HEM/ONC News

By Stacey Small

Accelerated Approval of Carfilzomib for Patients With Refractory Multiple Myeloma

On July 20, 2012, the US Food and Drug Administration (FDA) granted accelerated approval of carfilzomib (Kyprolis, Onyx Pharmaceuticals) for the treatment of patients with multiple myeloma who have received at least 2 prior therapies, including bortezomib (Velcade, Millennium Pharmaceuticals) and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completing their last therapy. The new drug application for carfilzomib was based primarily on a study published in the July 25 online issue of *Blood* by Siegel and associates. In this open-label, single-arm phase IIb study (PX-171-003-A1), 266 multiple myeloma patients who had received a median of 5 prior anti-myeloma regimens were enrolled. Using the International Myeloma Working Group (IMWG) criteria, an Independent Review Committee determined overall response rate (ORR), the primary efficacy endpoint. The ORR was 23.7%, with a median response duration of 7.8 months. The median overall survival was 15.6 months. The duration of clinical benefit, including in patients with minimal response, was 8.3 months. Adverse events were clinically manageable, with no new, unexpected, or cumulative toxicities. Enrollment is complete for the confirmatory phase III study, known as ASPIRE (Carfilzomib, Lenalidomide, and Dexamethasone versus Lenalidomide and Dexamethasone for the Treatment of Patients With Relapsed Multiple Myeloma). This trial is evaluating carfilzomib in combination with lenalidomide (Revlimid, Celgene) and low-dose dexamethasone versus lenalidomide and low-dose dexamethasone alone, in patients with relapsed multiple myeloma following 1–3 prior treatment regimens. The primary endpoint is progression-free survival (PFS). Secondary endpoints include overall survival, ORR, duration of response, disease control rate, safety, time-to-progression, and time-to-next treatment. Patients were randomized to receive carfilzomib (20 mg/m^2 on days 1 and 2 of cycle 1 only, then 27 mg/m^2 thereafter) in addition to a standard dosing schedule of lenalidomide (25 mg daily for 21-days-on, 7-days-off) and low-dose dexamethasone (40 mg per week in 4-week cycles), versus lenalidomide and low-dose dexamethasone alone.

Treatment With Everolimus Expanded to Include Patients With Advanced Breast Cancer

The indication of everolimus (Afinitor, Novartis) was expanded by the FDA on July 20, 2012 to include the treatment of postmenopausal women with advanced hormone receptor (HR)-positive, human epidermal growth factor receptor-2 (HER2)-negative breast cancer. Everolimus is indicated in combination with exemestane (Aromasin, Pfizer) after failure with letrozole (Femara, Novartis) or anastrozole (Arimidex, AstraZeneca). The expanded approval was based on data from the phase III BOLERO-2 trial (Breast Cancer Trials of Oral Everolimus-2), which randomized 724 postmenopausal patients with advanced HR-positive breast cancer who had recurrence or progression following prior therapy with letrozole or anastrozole to receive either everolimus plus exemestane or exemestane plus placebo (control group). The primary endpoint was median PFS. Treatment with everolimus plus exemestane more than doubled median PFS to 7.8 months, compared to 3.2 months with exemestane alone. Further analysis by an independent central radiology review revealed that everolimus plus exemestane extended median PFS to 11 months compared to 4.1 months with exemestane alone. For patients receiving combination treatment with everolimus plus exemestane, the objective response rate was 12.6%, compared with 1.7% in the control group. There were 3 complete responses (0.6%) and 58 partial responses (12%) in the combination treatment group, compared with no complete responses and 4 partial responses (1.7%) in the control group. Overall survival data were not yet mature at the time of the interim analysis, and no statistically significant difference in overall survival was noted between the 2 treatment arms. Stomatitis, infections, rash, fatigue, diarrhea, and decreased appetite were among the most common adverse events in patients treated with everolimus. Everolimus is the first mammalian target of rapamycin (mTOR) inhibitor approved for advanced HR-positive breast cancer. Several analyses of the BOLERO-2 trial, including updated efficacy results, health-related quality of life, effects in Asian populations, and safety in women over 65 years of age, were presented at the 2012 Annual Meeting of the American Society of Clinical Oncology (ASCO) in June.