[News * Analysis * Commentary * Controversy]

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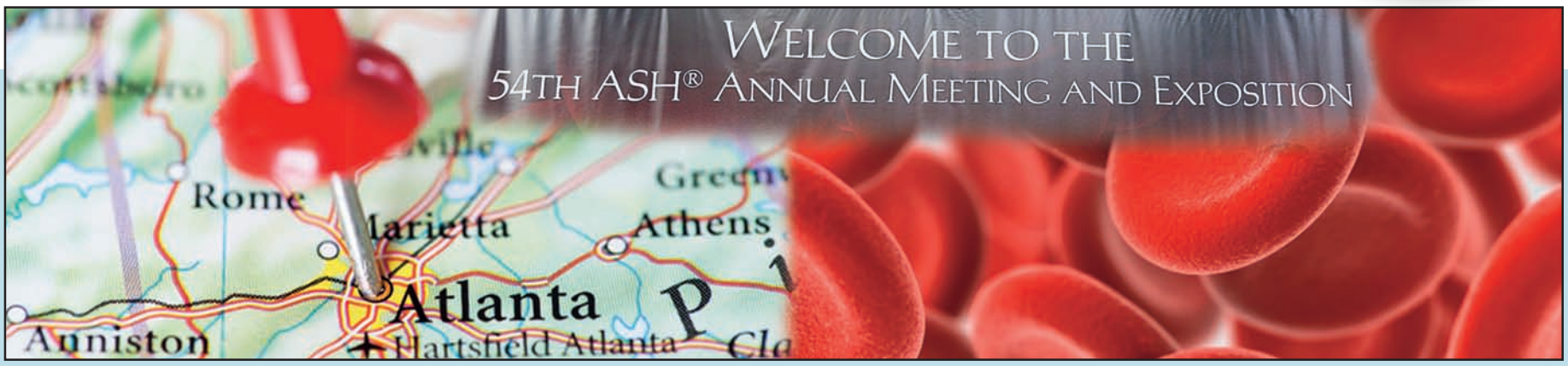

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PERIODICALS

[ALSO]

FDA Approves Iclusig for CML and Ph+ ALL

The U.S. Food and Drug Administration has approved the use of ponatinib (Iclusig, marketed by Ariad Pharmaceuticals) to treat adults with chronic myeloid leukemia and Philadelphia chromosome positive acute lymphoblastic leukemia. The drug—taken once a day—is used to treat patients with chronic, accelerated, and blast phases of the disease who are resistant to tyrosine kinase inhibitors by blocking proteins that help cancer cells develop. In CML, Iclusig targets cells with the TKI-resistant-T3151 mutation, which occurs in 10 to 15 percent of those patients and for whom no treatment options currently exist.

"The approval of Iclusig is important because it provides a treatment option to patients with CML who are not responding to other drugs, particularly those with the T315I mutation who have had few therapeutic options," Richard Pazdur, MD, Director of the FDA's Office of Hematology and Oncology Products, said in a news release. "Iclusig is the third drug approved to treat CML and the second drug approved to treat ALL [in 2012]."

The FDA approved Bosulif (bosutinib) (***OT, 10/10/12***) in September 2012 and Synribo (omacetaxine mepesuccinate) (***OT, 11/25/12***) in October 2012 to treat various phases of CML. Marqibo (vincristine sulfate liposome injection) (***OT, 9/10/12***) was approved in August 2012 to treat Philadelphia chromosome negative ALL.

Iclusig's approval came more than three months ahead of the product's prescription user fee goal date of March 27, 2013. Iclusig was reviewed under the FDA's priority review program, which provides for an expedited six-month review for drugs that may provide safe and effective therapy when no satisfactory alternative therapy exists, or offer significant improvement compared with marketed products.

Iclusig's safety and effectiveness were evaluated in a clinical trial of 449 patients with various phases of CML and Ph+ALL in which all patients were treated with the drug. The study showed:

- 54 percent of all patients and 70 percent of patients with the T315I mutation achieved a major cytogenetic response;
- 52 percent of patients with accelerated-phase CML experienced a major hematologic response for a median duration of 9.5 months;
- 31 percent of patients with blast-phase CML achieved major hematologic response for a median duration of 4.7 months; and
- 41 percent of patients with Ph+ ALL achieved a major hematologic response for a median duration of 3.2 months.

The label includes a Boxed Warning noting that the drug can cause blood clots and liver toxicity. The most common side effects reported during clinical trials include high blood pressure, rash, abdominal pain, fatigue, headache, dry skin, constipation, fever, joint pain, and nausea.

→SEKERES

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differentiation agent, arsenic trioxide (ATO), followed by post-remission therapy with ATO.

Both two-year event-free and overall survival were superior in patients randomized to the dual-differentiation agents (ATRA + ATO), at 97 percent vs. 87 percent (p = 0.03), and 99 percent vs. 91 percent (p = 0.03), respectively.

These results at the very least imply that it may be time to retire chemotherapy in patients with non-high risk APL.

Flat-out FLT3 Responses

The FLT3 story in AML has been maddening. A lesion is detected in up to one-third of AML patients that confers a terrible prognosis (particularly in the absence of an NPM1 mutation), yet is targetable. Attempts to treat patients who have the FLT3 internal tandem duplication abnormality have yielded reductions in blasts percentages when drugs have been given as monotherapy, and no clear response advantages when given in combination with cytotoxic regimens.

In an oral presentation by Cortes and colleagues from Philadelphia, Baltimore, Seattle, France, Germany, and the United Kingdom (***Abstract #48***), the investigators report on 134 patients with relapsed or refractory acute myeloid leukemia enrolled onto a phase 2 study of the FLT3 inhibitor quizartinib (AC220); 69 percent had FLT3 mutations, and the patients' median age was 70 years. The composite complete remission rate for FLT3-positive patients (which included complete remission [CR], CR with incomplete platelet recovery, and CR with incomplete hematologic recovery) was 54 percent, of whom almost all had a complete remission with incomplete hematologic recovery.

This was accompanied by a response duration of 12.7 weeks. Among the entire population, eight percent of patients went on to receive a hematopoietic stem cell transplantation. Another phase 2 study of quizartnib presented by Levis and colleagues reported on 137 relapsed or refractory AML patients (***Abstract #673***). The composite CR rate for FLT3+ patients was 44 percent, and for FLT3- patients, was 34 percent—again, almost entirely comprised of CR with incomplete hematologic recovery.

> "We need to come to some consensus over whether altering the definition of CR is appropriate in AML."

So, we aren't quite there yet with these drugs as monotherapy, and we need to come to some consensus over whether altering the definition of CR is appropriate in AML. What is encouraging is that this type of response rate may be "good enough" to transition patients topotentially curative therapy—and that will have an impact in a desperate population.

More 'Second Thoughts'!

Check out all the previous articles in Mikkael Sekeres' award-winning column in this collection on the *OT* website: **http://bit.ly/OT-SekeresCollection**