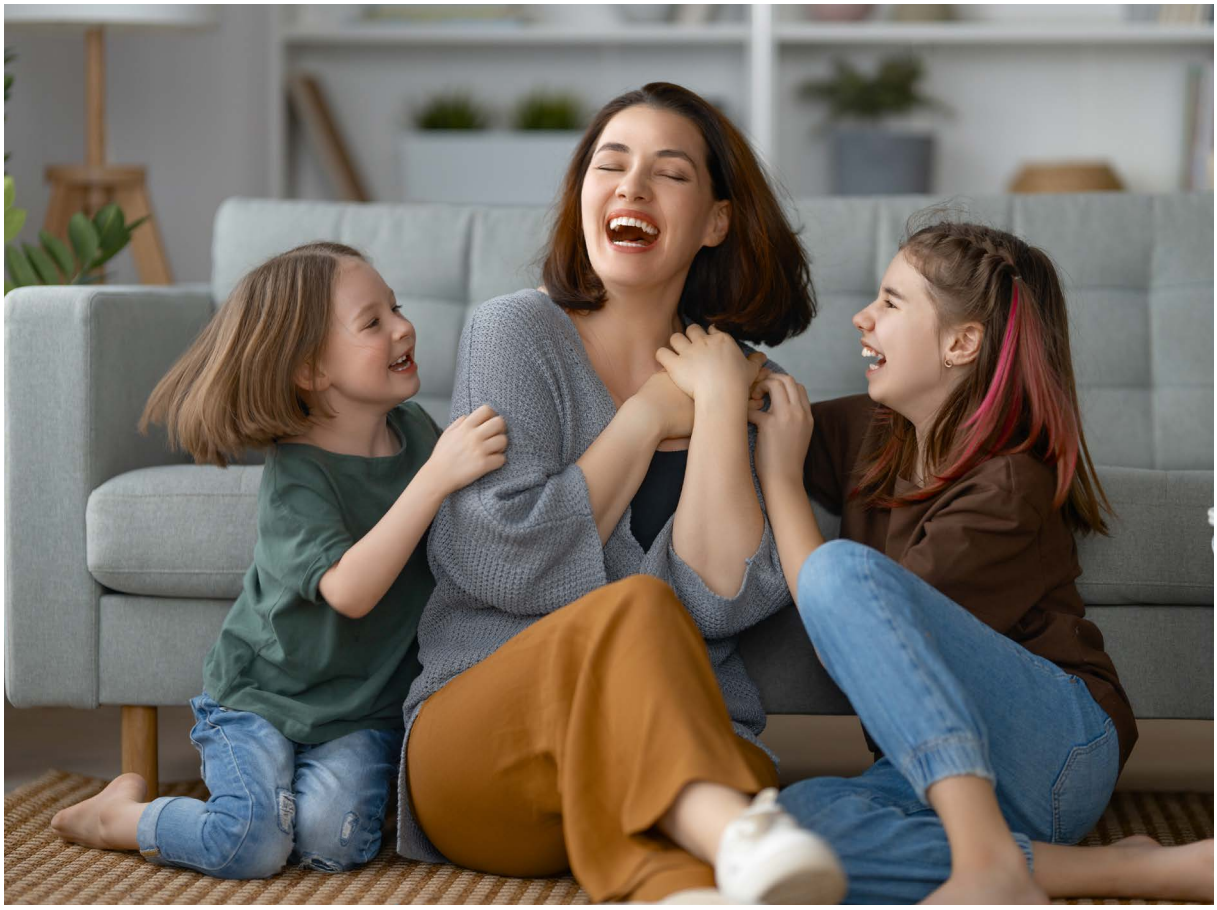
MASSIVEBIO

NEWSLETTER



Clinician Update: Melanoma

Immunotherapy's Expanding Role in Advanced Melanoma

Patients with metastatic or unresectable melanoma pose a significant clinical challenge. For some, an immune checkpoint inhibitor could offer an important therapeutic option.
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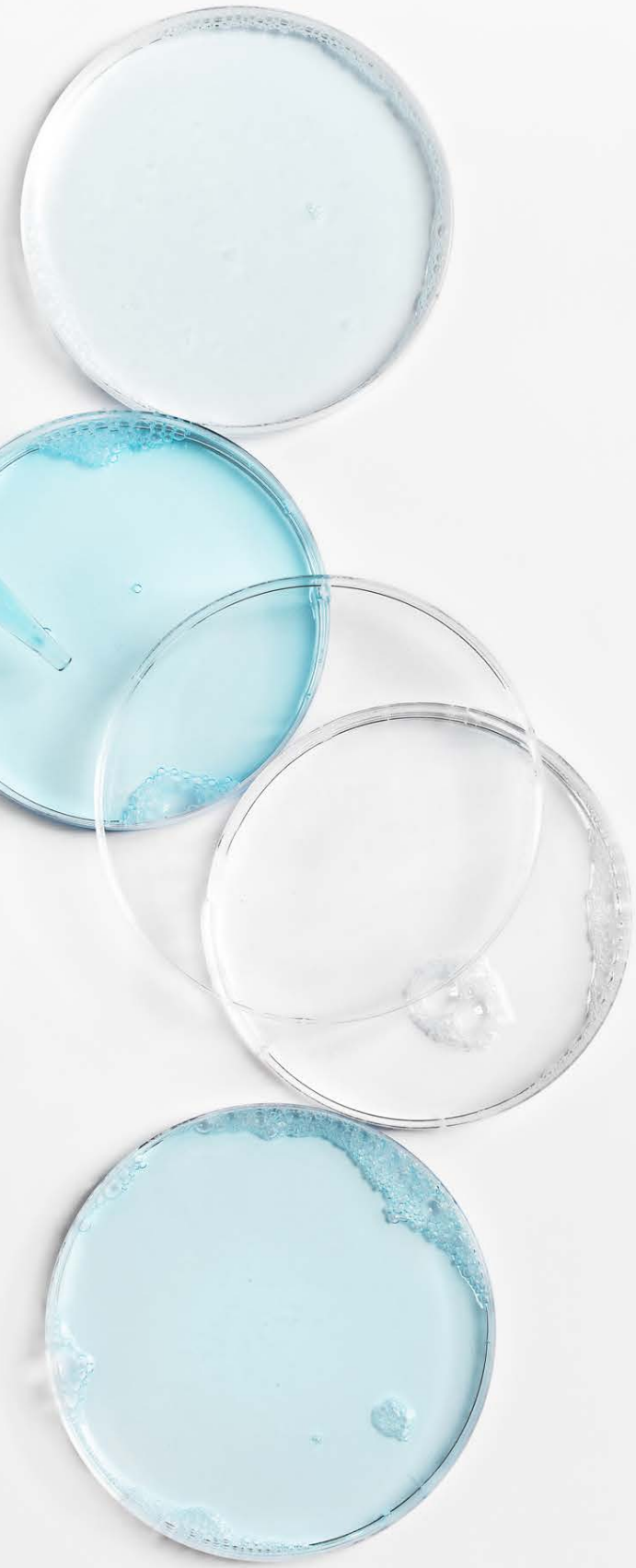
For Your Patients: Where To Turn for Support
The Melanoma Research Foundation



Immunotherapy's Expanding Role in Advanced Melanoma

The innovative class of immunotherapy drugs known as immune checkpoint inhibitors has revolutionized the management of advanced melanoma. Immune checkpoint inhibitors overcome cancer cells' ability to suppress and evade attack by T cells. While immune checkpoints are necessary for a healthy and normal immune response, when these proteins bind with partner proteins on some tumor cells, the ability of T cells to identify and destroy malignant cells is turned "off."

Immune checkpoint inhibitors block this binding of proteins and restore T cells' ability to recognize and fight cancer.

The immune checkpoint inhibitors approved for advanced melanoma include the following:

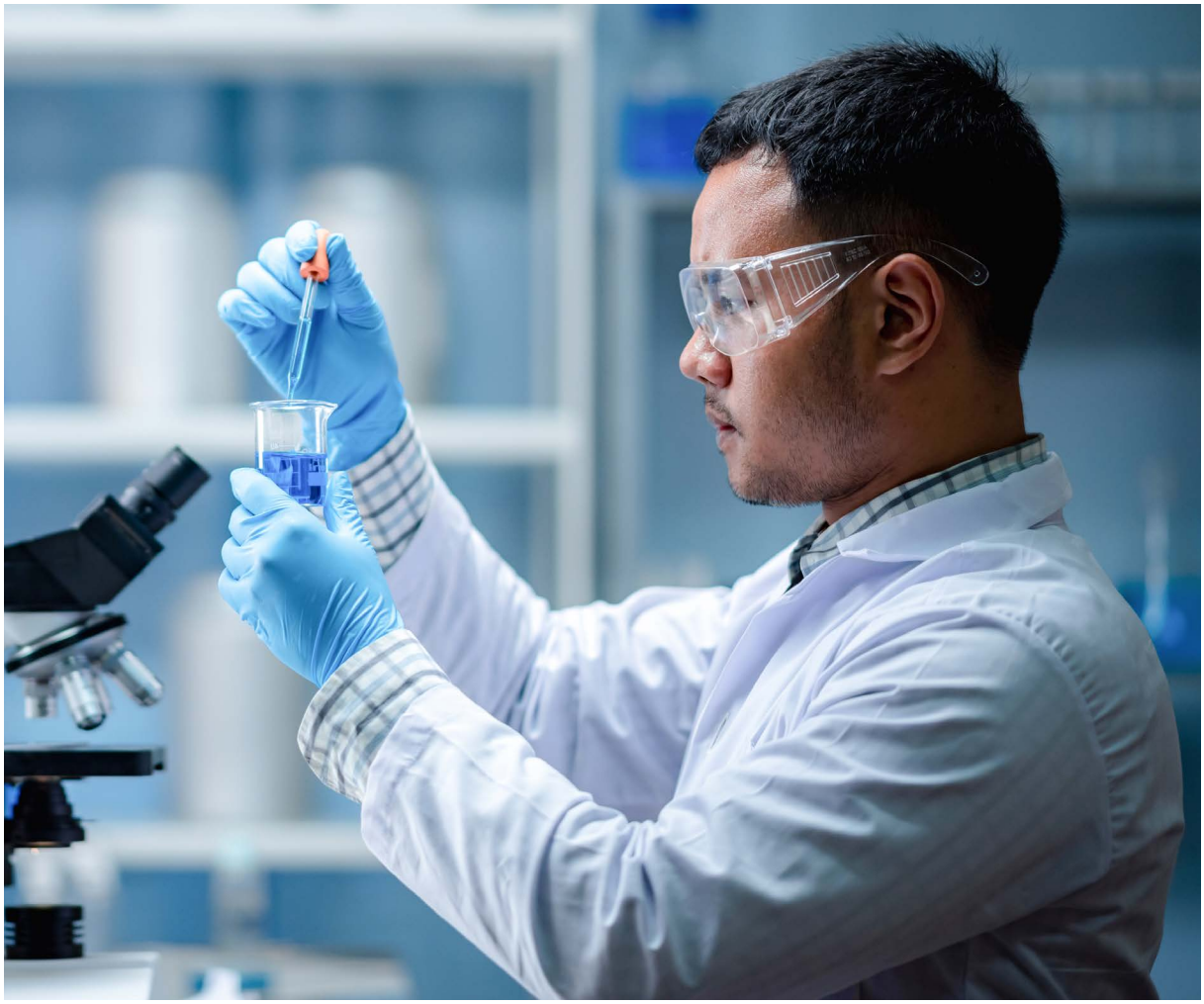
CTLA-4 inhibitors
Ipilimumab (*Yervoy*), which targets cytotoxic T lymphocyte antigen (CTLA)-4, was the first checkpoint inhibitor approved by the U.S. Food and Drug Administration (FDA) in 2011. It is indicated for unresectable or metastatic melanoma, as monotherapy or (in adults) in combination with nivolumab, and as adjuvant therapy in certain cases.

PD-1 inhibitors
The next immune checkpoint inhibitors for melanoma to be developed target programmed cell death protein 1 (PD-1), which is also known to suppress adaptive immunity. The first PD-1 inhibitor approved by the FDA was pembrolizumab (*Keytruda*), in 2015, which was followed by nivolumab (*Opdivo*) in 2017. Both are indicated for metastatic or unresectable melanoma (nivolumab may be used in combination with ipilimumab) and as adjuvant therapy in select cases.

PD-L1 inhibitors
Atezolizumab (*Tecentriq*), which blocks a protein related to PD-1 called programmed death ligand 1 (PD-L1), was approved (in combination with cobimetinib and vemurafenib) for patients with BRAF V600 mutation-positive unresectable or metastatic melanoma in 2020.

LAG-3 inhibitors
In April 2022, the FDA approved the first drug in a new class of immune checkpoint inhibitors that block a protein known as lymphocyte-activation gene 3 (LAG-3), called relatlimab. The first LAG-3 inhibitor is paired with the PD-1 inhibitor nivolumab to form a new combination therapy named *Opdualag*.

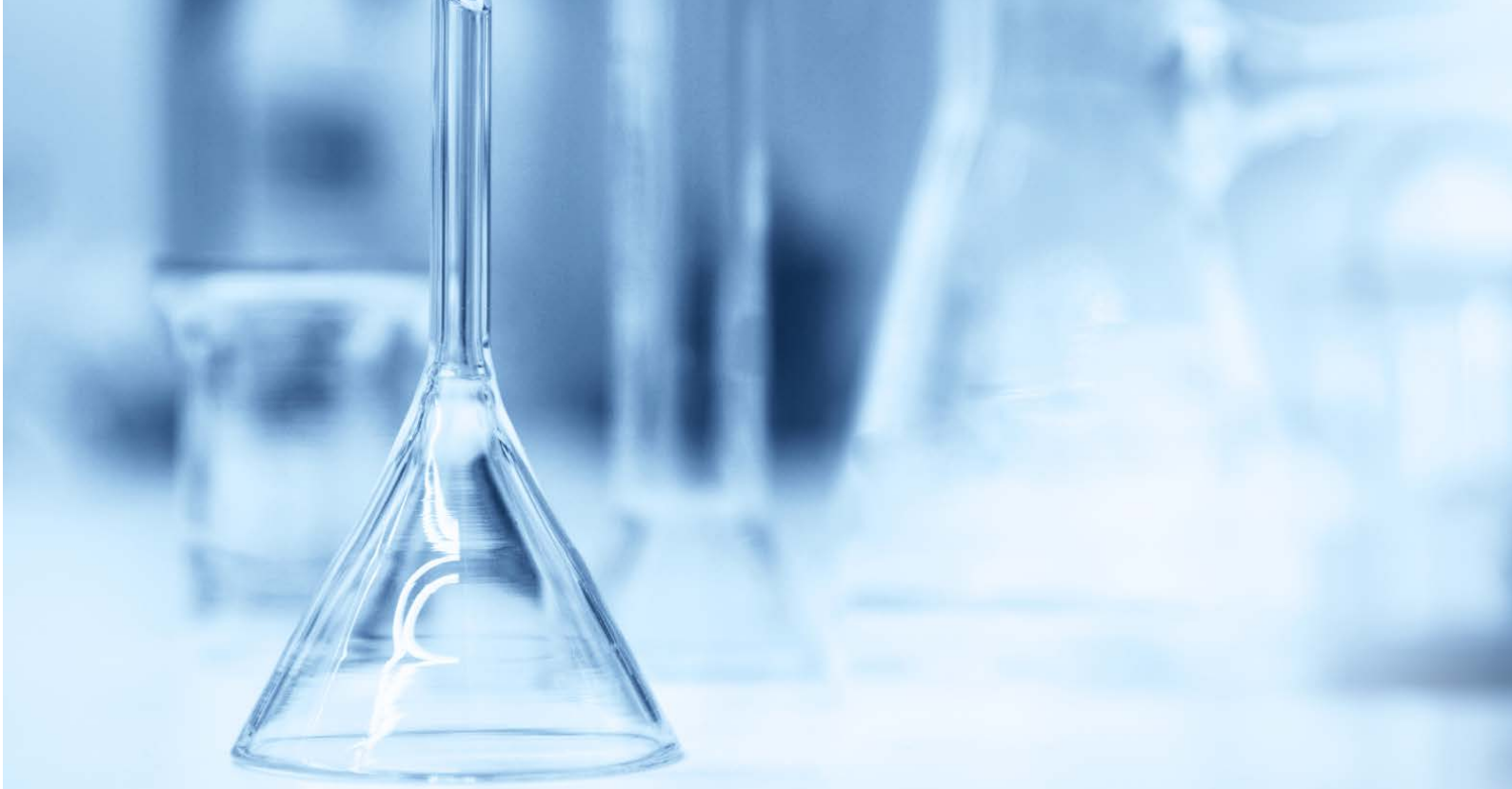
Opdualag gained approval on the basis of RELATIVITY-047, a phase 3 trial that evaluated the benefit and safety of combining a LAG-3 inhibitor and PD-1 inhibitor in patients with previously untreated metastatic or unresectable melanoma. In the trial, 714 patients were randomly assigned to receive relatlimab plus nivolumab (355 patients) or nivolumab monotherapy (359 patients). RELATIVITY-047 was conducted at 111 sites in



North America, Central America, South America, Europe, Australia, and New Zealand.

The study, published in the *New England Journal of Medicine*, found that median progression-free survival (PFS) in the relatlimab-nivolumab arm was 10.1 months compared with 4.6 months in the group receiving only nivolumab, with a hazard ratio for progression or death of 0.75. At 12 months, PFS was 47.7% versus 36.0%. *BRAF* mutation status didn't appear to affect PFS. Grade 3 or 4 treatment-related adverse events occurred in 18.9% of patients in the relatlimab–nivolumab group and in 9.7% of patients in the nivolumab group.

The immune checkpoint inhibitors have had a profound impact on management of metastatic melanoma. Whereas tumor regression and long-term control of melanoma metastases was formerly possible in only about 10% of patients, today close to half may enjoy good responses to therapy. Yet there remains an unmet need in the management of metastatic or unresectable melanoma. The search for other immune targets continues, and other approaches to treating advanced melanoma are being investigated, including in research studies conducted by our pharma partners. Contact Massive Bio at (844) 627 7246 or support@massivebio.com to learn more and find out if your patients might be candidates for clinical trials.

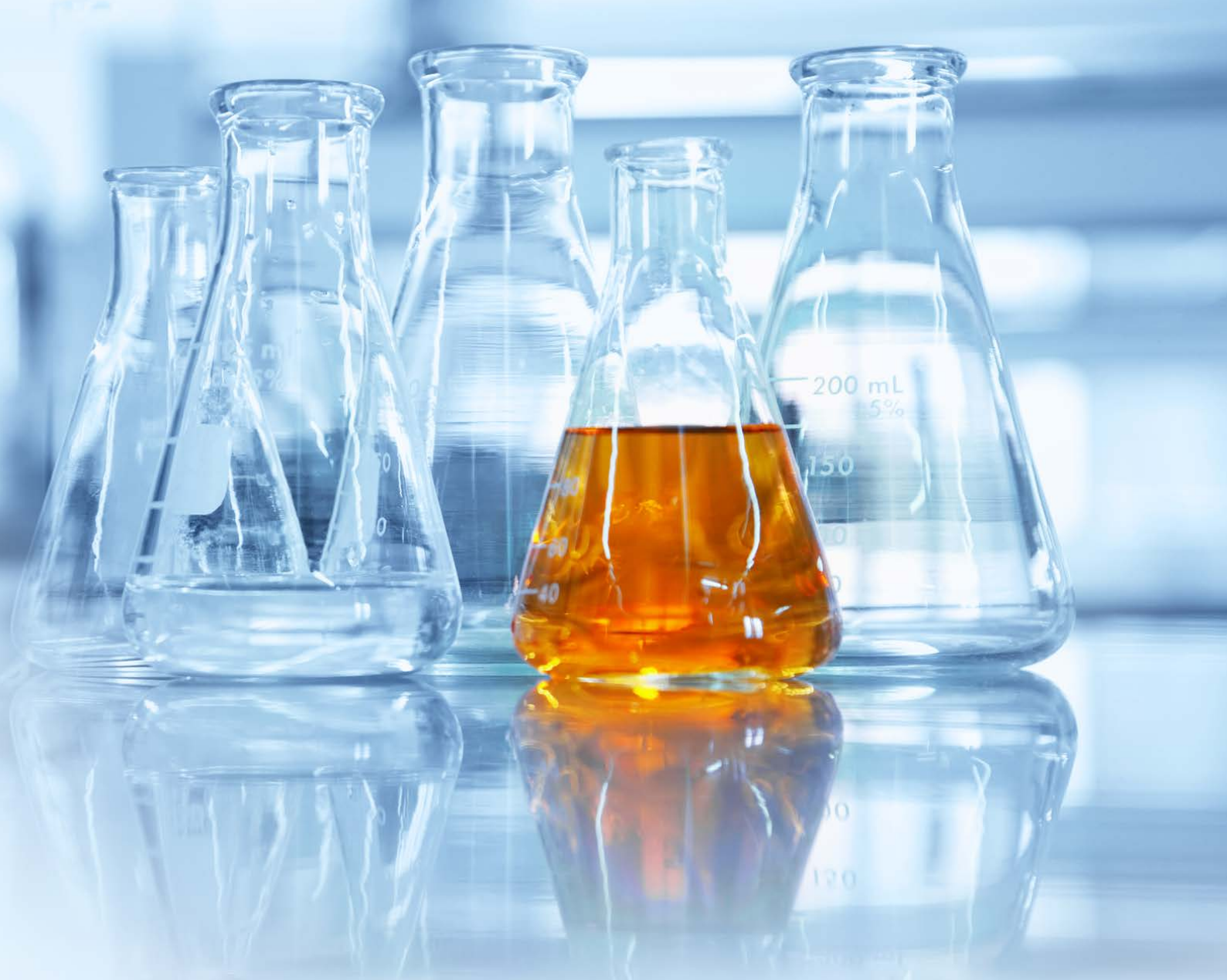


Clinical Trial News

Repurposed Drugs Could Increase Survival in End-Stage Melanoma

Thanks to the availability of high-throughput screening technology, it's now possible to rapidly learn whether existing drugs approved for treatment of one disease might have unexpected benefits for one or more other conditions. Known as drug repurposing, this strategy has the potential to identify novel therapies for hard-to-treat conditions, including advanced melanoma. In a phase II trial, researchers at Hunter Medical Research Institute (HMRI) at the University of Newcastle in Australia set out to learn whether a novel combination of existing drugs offered any benefit for patients with end-stage melanoma that had become resistant to immune checkpoint inhibitors. Specifically, they wanted to know if combining the chemotherapy drugs azacitidine, which is approved for treatment of myelodysplastic syndromes, and carboplatin, which is commonly used to treat ovarian cancer and other malignancies, could resensitize these patients to the immune checkpoint inhibitor avelumab (*Bavencio*, which is FDA-approved for treating several non-melanoma malignancies).

The study, published in *Cancer Research Communications*, included 20 patients with end-stage melanoma, who had run out of treatment options. The researchers found that the combination of azacitidine and carboplatin did resensitize some patients to the effects of immunotherapy. On average, patients survived for 47 weeks, and four remained alive when the results were published in September 2022. In a statement, lead author Nikola Bowman, an associate professor at HMRI, said that it seemed like some of the patients' tumors "were frozen in time and they stayed that way for a very long time." Some patients even experienced tumor reduction. Bowman and her colleagues continue to study the potential of drug repurposing for treating melanoma.

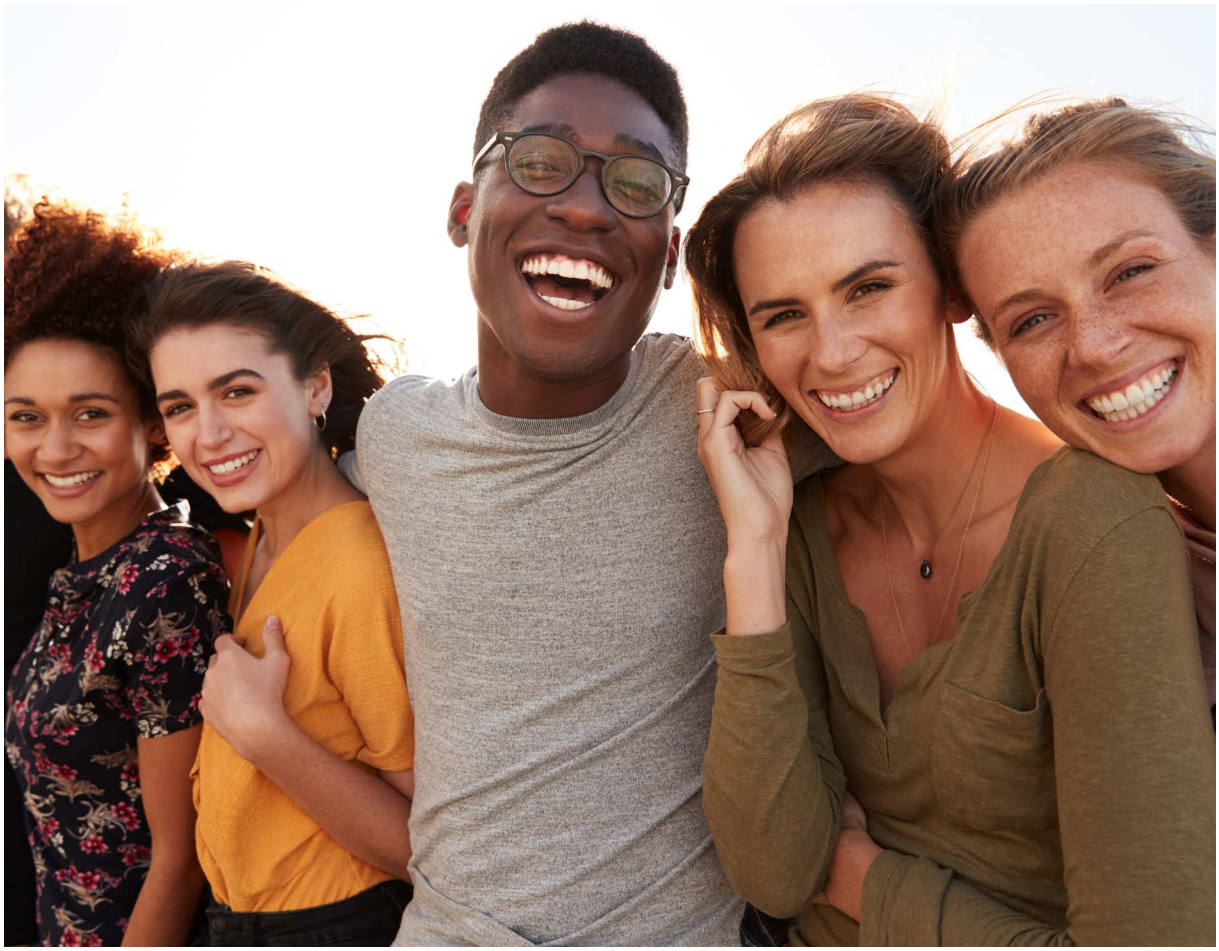


A New Option for Advanced Melanoma?
There are few approved options for patients with advanced melanoma who no longer respond to immunotherapy, but that could change in time. Iovance Biotherapeutics has submitted a rolling Biologics License Application (BLA) submission to the FDA for lifileucel, a tumor-infiltrating lymphocyte (TIL) therapy for patients with unresectable or metastatic melanoma who no longer respond to anti-PD-1/L1 therapy and, if *BRAF*-mutation positive, who have had prior treatment with BRAF or BRAF/MEK inhibitors. There are currently no FDA approved therapies for these patients.

In TIL therapy, the tumor is biopsied and TILs are removed and grown in a lab to increase their numbers. The patient undergoes chemotherapy, then TILs are infused back into the patient's bloodstream. TIL therapy is currently only available in clinical trials.

Iovance submitted the BLA based on the results of the phase 2 C-144-01 trial, which had four cohorts. In a pooled analysis of the 153 patients from cohorts 2 and 4, lifileucel induced an overall response rate of 31%, as determined by an independent review committee. The median duration of response had not been achieved at a median follow-up of 27.6 months. Cohort 2 (66 patients) had five complete responders and 18 partial responders.

Iovance is a late-stage biotechnology company based in San Carlos, California, that develops novel T cell-based cancer immunotherapies. Filing a rolling BLA allows the company to submit data to the FDA on an ongoing basis, with the goal of expediting review.



For Your Patients: Where To Turn for Support **The Melanoma Research Foundation**

The Melanoma Research Foundation (MRF) is the largest independent organization devoted to melanoma, offering support and resources for patients, caregivers, clinicians, and researchers. Whether you're newly diagnosed or have already undergone treatment for melanoma, the MRF website (melanoma.org) has a wealth of information about this form of skin cancer, including webinars on specific subjects, such as "Melanoma Clinical Trials: A Panel Discussion" and "COVID-19 and Melanoma: What You Need To Know." MRF also offers comprehensive support (both in person and online) for patients.