Genetic Ca Therapies May Hinge on Validated Tests

BY KERRI WACHTER

GAITHERSBURG, MD. — Cancer therapies targeting specific genetic mutations could be required to have corresponding validated diagnostic tests before the therapies can gain approval in the United States, judging by the 7-1 vote of a Food and Drug Administration advisory committee.

The Oncologic Drugs Advisory Committee agreed with the agency that a validated test for the Bcr-Abl T3151 mutation is required before omacetaxine mepesuccinate (Omapro)—a drug targeting that mutation—can be considered for approval.

ChemGenex Pharmaceuticals, a company with offices in Australia and Menlo Park, Calif., is seeking approval of omacetaxine for the treatment of adults with chronic myeloid leukemia (CML) after failure on prior therapy with imatinib (Gleevec) and with the Bcr-Abl T3151 mutation.

ChemGenex announced later that it had received a complete response letter from the FDA, which did not ask for a new trial or data on additional patients. The company said that it hoped to meet with the FDA to address the issues raised by the advisory committee.

The vote is an important one in light of the growing number of therapies targeting specific genetic mutations. The question of related diagnostic tests will come up more frequently.

The vote is an important one in light of the growing number of therapies targeting specific genetic mutations. ODAC chair Dr. S. Gail Eckhardt noted that the indication for this drug is molecularly defined—failure on imatinib *and* the T3151 mutation—and that the question of related diagnostic tests will come up more frequently. Dr. Eckhardt is head of medical oncology at the University of Colorado in Denver.

The T3151 mutation is thought to be a marker of tyrosine kinase inhibitor resistance. Patients with the mutation do not respond to any of the three approved therapies for CML and have a poor prognosis. T3151 mutation testing is available at a number of laboratories but is not standardized among facilities.

Omacetaxine, a new molecular entity and first in a class of cephalotaxines, is a synthetic formulation of homoharringtonine, a drug isolated from the evergreen tree Cephalotaxus in China.

The application to the FDA was based on the response rates in a single-arm trial in 66 patients deemed to have the T3151 mutation. In the open-label phase II dosing study CML-202, patients were given subcutaneous omacetaxine 1.25 mg/m^2 for 14 days of a 28-day cycle. If there was a hematologic response, patients received subcutaneous omacetaxine 1.25 mg/m^2 twice daily for 7 days of a 28-day cycle.

Patients in chronic, accelerated, or myeloid blast phases of CML were included in the study.

Prior imatinib therapy had to have failed, and the T3151 mutation had to be identified and confirmed prior to study enrollment.

Study end points included major cytogenetic response or complete hematologic response for patients with chronic phase CML and overall hematologic response (complete hematologic response, no evidence of leukemia, return to chronic phase) for patients in the accelerated or blast phases.

The study included 40 patients in the chronic phase, 16 in the accelerated phase, and 10 in the blast phase.

All of the patients were determined to have the T3151 mutation, but only 43 had central laboratory confirmation of T3151 status, meaning that roughly a third of the patients failed to meet at least one of the study criteria.

Perhaps more importantly, 10 patients who were initially identified as having the T3151 mutation were later determined by the central laboratories not to have the mutation.

The agency's primary concern was the use of multiple assay methods for the detection of T3151 mutation without any bridging studies between the tests to assess reliability, reproducibility, and concordance of results.

"The lack of having a uniform in vitro diagnostic test creates uncertainty about patient selection both in this trial and, more importantly, in a post-approval setting," the agency wrote in its charge to the committee.

The majority of panel members expressed the same concerns.

The agency also expressed concern that the results of a small, single-arm incomplete efficacy trial were insufficient for approval, given uncertainty in response determination and duration, and uncertainty of the clinical meaningfulness of response rates.

Among patients in the chronic phase, 25% had a major cytogenetic response with 6-month duration, and 85% had a complete hematologic response with 10-month duration.

Among those in the accelerated phase, 37% had an overall hematologic response with a 7-month duration.

Among those in the blast phase, 30% had an overall hematologic response with a 2-month duration.

However, several committee members noted that the numbers of patients, particularly in the accelerated and blast groups, were too small for meaningful analysis. ■

Disclosures: *Members of FDA advisory panels have been cleared of potential conflicts of interest by the FDA prior to the meeting.*

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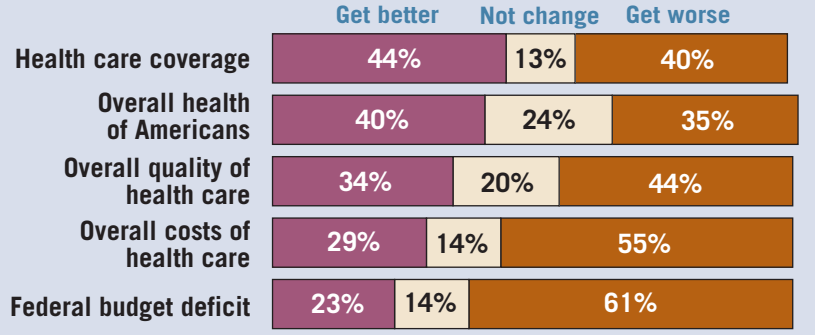

Notes: Based on a USA Today/Gallup poll of 1,033 adults conducted March 26-28. Don't know/refused responses not shown.

Source: Gallup Inc.