Amtagvi® (lifileucel) T-Cell Therapy: A Case Study

Melanoma is a life-threatening cancer once it advances beyond the possibility of surgical removal. In this case study, advanced melanoma refers to unresectable or metastatic disease. Immune checkpoint inhibitors and targeted BRAF and MEK therapies have transformed care for many patients with unresectable or metastatic disease, yet a substantial proportion never respond or ultimately progress, leaving limited options after standard therapy. This persistent gap has spurred efforts to harness the patient's own immune system to control solid tumors.

Amtagvi® (lifileucel) is a tumor-derived autologous T-cell therapy, also known as tumor-infiltrating lymphocyte (TIL) therapy, created from each patient's resected tumor, expanded *ex vivo*, and administered as a single, individualized infusion. On February 16, 2024, the U.S. Food and Drug Administration (FDA) granted accelerated approval to Amtagvi® for adults with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody and, if BRAF V600 positive, a BRAF inhibitor with or without a MEK inhibitor. This decision marked the first FDA approval of a cellular therapy for a solid tumor; Amtagvi® is also the first and only FDA-approved one-time T-cell therapy for previously treated melanoma.

FDA authorization and commercial availability in 2024 reflect decades of progress in adoptive cell transfer and the translation of that science into a scalable therapy by Iovance Biotherapeutics.

Epidemiological Features of Advanced Melanoma

Most patients are diagnosed at earlier stages, but a clinically significant minority present with distant metastases, and many patients who receive adjuvant therapy for high-risk early disease eventually recur with unresectable or metastatic melanoma. Cutaneous melanoma carries actionable genomic alterations, most prominently BRAF V600, that shape prognosis and treatment selection, while mucosal and acral subtypes are less likely to harbor BRAF V600 and more often harbor KIT or NRAS variants. Central nervous system (CNS) involvement is common over the disease course, with implications for survival and treatment planning.[1-3]

Feature	Typical estimate / note
Distant stage at first diagnosis (U.S.)	~4.7% of new melanoma cases (1999–2021)[1]
Five-year relative survival, distant stage	~35% in contemporary U.S. registry analyses[1]
Common driver alterations (cutaneous)	BRAF V600 ~40–50%; NRAS ~15–20%; KIT <5% (higher in mucosal/acral)[2]
CNS involvement	~10–20% at diagnosis of stage IV; cumulative risk ~40–60% during disease course[3]
Frequent metastatic sites	Lung, skin/soft tissue, brain, liver[2]

Management of Advanced Melanoma

First line care typically uses PD-1 based regimens (nivolumab plus ipilimumab, nivolumab plus relatlimab, or PD-1 monotherapy in selected patients). Guidelines endorse these options, and long term follow up suggests a survival plateau in some patients, particularly after nivolumab plus ipilimumab.[2,4,5]

For BRAF V600 mutant melanoma, BRAF inhibitor plus MEK inhibitor combinations can produce rapid tumor shrinkage and may be prioritized when immediate disease control is needed.[2,4,6] DREAMseq generally supports immunotherapy first, reserving targeted therapy first for rapidly progressive, organ threatening disease.[7]

For brain metastases, nivolumab plus ipilimumab can be effective in patients who are asymptomatic and not requiring corticosteroids, with stereotactic radiosurgery often integrated.[4]

After progression on PD-1 based therapy (and BRAF/MEK targeted therapy when indicated), Amtagvi® is an FDA accelerated approval option. In the FDA review population at the recommended dose, objective response rate was 31.5% with median time to response 1.5 months and median duration of response not reached; pooled C-144-01 analyses reported median progression free survival 4.1 months and median overall survival 13.9 months, and with longer follow up median duration of response 36.5 months with 5 year overall survival 19.7%.[8,9]

Development of Amtagvi®

Role of NIH/NCI

Over more than three decades, NCI's Surgery Branch led by surgeon-scientist Steven Rosenberg pioneered and refined tumor-infiltrating lymphocyte (TIL) therapy. In the late 1980s his team showed that TILs harvested from a patient's tumor and expanded with interleukin-2 could shrink metastatic melanoma. NCI investigators then improved the approach by optimizing manufacturing and adding lymphodepleting chemotherapy, establishing the clinical blueprint that ultimately enabled lifileucel.

To accelerate translation, NCI entered a Cooperative Research and Development Agreement with Lion Biotechnologies in 2011 (later Iovance Biotherapeutics), enabling protocol and process transfer for multicenter trials. NIH granted an exclusive patent license in 2015, with later updates expanding rights and non-exclusive access aligned with public health goals.

As the program matured, NIH and Iovance updated the licensing structure to balance broad public health access with continued innovation. In 2021 the parties executed an Amended and Restated NIH patent license that added rights and expanded non-exclusive access. In 2022 a Second Amended and Restated license added further exclusive rights and additional non-exclusive rights tied to TIL engineering and potency.

These NIH discoveries, patents, and partnering mechanisms set the stage for FDA's accelerated approval of Amtagvi® on February 16, 2024.

Role of Iovance Biotherapeutics

Iovance undertook the extensive effort required to turn NCI's TIL concept into a reproducible, commercial product. The company engineered a proprietary Gen 2 manufacturing platform that yields a cryopreserved lifileucel product in approximately 22 days, streamlining logistics for a one-time autologous therapy. Gen 2 incorporates gas permeable bioreactors and static culture systems to enable robust rapid expansion at clinical scale. Iovance also invested in dedicated capacity by opening the Iovance Cell Therapy Center in Philadelphia, a centralized GMP facility designed to supply thousands of patients each year.

As sponsor, Iovance led the multicenter C-144-01 program (including the registrational Cohort 4), generated the pivotal efficacy and safety data, and supported a rolling BLA (biologics license application) that led to FDA accelerated approval on February 16, 2024. The company then launched commercially, coordinating vein to vein logistics, quality release, and site readiness, with first commercial shipment on March 28, 2024 and the first patient infusion on April 4, 2024. These activities demonstrate Iovance's role across process development, clinical execution, regulatory strategy, and scale up to national distribution.

R&D Timeline

First TIL study[10] — December 22, 1988

NIH Provisional Filed for "Adoptive cell therapy with young T cells"[11] — August 26, 2009

NCI–Iovance CRADA[12] — August 5, 2011

IND submitted[13] — December 31, 2014

NIH license (exclusive)[11] — February 4, 2015

RMAT granted[13] — August 24, 2018

Pivotal cohort start[14] — April 2, 2019

BLA filed[15] — May 26, 2023

FDA approval[15] — February 16, 2024

First commercial infusion[16] — April 4, 2024

Public Health Benefits

Amtagvi® is a first in kind FDA approved treatment modality using live TIL cells. It is a first in kind FDA approved TIL therapy for the treatment of cancer.

Amtagvi® gives adults with previously treated unresectable or metastatic melanoma a needed option when no FDA approved second line therapy existed. In the registrational cohort, lifileucel produced an objective response rate of 31.5 percent with median duration of response not reached, and a median time to response of 1.5 months. Pooled analyses in a larger multicenter population show durable benefit, with 41.7 percent of responses maintained for at least 18 months. Amtagvi® is the first tumor derived T cell therapy approved by the FDA for a solid tumor, signaling an additional mechanism for patients whose disease progressed after checkpoint inhibitors and, when appropriate, BRAF targeted therapy. Together, these outcomes address a high unmet medical need and offer the possibility of sustained tumor control after standard options have failed.

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