Basket Study Yields Approval for Rare Cancer

In a regulatory first, the FDA expanded the indication for a targeted cancer therapy based only on the results of a basket study, a type of clinical trial design that tests drugs in a variety of cancer types with a specific mutation.

The new marketing authorization, announced on November 6, means that doctors can now prescribe vemurafenib (Zelboraf; Roche) for BRAF V600-mutant Erdheim–Chester disease (ECD), a rare blood disorder that has had no approved therapies.

“It’s an indication that the FDA is willing to entertain nontraditional datasets for approval if we can unequivocally demonstrate efficacy,” says David Hyman, MD, of Memorial Sloan Kettering Cancer Center in New York, NY, who co-led the VE-BASKET study upon which the approval was based (N Engl J Med. 2015;373:726–36).

In that phase II study, Hyman and his colleagues initially enrolled 122 patients with cancers of the lungs, colon, thyroid, blood, and other organ systems. All had tumors harboring the V600-mutant form of BRAF that’s targeted by vemurafenib, a drug approved in 2011 for advanced melanoma. The researchers then expanded enrollment in tumor types that showed the most promising signals of activity. One of these was ECD, a cancer characterized by excessive production of histiocytes, a type of white blood cell. More than half of all ECD cases are thought to carry the BRAF V600 mutation.

Hyman’s team ultimately recruited 22 patients with BRAF V600E-mutant ECD, one of whom had a complete response; 11 others experienced partial responses. However, “the response rate only tells part of the story here,” says Hyman. “Even in the so-called non-responders, we see what appears to be a dramatic departure from the natural history of the disease.”

Among 14 patients with ECD, including some defined by standard assessment criteria as having stable disease, PET scans showed that 11 had complete metabolic responses, whereas the other three had partial metabolic responses. Those results suggest the drug was working to some extent in practically everyone who received it, which helps explain why 2-year progression-free survival was 83%. It also indicates a durability of benefit that appears to surpass that seen in any other solid or hematologic malignancies.

The side effects documented in the trial were similar to those reported in patients with melanoma—joint pain, fatigue, rashes, hair loss, and skin tags among them.

Filip Janku, MD, PhD, of The University of Texas MD Anderson Cancer Center in Houston, TX, points out that the new approval for vemurafenib would have been difficult had the FDA insisted on data from a traditional clinical trial, because it’s challenging to run such trials for very rare cancers.

“It’s problematic for centers to open a study that actually enrolls so few patients or complete a study in a single center only,” he says. To date, Janku notes, there’s been only one ECD trial ever published, and it included just 10 participants recruited over 5.5 years (Blood 2015;126:1163–71). An ongoing trial at the NIH Clinical Center managed to enroll only six patients over 3 years—and even that required a “herculean effort,” Janku says.

The basket design provides a more realistic pathway to registration for rare cancers, notes Hyman. “We were able to incorporate this pivotal program into a broader effort,” he says. “There’s an economy of scale there that’s probably not achievable in a disease-specific context for such an orphan disease.”

—Elie Dolgin

JCAR015 in ALL: A Root-Cause Investigation

Last year, a study of Juno Therapeutics’ investigational CD19-targeting chimeric antigen receptor (CAR) T-cell therapy JCAR015 in adult patients with relapsed or refractory acute lymphoblastic leukemia (ALL) ground to a halt after five cases of fatal neurotoxicity occurred. The company probed possible reasons behind these deaths, and Chief Medical Officer Mark Gilbert, MD, presented a summary of their “root-cause investigation” during the Society for Immunotherapy of Cancer’s 2017 annual meeting in National Harbor, MD, in November.

The phase II ROCKET trial was placed on clinical hold by the FDA in July 2016, “when we first saw a shift in the rate and severity of cerebral edema,” Gilbert said. Three patients died, and Juno surmised that a protocol change—adding fludarabine to cyclophosphamide during lymphodepletion, which prepares
patients for CAR T-cell therapy—might have been to blame. Fludarabine was removed from the regimen, and the FDA allowed ROCKET to proceed. However, after two more deaths due to cerebral edema occurred, the company elected to shelve JCAR015.

One of the key findings from Juno’s retrospective analysis, Gilbert noted, was that all five patients who died experienced rapid, early expansion of their modified CAR-bearing T cells within a week of being infused, rather than the typical time frame of 12 to 14 days. High levels of the CD8+ subtype and, consequently, a sharp spike in cytokines such as IL2 and TNFα produced by these cytotoxic cells, were significantly correlated with fatal brain swelling, Gilbert added.

Autopsy results from two patients showed a complete breakdown of the blood–brain barrier, possibly due to this inflammatory cytokine surge, which—in line with findings from an unrelated study—may have driven their cerebral edema (Cancer Discov 2017;7:1404–19). “It wasn’t what I expected,” said ROCKET’s lead investigator Daniel DeAngelo, MD, PhD, of Dana-Farber Cancer Institute in Boston, MA. He had thought culprit would be CAR T cells or other immune cells infiltrating the brain.

Gilbert also reported that the patients who died were younger than 30 and had received fewer prior therapies. As well, they had higher baseline levels of IL15, another T-cell growth factor. Going on to look at ROCKET’s population as a whole, he noted that “those with Philadelphia chromosome–positive disease seemed to have a much better outcome with regard to the overall risk of neurotoxicity—an interesting signature we’re trying to confirm through a larger study.”

However, Gilbert cautioned that findings from Juno’s internal investigation shouldn’t be considered definitive, because “this wasn’t a planned analysis, but exploratory in nature.”

The company is moving ahead with additional CAR T-cell therapies, including evaluating JCAR017 in patients with relapsed or refractory non–Hodgkin lymphoma. Lessons learned from ROCKET have been duly applied: For instance, patients no longer receive infusions of a product with wide variability in its T-cell composition. Instead, JCAR017 consists of a fixed ratio of CD8+ cells as well as the CD4+ “helper” subtype. Its CAR construct also has 4-1BB, rather than CD28, as the costimulatory domain, which may better control the pace of cell proliferation. Eventually, Juno hopes to test this therapy in ALL, Gilbert said.

After JCAR015’s failure, the question was, ‘Should we even try CAR T-cell therapy in adult ALL?’” DeAngelo remarked. “The reality is that we saw a high, confirmed complete remission rate [47%]. We need to better control the product and also focus on patient characteristics that might predispose to neurotoxicity, but I still think this is the way to go.” —Alissa Poh

FDA Approves Second CAR T-cell Therapy

The FDA approved the chimeric antigen receptor (CAR) T-cell therapy axicabtagene ciloleucel (Yescarta; Kite Pharma) in late October, the second such treatment for blood cancers in the United States.

Axicabtagene ciloleucel is indicated for the treatment of adults with certain non–Hodgkin lymphomas, including diffuse large B-cell lymphoma, the most common form. Patients must have relapsed after, or not responded to, at least two other treatments before receiving axicabtagene ciloleucel. Treatment involves collecting and genetically modifying a patient’s T cells to express CARs so that they bind to and destroy CD19-expressing cancer cells and normal B cells.

The safety and efficacy of axicabtagene ciloleucel were established in a multicenter clinical trial of more than 100 adults with refractory or relapsed large B-cell lymphomas. The complete remission rate was 51%.

The first FDA-approved CAR T-cell therapy, tisagenlecleucel (Kymriah; Novartis), was approved in August. The two therapies work in much the same way, but they have different indications, with tisagenlecleucel approved to treat only acute lymphoblastic leukemia in patients age 25 or younger.

“These approvals represent a very important development in modern cancer treatment,” says Steven Rosenberg, MD, PhD, chief of the Surgery Branch at the NCI. “These treatments are very effective in patients with lymphomas and leukemias,” he notes, adding that the first case study of CAR T-cell therapy was published in 2010, and that that patient remains cancer-free. Rosenberg led the team that originally developed the therapy.

Axicabtagene ciloleucel carries boxed warnings for two potentially fatal side effects: neurologic toxicity and cytokine release syndrome (CRS), a flu-like systemic response to the proliferation of CAR T cells. In the phase II ZUMA-1 trial, CRS occurred in 94% of patients; 13% of patients experienced symptoms that required aggressive treatment or were considered life-threatening.

For this reason, axicabtagene ciloleucel’s use requires a risk evaluation and mitigation strategy. Sites administering the treatment must obtain special certification, including training on recognizing and managing side effects. Currently, 16 facilities are certified to dispense axicabtagene ciloleucel. Kite hopes to increase that number to 70 within the next 12 months.

The list price of axicabtagene ciloleucel is $373,000. However, the personalized nature of the treatment, the extensive monitoring program, and the relatively high response rate may justify the expense. “The best way to save clinical care dollars is to cure people rather than moving them from one...
CANCER DISCOVERY

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Cancer Discov 2018;8:4-5. Published OnlineFirst December 5, 2017.

Updated version

Access the most recent version of this article at:
doi:10.1158/2159-8290.CD-NB2017-169

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