also showed that it could be applicable to CD22-targeted CAR T-cell therapy.

“What’s really interesting is that they uncovered a gene transfer–related mechanism of relapse, which I don’t think has been seen before,” says Marcela Maus, MD, PhD, of Massachusetts General Hospital Cancer Center in Boston. Inadvertent CAR19 transduction aside, she notes, this single B cell likely possessed additional characteristics that enabled it to survive the therapy manufacturing process, because engineered T cells are typically quick to eliminate any leukemic cells in the patient-derived product.

Ruella agrees that “some combination of factors, possibly unique to this patient, triggered an exceptionally rare form of resistance.” In a retrospective analysis of data from 368 patients treated with tisagenlecleucel, the team found no other relapses driven by CD19 epitope masking. That said, “we thought it was worth alerting the scientific community to the fact that this could happen,” he says.

“It’s something to be on the lookout for with autologous CAR T-cell therapy,” Maus says, “and probably more specific to leukemia, among hematologic malignancies. With lymphoma or multiple myeloma, tumor cells usually aren’t found in large numbers in peripheral blood.”

Might the addition of a “kill switch” to the CAR19 construct have proven useful? “In hindsight, it does seem like we could have turned off that wave of CARB cells if a suicide gene had been incorporated,” Ruella observes. “But the data aren’t black-and-white on how completely such switches eliminate their target.”

No FDA-approved CAR T-cell therapies include kill switches; clinicians are figuring out other ways to manage potential toxicities, chiefly cytokine release syndrome. As such, “any proposed [CAR] construct modification would need careful evaluation, to not affect the remarkable clinical outcomes seen so far”—including with this patient, whose survival was ultimately extended with tisagenlecleucel, Ruella notes.

With CAR T-cell therapy being a young, evolving field, “we have a lot to learn, and this case suggests the need for further optimization of manufacturing protocols,” he adds. “There’s always room for improvement.” –Alissa Poh

Dacomitinib Approved, but Might Not Be Used

The FDA approved the EGFR inhibitor dacomitinib (Vizimpro; Pfizer) as a first-line therapy for patients with metastatic, EGFR-mutant non–small cell lung cancer (NSCLC). Clinicians, however, doubt that the drug will be used much in clinical practice, as it joins a crowded field of EGFR inhibitors that includes osimertinib (Tagrisso; AstraZeneca), the current standard of care. Instead, they are focused on the next wave of therapeutic options.

Dacomitinib was approved based on the results of the phase III ARCHER 1050 trial, in which patients treated with the drug had a median progression-free survival (PFS) of 14.7 months and a median overall survival of 34.1 months, compared with 9.2 months and 26.8 months, respectively, in patients who received the EGFR inhibitor gefitinib (Iressa; AstraZeneca) (Lancer Oncol 2017;18:1454–66; J Clin Oncol 2018;36:2244–50). Serious side effects, most commonly diarrhea, rash, and a skin condition called paronychia, affected 27% of patients.

In addition to gefitinib and osimertinib, the EGFR inhibitors erlotinib (Tarceva; Genentech and Astellas) and afatinib (Gilotrif; Boehringer Ingelheim Pharmaceuticals) are also approved as first-line therapies.

Lecia Sequist, MD, MPH, of Massachusetts General Hospital in Boston, MA, says that comparing dacomitinib to gefitinib made sense when the trial was designed. In the interim, however, osimertinib was approved and quickly became the new standard of care because it extended PFS and caused fewer side effects than gefitinib or erlotinib.

“More knowledge and more options are always important, but I’m not sure there’s going to be much uptake of dacomitinib in the front-line setting,” she says.

Benjamin Levy, MD, of Johns Hopkins University in Baltimore, MD, and Washington, DC, agrees, adding that a major benefit of osimertinib over dacomitinib is its toxicity profile: Osimertinib is generally well tolerated, whereas dacomitinib frequently causes diarrhea, acne, and rashes. Moreover, data from the phase III FLAURA trial suggests that osimertinib may be effective at treating brain metastases (J Clin Oncol 2018 Aug 28 [Epub ahead of print]).

“I still think that osimertinib remains the standard for first-line [therapy] based on toxicity, and based on its ability to elicit meaningful responses in patients with brain metastasis,” he says. Joshua Bauml, MD, of the Perelman School of Medicine at the University of Pennsylvania in Philadelphia, is interested in new therapeutic strategies to extend survival of patients who receive first-line osimertinib to address tumor heterogeneity and resistance.

“We have all these drugs, they’re highly active, but they are not cures. Patients will develop resistance, and they will unfortunately die from that,” he says. “What we need to really do is delve into the science and see how we can advance the care for these patients.”

Sequist and her colleagues recently established that acquired RET fusions drive resistance in some patients, and these patients may benefit from receiving osimertinib in combination with the RET inhibitor BLU-667 (Blueprint Medicines; Cancer Discov 2018 Sep 26 [Epub ahead of print]). Similarly, MET amplification can cause osimertinib resistance, but some research has shown that that can be countered with osimertinib plus the MET inhibitor savolitinib (AstraZeneca and Chi-Med). In addition, researchers are exploring the use of EGFR inhibitors with chemotherapy. Levy notes that there is also interest in testing combinations of immunotherapies, chemotherapy, and angiogenesis inhibitors.

“If you’re going to give osimertinib front line, the question really is, what do you do next and what are the most active therapies?” Levy says. –Catherine Caruso

Combining Biomarkers for Immunotherapy

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