

pathology analysis following a resection or biopsy, efforts should be taken in characterizing the immune cells that are present in tumors," he says. "Building that into any clinical trial or treatment program is essential to move forward because we now know that TRM cells are directly influencing outcomes."

—Janet Colwell ■

CAR T Cells Infiltrate Brain, Target Tumors

An autologous chimeric antigen receptor (CAR) T-cell therapy directed against the most common mutation in glioblastoma can engraft in the blood, traffic to the brain, and destroy target cells in patients with the deadly cancer. The treatment was also deemed safe in a newly reported phase I trial (*Sci Transl Med* 2017;9:eaaa0984). However, its efficacy may be undermined by the heterogeneity of antigen expression in brain cancer cells and the tendency of the modified T cells to trigger adaptive immune resistance in the tumor microenvironment.

In the 10-person trial, Donald O'Rourke, MD, of the University of Pennsylvania in Philadelphia, and colleagues recruited patients whose glioblastoma expressed EGFR variant III (EGFRvIII), a constitutively activated truncated form of the protein that's found in around 30% of newly diagnosed glioblastoma cases. The researchers harvested the patients' T cells, transduced them with an anti-EGFRvIII CAR, and infused a single dose of the engineered immune cells into the patients upon disease progression.

Based on their prognoses, two or three patients lived longer than expected, O'Rourke says. However, gauging efficacy of the T-cell therapy in any rigorous fashion wasn't possible, because seven of the 10 trial participants underwent additional surgery within a few months of their infusions. That means any clinical responses could have been due to either intervention, or both.

Tissue removed during surgery provided a treasure trove of molecular information, revealing that expression of EGFRvIII declined significantly

from pretreatment levels in five of the seven patients who underwent surgery and that the engineered cells made up the bulk of the tumor-infiltrating T-cell population. "We are getting cells in, and we're getting a lot more cells than are normally there physiologically," O'Rourke says.

The study is first to show that a peripherally infused CAR T-cell therapy can cross the blood-brain barrier and infiltrate tumors. "That's exactly what we want to see," says Gary Archer, PhD, a tumor immunologist at Duke University in Durham, NC, where clinicians will soon treat patients newly diagnosed with glioblastoma with a different EGFRvIII-directed CAR T-cell construct. Other anti-EGFRvIII CAR T-cell trials are ongoing at the NIH Clinical Center in Bethesda, MD, and the Beijing Sanbo Brain Hospital in China.

Notably, none of the subjects in the trial experienced cytokine release syndrome, a toxicity seen in some patients treated with anti-CD19 CAR T cells. Nor did the therapy show signs of off-tumor cross-reactivity to wild-type EGFR. "It's good to see that the targeting of the tumor-specific antigen was safe," says Duke neurosurgeon John Sampson, MD, PhD.

However, the surrounding tumor microenvironment showed signs of inhibitory molecules and immunosuppressive regulatory T cells. In several tumor specimens, the researchers also documented spatial variation in EGFRvIII expression, with many cancer cells lacking the mutant antigen altogether—suggesting that combinations with other immunotherapies or multipronged CAR T cells will be needed to achieve meaningful benefit.

"What I would like to do next," says senior author Marcela Maus, MD, PhD, of Massachusetts General Hospital in Boston, "is take what we learned from this trial—particularly, the heterogeneity of antigen expression, the persistence of the cells, and the increase in adaptive resistance—and use preclinical models to tease out how we can improve the potency."

—Elie Dolgin ■

NOTED

The Senate passed a bill that reauthorizes the FDA to collect fees from drug companies and medical device manufacturers for the next 5 years, money that accounts for more than a quarter of the agency's budget. The funds are used to help speed up the review of new agents and devices. Already approved by the House, the legislation will be sent to President Donald Trump for his signature.

Bristol-Myers Squibb announced that **the FDA granted accelerated approval to nivolumab (Opdivo) for the treatment of certain patients with metastatic colorectal cancer**—specifically, patients age 12 and older with mismatch repair-deficient and microsatellite instability-high disease that has progressed following fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

The U.S. Court of Appeals for the Federal Circuit ruled that a patent on bortezomib (Velcade; Takeda) is valid until 2022, preventing the launch of lower-cost generic versions by Teva Pharmaceuticals and other competitors. A lower court had ruled in favor of the generic drug makers in 2015, saying that the compound covered by the patent was "the inherent result of an obvious process."

The Leukemia & Lymphoma Society announced the expansion of its Beat AML Master Trial, a precision medicine study launched last year to test investigational agents for the disease. Currently, four major pharmaceutical companies are providing the therapies, which are prescribed based on genetic markers.

The U.S. Preventive Services Task Force will continue to recommend against screening for ovarian cancer in asymptomatic women. The committee that developed the draft recommendation, available at www.uspreventiveservices-taskforce.org, found that screening does not reduce ovarian cancer deaths, and that it yields many false-positive results, which can lead to unnecessary surgery.

A nationwide survey of 1,000 adults commissioned by Research!America found that 86% of **Americans say that health care providers should discuss clinical trials with patients** diagnosed with a disease as part of their standard care.

For more news on cancer research, visit *Cancer Discovery* online at <http://cancerdiscovery.aacrjournals.org/content/early/by/section>.

CANCER DISCOVERY

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