classification Class > 1 • Any irreversible cardiac wall movement • FEV1 of ≤ 60% that is irreversible after bronchodilator challenge • Pregnant or breastfeeding female patients

Note. AIDS = acquired immunodeficiency syndrome; AJCC = American Joint Committee on Cancer; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; FEV1 = forced expiration volume in 1 second; HIV = human immunodeficiency virus; IL-2 = interleukin-2; NYHA = New York Heart Association; SCID = severe combined immunodeficiency; TIL = tumor-infiltrating lymphocyte; ULN = upper limit of normal.

dose may be used as bridging therapy for patients with *BRAF* wild-type melanoma (Betof Warner et al., 2023). Patients receiving ICIs may continue treatment with these agents as bridging therapy if they appear beneficial in controlling tumor growth (Topp et al., 2021). Palliative radiation may also be administered as bridging therapy in patients awaiting TIL infusion (Rogers et al., 2023). Although rare, patients with a high tumor burden may require surgery to mitigate tumor progression while awaiting TIL cell therapy (Mullinax et al., 2022).

If bridging therapy is indicated, APPs should ensure adherence to appropriate bridging regimens. Bridging therapy should be stopped before lymphodepletion, and a washout period may be implemented to allow for adequate recovery from any treatment-related AEs. If bridging therapy includes the use of cytotoxic agents, patients should be assessed to ensure adequate hematopoietic, renal, and hepatic recovery before initiating lymphodepletion. If bridging therapy includes the use of agents with known cardiac toxicities, ejection fraction should be reevaluated. For patients receiving bridging agents with known pulmonary toxicities, pulmonary function tests should be repeated before initiating lymphodepletion.

Lymphodepletion

Preparative lymphodepletion, which increases the persistence of TIL, is administered before TIL infusion, which in turn increases antitumor response and response durability (Kumar et al., 2021). The lymphodepletion regimen for lifileucel consists of cyclophosphamide (60 mg/kg/d) for

Table 2. Patient Workup

Demographic data and PS	Medical history	Physical exam and vital signs	Blood and urinalysis	Cardiac and pulmonary evaluation	Imaging and tumor assessments	Other
• Age • Sex • Race/ethnic origin • ECOG PS	• *BRAF* mutation status • Prior cancer therapies » All systemic therapies » Surgery » Radiotherapy » Neoadjuvant and adjuvant therapy » Palliative therapy » Most recent therapy	• Body weight, BSA, BMI • Temperature • Blood pressure • Pulse • Respiration	• Hematologic parameters • Coagulation parameters » INR and PT or INR and aPTT • Serum chemistry • Urinalysis • Infectious disease testing » HIV1 and HIV2 antibody titer » HBsAg, anti-HBc and anti-HCV antibody » Syphilis assay	• ECG • ECHO or MUGA • Cardiac stress test for patients aged ≥ 60 years or those who have a history of clinically relevant cardiac disease • Pulmonary function tests	• CT of chest, abdomen, pelvis, and additional anatomic regions per disease history and clinical symptoms • MRI of the brain • Tumor assessment per RECIST v1.1	• Serum pregnancy test

Note. aPTT = activated partial thromboplastin time; BMI = body mass index; BSA = body surface area; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; HBc = hepatitis B core; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PD-L1 = programmed cell death-ligand 1; PS = performance status; PT = prothrombin time; RECIST = Response Evaluation Criteria in Solid Tumors.

2 days followed by fludarabine (25 mg/m^2/d) for 5 days (Iovance Biotherapeutics, 2024) administered in the inpatient or outpatient setting.

Before initiating lymphodepletion, APPs should reassess and document whether the patient continues to meet TIL cell therapy eligibility criteria as previously listed. Patients with symptomatic or recurrent pleural effusions that require drainage should not proceed to lymphodepletion without prior placement of a temporary in-dwelling pleural drain.

Pharmacists should verify that cyclophosphamide and fludarabine are appropriately dosed based on the patient's actual body weight before dispensing. Additionally, pharmacists play a key role in patient safety, assessing for drug-drug interactions, monitoring for adverse drug reactions, and providing patient education throughout the course of treatment. All patients who undergo lymphodepletion (and IL-2 administration) experience cytopenias, including neutropenia, lymphopenia, anemia, and thrombocytopenia, and prolonged decrease in CD4+ T cells (Kumar et al., 2021). Granulocyte colony-stimulating factor and transfusion of blood-derived components may be used to manage hematologic toxicities (Dudley et al., 2005).

Common nonhematologic AEs related to lymphodepletion are diarrhea, cyclophosphamide-related hepatotoxicity, and fludarabine-related neurotoxicity (Ding et al., 2008; Kumar et al., 2021; McQuade et al., 2016; National Institutes of Health, 2017). Noninfectious diarrhea can be managed with medications, such as loperamide, octreotide (McQuade et al., 2016), or diphenoxylate/atropine (Jain & Wylie, 2024). Patients receiving cyclophosphamide generally experience mild, transient elevations in serum aminotransferase levels (National Institutes of Health, 2017). Neurotoxicity with high doses of fludarabine can result in encephalopathy, coma, and death (Cheson et al., 1994; Ding et al., 2008). Ocular toxicities can occur with fludarabine regardless of dose and manifest as visual aberrations (e.g., floaters), hallucinations, fluctuations in visual acuity, and eventual deterioration of vision and light perception (Ding et al., 2008). As fludarabine-induced neurotoxicity (including ocular toxicity) is irreversible, close monitoring of patients receiving fludarabine is recommended (Ding et al., 2008).

A small number of patients may incur opportunistic infections (e.g., *Pneumocystis jirovecii* or herpes zoster reactivation); prophylactic anti-infective

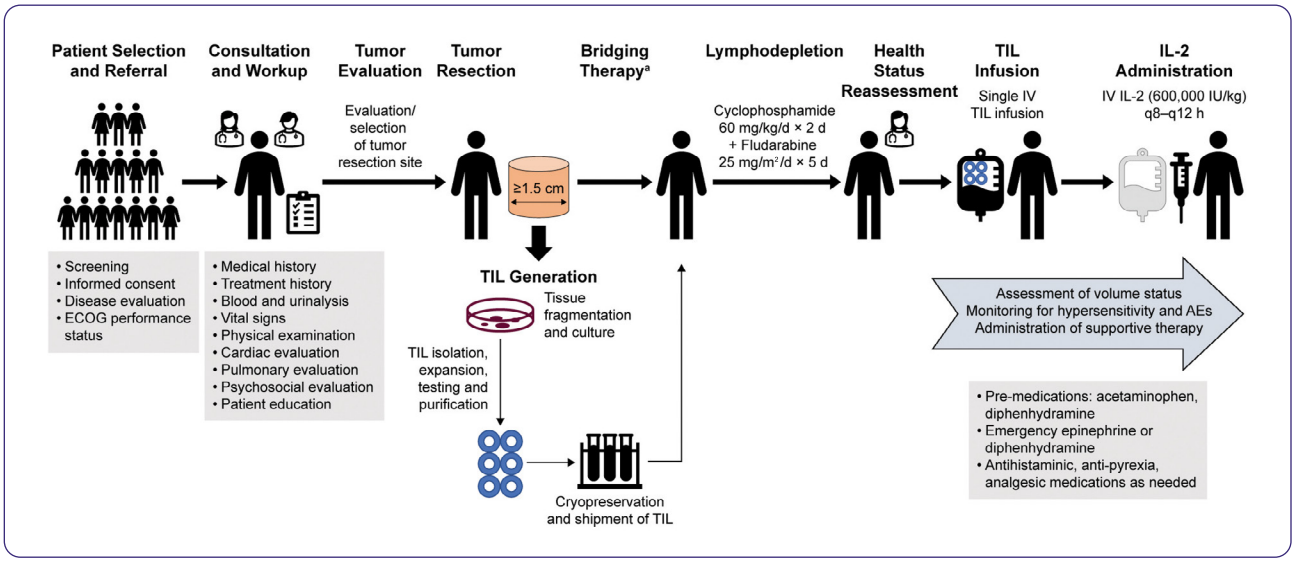

Figure 1. TIL cell therapy for patients with advanced melanoma. AE = adverse event; ECOG = Eastern Cooperative Oncology Group; IL-2 = interleukin-2; IV = intravenous; q = every; TIL = tumor-infiltrating lymphocyte; WT = wild-type.
[a]Administered as needed.

therapy can be administered according to institutional protocols during lymphodepletion and through the time of hematologic recovery (Kumar et al., 2021). Advanced practice providers play a key role in managing infection prophylaxis and monitoring CD4+ T-cell counts. *Pneumocystis jirovecii* pneumonia prophylaxis should be stopped following CD4+ T-lymphocyte count recovery to > 200 cells/μL (Kaplan et al., 2009). Selection of antibacterial, antifungal, and antiviral prophylaxis should be initiated at the onset of neutropenia and continued until absolute neutrophil count recovery (> 500 cells/mm^3) per institutional protocols.

Prophylaxis with antiemetic agents (e.g., ondansetron, prochlorperazine, lorazepam) can be used to prevent nausea and vomiting associated with cyclophosphamide (Costa et al., 2015); however, prophylaxis with systemic corticosteroids should be avoided as it may suppress TIL activity and proliferation (Draghi et al., 2019). Because hemorrhagic cystitis can occur in patients receiving high-dose cyclophosphamide, prophylactic therapy with intravenous hydration and mesna (sodium 2-mercaptoethanesulfonate) is recommended (Reddy & Winston, 2023).

Patients receiving intravenous fluids to prevent hematuria related to cyclophosphamide are susceptible to volume overload/depletion, electrolyte imbalance, and heart failure; careful evaluation of volume status by the APP is essential (Kalantari et al., 2013; Paydas et al., 2021).

TIL Infusion

Upon availability of the TIL product, APPs and registered nurses will generally coordinate inpatient admission and scheduling. The patient's health status should be reassessed and confirmed as acceptable for TIL infusion and IL-2 administration. Patients should be hospitalized for TIL infusion and remain hospitalized until completion of IL-2 administration and resolution of toxicities (depending on institutional protocols). Within 30 to 60 minutes before TIL infusion, patients should receive the following premedications: acetaminophen (650 mg or equivalent) and diphenhydramine (25–50 mg intravenous) or another H1 histamine antagonist. Medical tubing should be primed with normal saline from intravenous saline flush bags. A Y-type blood filter with a minimum pore size of 150 to 200 μM should be used; leukocyte-depleting filters should not be used to avoid TIL retention within the filter (Kumar et al., 2006).

For lifileucel, infusion of the TIL product should be initiated as early as possible after 24 hours have elapsed following the last dose of

fludarabine but no later than 4 days after the last fludarabine dose (Iovance Biotherapeutics, 2024). The TIL product should be infused by gravity as soon as it is thawed at a rate of 1 mL/min for the first 5 minutes; if no AEs occur, infusion rate can be increased to 5 to 10 mL/min. Vital signs should be evaluated every 15 minutes during TIL infusion. The entire contents of one bag should be infused within a 3-hour period before the next bag is thawed; the full dose is provided in one to four patient-specific infusion bags. Each patient should receive the entire contents of all bags to ensure the full dose is administered.

The clinical nurse should continuously monitor patients during infusion for potential signs and symptoms of hypersensitivity or anaphylaxis. Lifileucel is a live cell suspension formulated in CryoStor CS10 (BioLife Solutions, Inc.) cryopreservation medium (primarily dimethyl sulfoxide [DMSO] and dextran-40) diluted with Plasma-Lyte A (Baxter Healthcare Corporation), human serum albumin, IL-2, and small quantities of gentamicin, streptomycin, and aminoglycoside antibiotics, and hypersensitivity reactions have been associated with ≥ 1 of the formulation components. For mild hypersensitivity reactions, infusion should be paused, antihistamines administered as clinically indicated, and vital signs evaluated. If vital signs are stable, infusion can be resumed at 5 mL/min and increased accordingly. Emergency medications, such as epinephrine and diphenhydramine, should be readily available at the bedside in the event of serious hypersensitivity or anaphylactic reactions. The DMSO metabolite produces a foul odor when excreted through the lungs and induces a histamine release leading to flushing, dyspnea, abdominal cramps, and cardiovascular events (Kollerup Madsen et al., 2018). Thus, patients should be monitored and treated for these symptoms. Cardiac function may be monitored within 24 hours of TIL infusion to detect changes in heart rhythm (Kollerup Madsen et al., 2018) and as clinically indicated.

In addition to the above, other reactions that may occur during TIL infusion include fever, fatigue, dyspnea, chills, sinus tachycardia, flushing, pruritus, rash, and hypotension. Antipyretic, analgesic, and antihistaminic agents may be administered per institutional protocols.

IL-2 Administration

IL-2 binds to receptors on T cells, which enhances immune recognition and targeted tumor cell destruction (Pachella et al., 2015). High concentrations of IL-2 facilitate a robust T-cell–mediated immune response against cancer cells (Pachella et al., 2015). Pharmacists should ensure that IL-2 doses are administered according to the patient's actual body weight. A short course of high-dose IL-2 (600,000 IU/kg per dose) administration can begin as early as 3 hours after but no later than 24 hours after completion of TIL infusion. Additional IL-2 doses may be administered every 8 to 12 hours; for lifileucel, a maximum of 6 doses is recommended. Evidence from the lifileucel study in patients with advanced melanoma who received up to 6 doses of IL-2 (Sarnaik et al., 2021) suggests treatment response and duration of response were not associated with the number of IL-2 doses (Hassel et al., 2022).

Interleukin-2 must be administered in the inpatient setting by experienced staff and may require continuous monitoring of cardiac parameters (e.g., blood pressure and heart rate) using telemetry (site specific) and oxygen saturation levels (Dutcher et al., 2014). In preparation for IL-2 administration, patients should undergo vital sign assessments, physical examinations, and clinical laboratory tests to ensure they are fit to receive treatment (Table 3). The patient's normal blood pressure should be used to establish the target blood pressure during IL-2 administration. Patients with a history of hypertension should discontinue antihypertensive medications before IL-2 administration (Dutcher et al., 2014). As IL-2 administration may increase the risk of infection (including sepsis and bacterial endocarditis) due to reduced neutrophil chemotaxis (Moreno et al., 2006), preexisting bacterial infections should also be adequately treated prior to the start of IL-2 administration. Patients with indwelling central lines may be prone to bacterial infections; prophylaxis with oxacillin, nafcillin, ciprofloxacin, and vancomycin may reduce the incidence of staphylococcal infections.

Patients and their caregivers should be counseled on the potential side effects of IL-2 administration. Interleukin-2 toxicities may include fever, chills, hypotension, dyspnea, tachycardia, nausea,

Table 3. Pretreatment Checklist for IL-2 Administration

Patient preparation

- Position the patient near a nursing station
- Counsel patient and caretaker regarding possible side effects of IL-2 administration[a]
- Ensure patient has central venous access
- Ensure proper fluid status and minimize use of unnecessary IV fluids
- Establish target SBP

Normal SBP	Target SBP During IL-2 Administration
< 100 mm Hg	> 80 mm Hg
100–120 mm Hg	> 85 mm Hg
> 120 mm Hg	> 90 mm Hg

Medications

- Discontinue antihypertensive medications
- Initiate scheduled pre-medications 30–60 minutes before initial IL-2 dose
  - » Acetaminophen 650 mg
  - » Indomethacin 50–75 mg or other NSAID every 6 hours[b]
  - » Ranitidine 150 mg every 12 hours
  - » Meperidine 20–50 mg and/or hydromorphone as needed for chills, antiemetics, H2 blockers, and other medications[c]

Assessments before each IL-2 administration

- Check vital signs and urine output 2 hours before IL-2 administration and address abnormalities
  - » Maintain urine output 150 mL over an 8-hour period
  - » Supplement with oxygen if SpO_2 < 95%
- Perform physical examination
  - » General (fatigue, fever, chills)
  - » Pulmonary (cough, dyspnea)
  - » Cardiac (arrhythmia, edema, hypotension)
  - » Dermatologic (dry skin, erythema, pruritus, rash)
  - » Gastrointestinal (anorexia, diarrhea, mouth dryness, nausea, vomiting)
  - » Neurologic (MMSE) (Interprofessional Comprehensive Geriatric Toolkit, 1999)
  - » Laboratory (serum chemistry, hematology)
  - » Vital signs (temperature, BP, pulse, respiration)
  - » Renal (urine input/output)

Laboratory parameters

- Renal
  - » Serum creatinine < 4 mg/dL
  - » Hydration as needed
- Hepatic
  - » Liver function tests within normal limits
  - » Total bilirubin < 2 mg/dL
- Electrolytes within normal limits
  - » Hematologic
  - » Hemoglobin > 8.5 g/dL
  - » Platelets > 30,000 cells/μL
  - » Blood transfusions as necessary

Note. BP = blood pressure; IL-2 = interleukin-2; IV = intravenous; MMSE = Mini Mental State Examination; NSAID = nonsteroidal anti-inflammatory drug;
SBP = systolic blood pressure; SpO_2 = oxygen saturation.
[a]Includes hypotension, fever, chills, nausea, vomiting, diarrhea, shortness of breath, pulmonary edema, confusion, renal failure, pancytopenia, rash, malaise, infections, and abnormal liver function tests.
[b]Avoid if there is baseline renal dysfunction and discontinue if there are any signs of decreasing urine output, rising creatinine levels, or platelet counts below 50,000 cells/μL.
[c]As per institutional protocols.

vomiting, diarrhea, rash, and change in mental status (Table 4; Dutcher et al., 2014). Application of institutional protocols for IL-2 administration and toxicity management are crucial to patient care. Premedications of acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and ondansetron should be initiated 30 minutes before the first IL-2 administration. Supportive therapy measures, including NSAIDs, histamine H2 antagonists, antiemetic medications, vasopressors, and auto-adjusting positive airway pressure devices, should also be readily available. Acute IL-2 toxicities between doses peak approximately 4 to 6 hours after each dose (Dutcher et al., 2014). Parenteral opioids should be administered at the onset of chills. Before each subsequent dose, patients should have returned to baseline heart rate, oxygen saturation levels, and blood pressure. Dosing of IL-2 should be performed according to the patient's level of tolerability. Additional IL-2 doses may be administered if toxicities resolve or return to low-grade severity within 24 hours using supportive measures. Administration of IL-2 should be stopped in the event of serious or life-threatening toxicities.

During IL-2 administration, the patient's blood pressure, pulse, respiration, oxygen saturation, and body temperature should be monitored at least every 4 hours or as clinically indicated (Dutcher et al., 2014). Blood work (comprehensive metabolic profile analysis and complete blood count with differential) should be performed daily and cardiac parameters should be monitored for new-onset cardiac events. The patient's mental status should be periodically evaluated using

Table 4. Management of Anticipated Toxicities Associated With IL-2 Administration

Toxicity	Management
Fevers	• Neutropenic fever protocols including empiric antibiotics • Acetaminophen and NSAIDs
Chills/rigors	• Meperidine or other parenteral opioid medication at the first sign of chills or rigors
Hypotension	• Fluids followed by vasopressor support as needed • Stop, if hypotension persists despite all supportive measures
Oliguria[a]	• Fluids followed by dopamine at renal doses as needed • Hold, if oliguria is uncontrolled despite all supportive measures
Dyspnea	• Avoid use of inhaled steroids • Oxygen therapy if oxygen saturation is < 95% • Stop, if persistent oxygen support or ventilatory support is required
Sinus tachycardia	• Correction of the underlying cause(s) of fever, hypotension, hypoxia, anemia • Discontinuation of dopamine if used • Fluids as needed • Stop, if sinus tachycardia persists despite all supportive measures
Nausea/vomiting	• Antiemetics (ondansetron, granisetron) • Prochlorperazine
Noninfectious diarrhea	• Antidiarrheals (loperamide, diphenoxylate/atropine)
Confusion	• If clinically indicated after neurologic evaluation, antipsychotic drugs for progressive development of confusion, disorientation, and hallucination
Pruritus	• Topical nonsteroidal, alcohol-free lotions • Antihistamines (hydroxyzine, diphenhydramine)
Infection	• Treat infection as indicated per institutional protocols • Broad-spectrum antibiotics for neutropenic fever
Edema	• Elevate symptomatic extremity • Administer albumin • Diuretics after blood pressure stabilization and final IL-2 dose administration

Note. HCl = hydrochloride; IL-2 = interleukin-2; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; PO = oral; PR = rectal; PRN = as needed; TIL = tumor-infiltrating lymphocyte; q = every. Information from Betof Warner et al. (2024); Schwartzentruber (2001).
[a]Indicates oliguria due to hypotension.

a validated instrument such as the Mini Mental State Examination (Kurlowicz & Wallace, 1999). Patients receiving IL-2 whose care is managed outside the intensive care unit (ICU) should be promptly transferred to the ICU if symptoms cannot be controlled with standard institutional management protocols or if their condition worsens (e.g., in cases of cardiac arrhythmia, respiratory failure, bacterial sepsis), and IL-2 administration should be stopped. The ICU APPs and other clinical staff should be trained in the management of patients receiving IL-2 administration.

Discharge and Posttreatment Follow-Up

Postdischarge planning should be initiated before admission and continued throughout the course of the patient's hospital stay. Criteria for discharge include ensuring hematologic parameters and renal function have returned to baseline or near-baseline levels. Resolution of all toxicities related to TIL infusion or IL-2 administration is also required. Vasopressors should be tapered and stopped prior to discharge; blood pressure should be stable during assisted ambulation (Dutcher et al., 2014). Patients with preexisting hypertension may resume antihypertensive medications as indicated after discharge (Dutcher et al., 2014).

Patients and their caregivers should be made aware of what to expect and the routines to be followed at home during the initial days after discharge. Advanced practice providers should provide information on the potential treatment-related side effects patients may experience. Due to IL-2–mediated effects on the central nervous system (CNS) that can alter concentration, patients should be cautioned against driving or using

dangerous equipment until they have recovered from CNS-related adverse events (Tyre & Quan, 2007). Other CNS effects of high-dose IL-2 include sleep disturbances and vivid dreams. An assessment of sleep quality before discharge should therefore be conducted (Tyre & Quan, 2007). As patients are likely to have peripheral edema at the time of discharge, diuretics may be prescribed with caution given the associated risk of hypovolemia (Dutcher et al., 2014). All patients should continue to refrain from using systemic corticosteroids except in life-threatening situations.

It is recommended that patients reside within a short distance of the treatment center for the first 30 days after discharge. Medical social workers may assist patients with finding local housing accommodations during the early post-discharge period. Advanced practice providers are essential in monitoring patients post discharge and assisting with the management of posttreatment toxicities. During the first few weeks after discharge, nurses may conduct follow-up calls to monitor patient recovery. Alternatively, patients may return to the Authorized Treatment Center for weekly follow-up visits and laboratory testing as needed. Scans to assess disease status should be performed every 6 to 12 weeks after TIL cell therapy. Thyroid function should be monitored during follow-up visits, as patients may experience IL-2–related hypothyroidism several weeks to months after TIL cell therapy (Bhattacharya et al., 2020; Dutcher et al., 2014).

CONCLUSIONS

Tumor-infiltrating lymphocyte cell therapy may change the treatment paradigm for patients with solid tumors by enhancing the immune system's ability to target and eliminate cancer cells. Lifileucel is a one-time, autologous TIL cell therapy that has demonstrated robust and durable responses in patients with advanced melanoma that progressed with or after anti–PD-1/PD-L1 or anti–CTLA-4 therapy and targeted therapy (where appropriate).

Appropriate patient selection for TIL cell therapy is crucial, and APPs are important in that process. Advanced practice providers play a central role in the management of patients in the trajectory of TIL cell therapy, working collaboratively with physicians, nurses, pharmacists, and medical social workers to ensure safe and successful implementation of TIL cell therapy. Posttreatment follow-up care consists of managing long-term toxicities and assessing disease status. Advanced practice providers can assist in the creation of well-established workflows, appropriate education, and close communication and coordination between members of the health-care team, which will ensure patients derive the maximum treatment benefit. ●

Acknowledgment

Medical writing and editorial support were provided by Kalpana Vijayan, PhD, and Sarah Huh, PharmD, of Peloton Advantage, LLC, an OPEN Health company, and funded by Iovance.

Disclosure

This review manuscript was sponsored by Iovance Biotherapeutics, Inc. (San Carlos, CA, USA). Lisa Kottschade is a consultant for Immunocore. Emily Webb Rodriguez has nothing to disclose. Susan Harding has nothing to disclose. Smita Ranjan has nothing to disclose. Lori McIntyre has nothing to disclose. Peter A. Prieto is employed by Iovance Biotherapeutics and holds stock or stock options in the company. He has also had travel, accommodations, and expenses covered by Iovance Biotherapeutics. Lissa Gray is employed by Iovance Biotherapeutics and holds stock or stock options in the company. She has also had travel, accommodations, and expenses covered by Iovance Biotherapeutics. Jannakie Joseph is employed by Iovance Biotherapeutics and holds stock or stock options in the company. She has also had travel, accommodations, and expenses covered by Iovance Biotherapeutics. Jennifer Swank is a consultant for Iovance Biotherapeutics.

References

American Cancer Society. (2023). Melanoma skin cancer stages. https://www.cancer.org/cancer/types/melanoma-skin-cancer/detection-diagnosis-staging/melanoma-skin-cancer-stages.html

Antohe, M., Nedelcu, R. I., Nichita, L., Popp, C. G., Cioplea, M., Brinzea, A.,...Turcu, G. (2019). Tumor infiltrating lymphocytes: The regulator of melanoma evolution. *Oncology Letters*, *17*(5), 4155–4161. https://doi.org/10.3892/ol.2019.9940

Array BioPharma Inc. (2018). Mektovi (binimetinib) package

insert. Boulder, CO, USA: Array BioPharma Inc. https://labeling.pfizer.com/ShowLabeling.aspx?id=12988

Array BioPharma Inc. (2020). Braftovi (encorafenib) package insert. Boulder, CO, USA: Array BioPharma Inc. https://labeling.pfizer.com/ShowLabeling.aspx?id=12988

Ascierto, P. A., Dréno, B., Larkin, J., Ribas, A., Liszkay, G., Maio, M.,...McArthur, G. A. (2021). 5-year outcomes with cobimetinib plus vemurafenib in BRAFV600 mutation-positive advanced melanoma: Extended follow-up of the coBRIM study. *Clinical Cancer Research*, *27*(19), 5225–5235. https://doi.org/10.1158/1078-0432.ccr-21-0809

Ascierto, P. A., Lipson, E. J., Dummer, R., Larkin, J., Long, G. V., Sanborn, R. E.,...Grob, J. J. (2023). Nivolumab and relatlimab in patients with advanced melanoma that had progressed on anti-programmed death-1/programmed death ligand 1 therapy: Results from the phase I/IIa RELATIVITY-020 trial. *Journal of Clinical Oncology*, *41*(15), 2724–2735. https://doi.org/10.1200/jco.22.02072

Betof Warner, A., Corrie, P. G., & Hamid, O. (2023). Tumor-infiltrating lymphocyte therapy in melanoma: Facts to the future. *Clinical Cancer Research*, *29*(10), 1835–1854. https://doi.org/10.1158/1078-0432.ccr-22-1922

Betof Warner, A., Hamid, O., Komanduri, K., Amaria, R., Butler, M. O., Haanen, J.,...Schoenfeld, A. J. (2024). Expert consensus guidelines on management and best practices for tumor-infiltrating lymphocyte cell therapy. *Journal for Immunotherapy of Cancer*, *12*(2). https://doi.org/10.1136/jitc-2023-008735

Bhattacharya, S., Goyal, A., Kaur, P., Singh, R., & Kalra, S. (2020). Anticancer drug-induced thyroid dysfunction. *European Endocrinology*, *16*(1), 32–39. https://doi.org/10.17925/ee.2020.16.1.32

Bristol-Myers Squibb. (2022). Opdualag (nivolumab and relatlimab-rmbw) package insert. Princeton, NJ, USA: Bristol-Myers Squibb. https://packageinserts.bms.com/pi/pi_opdualag.pdf

Bristol-Myers Squibb. (2023). Yervoy (ipilimumab) package insert. Princeton, NJ, USA: Bristol-Myers Squibb. http://packageinserts.bms.com/pi/pi_yervoy.pdf

Bristol-Myers Squibb Company. (2023). Opdivo (nivolumab) package insert. Princeton, NJ, USA: Bristol-Myers Squibb Company. https://packageinserts.bms.com/pi/pi_opdivo.pdf

Chapman, P. B., Jayaprakasam, V. S., Panageas, K. S., Callahan, M., Postow, M. A., Shoushtari, A. N.,...Betof Warner, A. (2021). Risks and benefits of reinduction ipilimumab/nivolumab in melanoma patients previously treated with ipilimumab/nivolumab. *Journal for Immunotherapy of Cancer*, *9*(10). https://doi.org/10.1136/jitc-2021-003395

Cheng, L., Lopez-Beltran, A., Massari, F., MacLennan, G. T., & Montironi, R. (2018). Molecular testing for BRAF mutations to inform melanoma treatment decisions: A move toward precision medicine. *Modern Pathology*, *31*(1), 24–38. https://doi.org/10.1038/modpathol.2017.104

Chesney, J., Lewis, K. D., Kluger, H., Hamid, O., Whitman, E., Thomas, S.,...Sarnaik, A. (2022). Efficacy and safety of lifileucel, a one-time autologous tumor-infiltrating lymphocyte (TIL) cell therapy, in patients with advanced melanoma after progression on immune checkpoint inhibitors and targeted therapies: Pooled analysis of consecutive cohorts of the C-144-01 study. *Journal for Immunotherapy of Cancer*, *10*(12). https://doi.org/10.1136/jitc-2022-005755

Cheson, B. D., Vena, D. A., Foss, F. M., & Sorensen, J. M. (1994). Neurotoxicity of purine analogs: A review. *Journal of Clinical Oncology*, *12*(10), 2216–2228. https://doi.org/10.1200/jco.1994.12.10.2216

Costa, A. L., Abreu, C., Pacheco, T. R., Macedo, D., Sousa, A. R., Pulido, C.,...Costa, L. (2015). Prevention of nausea and vomiting in patients undergoing oral anticancer therapies for solid tumors. *BioMed Research International*, *2015*, 309601. https://doi.org/10.1155/2015/309601

Crompton, J. G., Klemen, N., & Kammula, U. S. (2018). Metastasectomy for tumor-infiltrating lymphocytes: An emerging operative indication in surgical oncology. *Annals of Surgical Oncology*, *25*(2), 565–572. https://doi.org/10.1245/s10434-017-6266-8

De Risi, I., Sciacovelli, A. M., & Guida, M. (2022). Checkpoint inhibitors immunotherapy in metastatic melanoma: When to stop treatment? *Biomedicines*, *10*(10), 2424. https://doi.org/10.3390/biomedicines10102424

Ding, X., Herzlich, A. A., Bishop, R., Tuo, J., & Chan, C. C. (2008). Ocular toxicity of fludarabine: A purine analog. *Expert Review of Ophthalmology*, *3*(1), 97–109. https://doi.org/10.1586/17469899.3.1.97

Draghi, A., Borch, T. H., Radic, H. D., Chamberlain, C. A., Gokuldass, A., Svane, I. M., & Donia, M. (2019). Differential effects of corticosteroids and anti-TNF on tumor-specific immune responses: Implications for the management of irAEs. *International Journal of Cancer*, *145*(5), 1408–1413. https://doi.org/10.1002/ijc.32080

Dudley, M. E., Wunderlich, J. R., Yang, J. C., Sherry, R. M., Topalian, S. L., Restifo, N. P.,...Rosenberg, S. A. (2005). Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. *Journal of Clinical Oncology*, *23*(10), 2346–2357. https://doi.org/10.1200/jco.2005.00.240

Dummer, R., Flaherty, K. T., Robert, C., Arance, A., de Groot, J. W. B., Garbe, C.,...Ascierto, P. A. (2022). COLUMBUS 5-year update: A randomized, open-label, phase III trial of encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF V600-mutant melanoma. *Journal of Clinical Oncology*, *40*(36), 4178–4188. https://doi.org/10.1200/jco.21.02659

Dutcher, J. P., Schwartzentruber, D. J., Kaufman, H. L., Agarwala, S. S., Tarhini, A. A., Lowder, J. N., & Atkins, M. B. (2014). High dose interleukin-2 (Aldesleukin) - expert consensus on best management practices-2014. *Journal for Immunotherapy of Cancer*, *2*(1), 26. https://doi.org/10.1186/s40425-014-0026-0

Gastman, B., Agarwal, P. K., Berger, A., Boland, G., Broderick, S., Butterfield, L. H.,...Kaufman, H. L. (2020). Defining best practices for tissue procurement in immuno-oncology clinical trials: Consensus statement from the Society for Immunotherapy of Cancer Surgery Committee. *Journal for Immunotherapy of Cancer*, *8*(2). https://doi.org/10.1136/jitc-2020-001583

Genentech USA. (2020). Zelboraf (vemurafenib) package insert. South San Francisco, CA, USA: Genentech USA. https://www.gene.com/download/pdf/zelboraf_prescribing.pdf

Genentech USA, Inc. (2023). Cotellic (cobimetinib) package insert. South San Francisco, CA, USA: Genentech USA, Inc. https://www.gene.com/download/pdf/cotellic_prescribing.pdf

Goff, S. L., Dudley, M. E., Citrin, D. E., Somerville, R. P., Wunderlich, J. R., Danforth, D. N.,...Rosenberg, S. A. (2016).

Randomized, prospective evaluation comparing intensity of lymphodepletion before adoptive transfer of tumor-infiltrating lymphocytes for patients with metastatic melanoma. *Journal of Clinical Oncology*, *34*(20), 2389–2397. https://doi.org/10.1200/jco.2016.66.7220

Goff, S. L., & Rosenberg, S. A. (2019). BRAF inhibition: Bridge or boost to T-cell therapy? *Clinical Cancer Research*, *25*(9), 2682–2684. https://doi.org/10.1158/1078-0432.ccr-19-0286

Hassel, J. C., Sarnaik, A., Chesney, J., Medina, T., Hamid, O., Thomas, S.,...Kluger, H. (2022). Number of IL-2 doses and clinical outcomes of tumor-infiltrating lymphocyte (TIL) cell therapy: Post hoc analysis of the C-144-01 trial of lifileucel in patients with advanced melanoma [abstract 35MO]. *Immuno-Oncology and Technology*, *16*(suppl 1), 100140. https://doi.org/10.1016/j.iotech.2022.100140

Hopewell, E. L., Cox, C., Pilon-Thomas, S., & Kelley, L. L. (2019). Tumor-infiltrating lymphocytes: Streamlining a complex manufacturing process. *Cytotherapy*, *21*(3), 307–314. https://doi.org/10.1016/j.jcyt.2018.11.004

Iovance Biotherapeutics. (2024). Amtagvi (lifileucel) package insert. Philadelphia, PA: Iovance Biotherapeutics. https://www.iovance.com/AMTAGVI_USPI

Jain, M., & Wylie, W. P. (2024). Diphenoxylate and atropine. In *StatPearls*. StatPearls Publishing.

Kalantari, K., Chang, J. N., Ronco, C., & Rosner, M. H. (2013). Assessment of intravascular volume status and volume responsiveness in critically ill patients. *Kidney International*, *83*(6), 1017–1028. https://doi.org/10.1038/ki.2012.424

Kaplan, J. E., Benson, C., Holmes, K. K., Brooks, J. T., Pau, A., & Masur, H. (2009). Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *Morbidity and Mortality Weekly Report: Recommendations and Reports*, *58*(Rr-4), 1–207.

Kazemi, M. H., Sadri, M., Najafi, A., Rahimi, A., Baghernejadan, Z., Khorramdelazad, H., & Falak, R. (2022). Tumor-infiltrating lymphocytes for treatment of solid tumors: It takes two to tango? *Frontiers in Immunology*, *13*, 1018962. https://doi.org/10.3389/fimmu.2022.1018962

Kollerup Madsen, B., Hilscher, M., Zetner, D., & Rosenberg, J. (2018). Adverse reactions of dimethyl sulfoxide in humans: A systematic review. *F1000Res*, *7*, 1746. https://doi.org/10.12688/f1000research.16642.2

Kumar, A., Watkins, R., & Vilgelm, A. E. (2021). Cell therapy with TILs: Training and taming T cells to fight cancer. *Frontiers in Immunology*, *12*, 690499. https://doi.org/10.3389/fimmu.2021.690499

Kumar, H., Gupta, P. K., Mishra, D. K., Sarkar, R. S., & Jaiprakash, M. (2006). Leucodepletion and blood products. *Medical Journal Armed Forces India*, *62*(2), 174–177. https://doi.org/10.1016/s0377-1237(06)80064-x

Kurlowicz, L., & Wallace, M. (1999). *The Mini Mental State Examination (MMSE)*. Interprofessional Comprehensive Geriatric Toolkit. https://cgatoolkit.ca/Uploads/ContentDocuments/MMSE.pdf

Larkin, J., Sarnaik, A., Chesney, J. A., Khushalani, N. I., Kirkwood, J. M., Weber, J. S.,...Hamid, O. (2021). Lifileucel (LN-144), a cryopreserved autologous tumor infiltrating lymphocyte (TIL) therapy in patients with advanced melanoma: Evaluation of impact of prior anti-PD-1 therapy [abstract]. *Journal of Clinical Oncology*, *39(15 suppl)*, 9505. https://doi.org/10.1200/JCO.2021.39.15_suppl.9505

Lim, S. Y., Shklovskaya, E., Lee, J. H., Pedersen, B., Stewart, A., Ming, Z.,...Rizos, H. (2023). The molecular and functional landscape of resistance to immune checkpoint blockade in melanoma. *Nature Communication*, *14*(1), 1516. https://doi.org/10.1038/s41467-023-36979-y

Lopes, J., Rodrigues, C. M. P., Gaspar, M. M., & Reis, C. P. (2022). Melanoma management: From epidemiology to treatment and latest advances. *Cancers*, *14*(19). https://doi.org/10.3390/cancers14194652

McQuade, R. M., Stojanovska, V., Abalo, R., Bornstein, J. C., & Nurgali, K. (2016). Chemotherapy-induced constipation and diarrhea: Pathophysiology, current and emerging treatments. *Frontiers in Pharmacology*, *7*, 414. https://doi.org/10.3389/fphar.2016.00414

Mehta, G. U., Malekzadeh, P., Shelton, T., White, D. E., Butman, J. A., Yang, J. C.,...Sherry, R. M. (2018). Outcomes of adoptive cell transfer with tumor-infiltrating lymphocytes for metastatic melanoma patients with and without brain metastases. *Journal of Immunotherapy*, *41*(5), 241–247. https://doi.org/10.1097/cji.0000000000000223

Merck & Co., Inc. (2023). Keytruda (pembrolizumab) package insert. Rahway, NJ, USA: Merck & Co., Inc. https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf

Moreno, S. E., Alves-Filho, J. C., Bertozi, G., Alfaya, T. M., Thèze, J., Ferreira, S. H., & Vargaftig, B. B. (2006). Systemic administration of interleukin-2 inhibits inflammatory neutrophil migration: Role of nitric oxide. *British Journal of Pharmacology*, *148*(8), 1060–1066. https://doi.org/10.1038/sj.bjp.0706835

Mullinax, J. E., Egger, M. E., McCarter, M., Monk, B. J., Toloza, E. M., Brousseau, S.,...Sarnaik, A. (2022). Surgical considerations for tumor tissue procurement to obtain tumor-infiltrating lymphocytes for adoptive cell therapy. *Cancer Journal*, *28*(4), 285–293. https://doi.org/10.1097/ppo.0000000000000608

National Cancer Institute. (2024). *SEER Cancer Stat Facts: Melanoma of the Skin*. https://seer.cancer.gov/statfacts/html/melan.html

National Institutes of Health. (2017). Cyclophosphamide. In *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]*. National Institutes of Health.

Novartis Pharmaceuticals. (2022). Tafinlar (dabrafenib) package insert. East Hanover, NJ, USA: Novartis Pharmaceuticals. https://www.novartis.com/us-en/sites/novartis_us/files/tafinlar.pdf

Novartis Pharmaceuticals Corporation. (2022). Mekinist (trametinib) package insert. East Hanover, NJ, USA: Novartis Pharmaceuticals Corporation. https://www.novartis.com/us-en/sites/novartis_us/files/mekinist.pdf

Olson, D. J., Eroglu, Z., Brockstein, B., Poklepovic, A. S., Bajaj, M., Babu, S.,...Luke, J. J. (2021). Pembrolizumab plus ipilimumab following anti-PD-1/L1 failure in melanoma. *Journal of Clinical Oncology*, *39*(24), 2647–2655. https://doi.org/10.1200/jco.21.00079

Pachella, L. A., Madsen, L. T., & Dains, J. E. (2015). The toxicity and benefit of various dosing strategies for interleukin-2 in metastatic melanoma and renal cell carcinoma.

Journal of the Advanced Practitioner in Oncology, *6*(3), 212–221. https://doi.org/10.6004/jadpro.2015.6.3.3

Paydas, S., Ozonur, H., Paydas, S., Kaya, B., & Efe, C. (2021). The assessment of volume status with body composition monitor in cancer patients. *Eurasian Journal of Medical Investigation*, *5*(2), 246–250. https://doi.org/10.14744/ejmi.2021.40162

Pires da Silva, I., Ahmed, T., Reijers, I. L. M., Weppler, A. M., Betof Warner, A., Patrinely, J. R.,...Long, G. V. (2021). Ipilimumab alone or ipilimumab plus anti-PD-1 therapy in patients with metastatic melanoma resistant to anti-PD-(L)1 monotherapy: A multicentre, retrospective, cohort study. *Lancet Oncology*, *22*(6), 836–847. https://doi.org/10.1016/s1470-2045(21)00097-8

Reddy, V., & Winston, N. R. (2023). Mesna. In *StatPearls*. StatPearls Publishing LLC.

Robert, C., Grob, J. J., Stroyakovskiy, D., Karaszewska, B., Hauschild, A., Levchenko, E.,...Long, G. V. (2019b). Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. *New England Journal of Medicine*, *381*(7), 626–636. https://doi.org/10.1056/NEJMoa1904059

Robert, C., Ribas, A., Schachter, J., Arance, A., Grob, J. J., Mortier, L.,...Long, G. V. (2019a). Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): Post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. *Lancet Oncology*, *20*(9), 1239–1251. https://doi.org/10.1016/s1470-2045(19)30388-2

Rogers, M., McKenzie, G., Rattani, A., Yusuf, M., Chesney, J. A., & Dunlap, N. E. (2023). Tolerability and response of palliative radiotherapy in patients receiving tumor-infiltrating lymphocyte therapy [abstract]. *Journal of Clinical Oncology*, *41*(16 suppl), e14527. https://doi.org/10.1200/JCO.2023.41.16_suppl.e14527

Rohaan, M. W., Borch, T. H., van den Berg, J. H., Met, Ö., Kessels, R., Geukes Foppen, M. H.,...Haanen, J. (2022). Tumor-infiltrating lymphocyte therapy or ipilimumab in advanced melanoma. *New England Journal of Medicine*, *387*(23), 2113–2125. https://doi.org/10.1056/NEJMoa2210233

Rosenberg, S. A., Packard, B. S., Aebersold, P. M., Solomon, D., Topalian, S. L., Toy, S. T.,...White, D. (1988). Use of tumor-infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma. A preliminary report. *New England Journal of Medicine*, *319*(25), 1676–1680. https://doi.org/10.1056/nejm198812222319252 7

Rosenberg, S. A., Yang, J. C., Sherry, R. M., Kammula, U. S., Hughes, M. S., Phan, G. Q.,...Dudley, M. E. (2011). Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. *Clinical Cancer Research*, *17*(13), 4550–4557. https://doi.org/10.1158/1078-0432.ccr-11-0116

Rosenberg, S. A., Yannelli, J. R., Yang, J. C., Topalian, S. L., Schwartzentruber, D. J., Weber, J. S.,...White, D. E. (1994). Treatment of patients with metastatic melanoma with autologous tumor-infiltrating lymphocytes and interleukin 2. *Journal of the National Cancer Institute*, *86*(15), 1159–1166. https://doi.org/10.1093/jnci/86.15.1159

Sarnaik, A. A., Hamid, O., Khushalani, N. I., Lewis, K. D., Medina, T., Kluger, H. M.,...Chesney, J. A. (2021). Lifileucel, a tumor-infiltrating lymphocyte therapy, in metastatic melanoma. *Journal of Clinical Oncology*, *39*(24), 2656–2666. https://doi.org/10.1200/jco.21.00612

Savoia, P., Zavattaro, E., & Cremona, O. (2020). Clinical implications of acquired BRAF inhibitors resistance in melanoma. *International Journal of Molecular Sciences*, *21*(24). https://doi.org/10.3390/ijms21249730

Schwartzentruber, D. J. (2001). Guidelines for the safe administration of high-dose interleukin-2. *Journal of Immunotherapy*, *24*(4), 287–293. https://doi.org/10.1097/00002371-200107000-00004

Seth, R., Agarwala, S. S., Messersmith, H., Alluri, K. C., Ascierto, P. A., Atkins, M. B.,...Weber, J. (2023). Systemic therapy for melanoma: ASCO guideline update. *Journal of Clinical Oncology*, *41*(30), 4794-4820. https://doi.org/10.1200/jco.23.01136

Tawbi, H. A., Schadendorf, D., Lipson, E. J., Ascierto, P. A., Matamala, L., Castillo Gutiérrez, E.,...Long, G. V. (2022). Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. *New England Journal of Medicine*, *386*(1), 24–34. https://doi.org/10.1056/NEJMoa2109970

Topalian, S. L., Solomon, D., Avis, F. P., Chang, A. E., Freerksen, D. L., Linehan, W. M.,...Simon, P. (1988). Immunotherapy of patients with advanced cancer using tumor-infiltrating lymphocytes and recombinant interleukin-2: A pilot study. *Journal of Clinical Oncology*, *6*(5), 839–853. https://doi.org/10.1200/jco.1988.6.5.839

Topp, B. G., Thiagarajan, K., De Alwis, D. P., Snyder, A., & Hellmann, M. D. (2021). Lesion-level heterogeneity of radiologic progression in patients treated with pembrolizumab. *Annals of Oncology*, *32*(12), 1618–1625. https://doi.org/10.1016/j.annonc.2021.09.006

Tyre, C. C., & Quan, W. (2007). Nursing care of patients receiving high-dose, continuous-infusion interleukin-2 with pulse dose and famotidine. *Clinical Journal of Oncology Nursing*, *11*(4), 513–519. https://doi.org/10.1188/07.cjon.513-519

VanderWalde, A., Bellasea, S. L., Kendra, K. L., Khushalani, N. I., Campbell, K. M., Scumpia, P. O.,...Ribas, A. (2023). Ipilimumab with or without nivolumab in PD-1 or PD-L1 blockade refractory metastatic melanoma: A randomized phase 2 trial. *Nature Medicine*, *29*(9), 2278–2285. https://doi.org/10.1038/s41591-023-02498-y

Villani, A., Potestio, L., Fabbrocini, G., Troncone, G., Malapelle, U., & Scalvenzi, M. (2022). The treatment of advanced melanoma: Therapeutic update. *International Journal of Molecular Sciences*, *23*(12). https://doi.org/10.3390/ijms23126388

Wolchok, J. D., Chiarion-Sileni, V., Gonzalez, R., Grob, J. J., Rutkowski, P., Lao, C. D.,...Hodi, F. S. (2022). Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. *Journal of Clinical Oncology*, *40*(2), 127–137. https://doi.org/10.1200/jco.21.02229

Zhao, Y., Deng, J., Rao, S., Guo, S., Shen, J., Du, F.,...Li, J. (2022). Tumor infiltrating lymphocyte (TIL) therapy for solid tumor treatment: Progressions and challenges. *Cancers*, *14*(17). https://doi.org/10.3390/cancers14174160