HEM/ONC News

By Stacey Small

Crizotinib Approved for Use in ALK-Positive Locally Advanced and Metastatic NSCLC

On August 26, the US Food and Drug Administration (FDA) announced its approval of crizotinib (Xalkori, Pfizer), a kinase inhibitor, for the treatment of locally advanced and metastatic non–small-cell lung cancers (NSCLC) that express an abnormal anaplastic lymphoma kinase (ALK) gene. A diagnostic test for the ALK gene abnormality, the Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc.), was approved concurrently. Approval of crizotinib was based on combined results from 2 single-arm trials: PROFILE 1005 (Phase II, Open-Label Single Arm Study of the Efficacy and Safety of PF-02341066 in Patients With Non-Small Cell Lung Cancer Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase Gene; 136 patients) and a part 2 expansion cohort of a phase I study, known as Study 1001 (119 patients). The primary endpoint was objective response rate (ORR). A total of 255 patients with locally advanced or metastatic ALK-positive NSCLC received 250 mg of crizotinib twice daily. The ORR was 50% in PROFILE 1005 and 61% in Study 1001. The median response duration for PROFILE 1005 and Study 1001 was 42 weeks and 48 weeks, respectively. Common adverse events included vision disorders, nausea, diarrhea, vomiting, edema, and constipation. Grade 3/4 events that occurred in at least 4% of patients were increased alanine transaminase and neutropenia. Severe, life-threatening, or fatal treatment-related pneumonitis has been reported with a frequency of 1.6% in crizotinib clinical trials.

Bendamustine Plus Rituximab Is Effective in the Relapsed/Refractory CLL Setting

In a phase II trial of the German Chronic Lymphocytic Leukemia Study Group, Fischer and associates evaluated the safety and efficacy of bendamustine (Treanda, Cephalon) in combination with rituximab (Rituxan, Genentech/Idec Pharmaceuticals) in patients with relapsed or refractory chronic lymphocytic leukemia (CLL). The study was published in the August 15 online edition of the *Journal of Clinical Oncology*. A total of 83 patients were enrolled, with at least 1 dose of treatment administered in 78 patients. Patients had received a median of 2 prior therapies; 22 patients were refractory to fludarabine. Many patients had unfavorable genetic markers, such as a deletion of chromosome 17p13 (17.9%), del(11q) (20.5%), and unmutated *IGHV* (65.4%). Early treatment discontinuation occurred in 34 patients; 15 patients stopped treatment due to toxicity. The overall response rate was 59%. Complete response, partial response, and nodular partial response were achieved in 9%, 47.4%, and 2.6% of patients, respectively. The overall response rate was 45.5% for fludarabine-refractory patients and 60.5% for fludarabine-sensitive patients. A response to treatment was observed in 92.3% of patients with del(11q), 100% of patients with trisomy 12, 7.1% of patients with del(17p), and 58.7% of patients with unmutated *IGHV*. At a median follow-up of 24 months, the median event-free survival was 14.7 months, the median progression-free survival was 15.2 months, and the median overall survival was 33.9 months. Among responders, the median duration of response was 15.2 months. There were 28 deaths, 3 of which were due to treatment-related infections. Adverse events of at least grade 3, including hematologic toxicities and infections, occurred in 46 patients (59%).

Vemurafenib Approved for Use in Advanced Melanomas With the BRAF V600E mutation

Vemurafenib (Zelboraf, Plexxikon/Roche), which targets the *BRAF* V600E mutation, received FDA approval on August 17 for the first-line treatment of metastatic and unresectable melanomas. The cobas 4800 *BRAF* V600 Mutation Test (Roche Molecular Systems, Inc.) was approved as a companion diagnostic test. Approval of vemurafenib was based on the randomized, open-label, phase III BRIM-3 (*BRAF* Inhibitor in Melanoma) study. Preliminary results were reported in the June 30 issue of the *New England Journal of Medicine* by Chapman and colleagues. The study screened 2,107 patients with unresectable stage III or IV melanoma and identified the *BRAF* mutation in 47%. From January 2010 through December 2010, 675 patients were accrued. (Not all patients were included in the analysis, however, because the trial was stopped—based on early positive results—before they had been enrolled for a sufficient time.) Patients were randomized to 960 mg of vemurafenib orally twice daily or 1,000 mg/m^2 of dacarbazine intravenously every 3 weeks. Vemurafenib patients had a relative reduction of 63% in the risk of death and a 74% reduction in the risk of disease progression or death compared with patients receiving dacarbazine (hazard ratio, 0.26; P<.001). The median time to progression was 5.3 months in the vemurafenib group, compared with 1.6 months in the dacarbazine group. At 6 months, the estimated overall survival was 84% (95% confidence interval [CI], 78–89) in the vemurafenib group and 64% (95% CI, 56–73) in the dacarbazine group. Less than 10% of patients who received vemurafenib experienced toxicities such as skin rashes, photosensitivity, and joint pain of grade 3 or higher.