HEM/ONC News

By Stacey Small

Benefits of Zoledronic Acid in Early-Stage Breast Cancer Maintained: 62-Month Follow-Up of the ABCSG-12 Trial

Results from a 62-month follow-up of the ABCSG-12 (Austrian Breast and Colorectal Cancer Study Group trial-12) study showed that the addition of zoledronic acid improved disease-free survival (DFS) in patients who received anastrozole or tamoxifen. Gnant and associates evaluated the efficacy and safety of anastrozole (1 mg per day) or tamoxifen (20 mg per day) with or without zoledronic acid (4 mg every 6 months) for 3 years in premenopausal women with endocrine-receptor-positive, stage I–II breast cancer who were receiving goserelin (3.6 mg every 28 days). Results were reported in the July issue of *The Lancet Oncology*. A total of 1,803 patients were randomized on a 1:1:1:1 ratio based on the Pocock and Simon minimization method in order to balance the 4 treatment arms across 8 prognostic variables (age, neoadjuvant chemotherapy, pathologic tumor stage, lymph node involvement, type of surgery or locoregional therapy, complete axillary dissection, intraoperative radiation therapy, and geographic region). The primary endpoint was DFS, defined as disease recurrence or death. There were 186 DFS events reported (53 events in 450 patients on tamoxifen alone, 57 events in 453 patients on anastrozole alone, 36 events in 450 patients on tamoxifen plus zoledronic acid, and 40 events in 450 patients on anastrozole plus zoledronic acid) after a median follow-up of 62 months (range, 0–114.4 months). The overall risk of DFS events was reduced with zoledronic acid (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.51–0.91; *P*=.009). However, the difference was not significant in the tamoxifen arm (HR, .67; 95% CI, 0.44–1.03; *P*=.067) or the anastrozole arm (HR, 0.68; 95% CI, 0.45–1.02; *P*=.061), which were separately assessed. The risk of death was not significantly affected by zoledronic acid (30 deaths with zoledronic acid vs 43 deaths without; HR, 0.67; 95% CI, 0.41–1.07; *P*=.09). Although there was no difference in DFS between patients receiving tamoxifen alone versus anastrozole alone (HR, 1.08; 95% CI, 0.81–1.44; *P*=.591), treatment with anastrozole produced an inferior overall survival than did treatment with tamoxifen (46 vs 27 deaths; HR, 1.75; 95% CI, 1.08–2.83; *P*=.02). There were no observations of renal failure or osteonecrosis of the jaw, and treatments were well tolerated in general. Reports of adverse events included bone pain in 601 patients (33%; 349 patients who received zoledronic acid vs 252 who did not receive the drug); fatigue in 361 patients (20%; 192 vs 169, respectively), headache in 280 patients (16%; 147 vs 133, respectively), and arthralgia in 266 patients (15%; 145 vs 121, respectively). These data demonstrate the benefits of zoledronic acid in premenopausal patients with early-stage breast cancer and support its addition to adjuvant endocrine therapy.

Predictive Biomarkers for Determining Best Response to Cetuximab: A Retrospective Analysis of FLEX Study Data

A follow-up analysis to the FLEX (Cetuximab Plus Chemotherapy in Patients with Non–Small Cell Lung Cancer) study, which showed a benefit from the addition of cetuximab (Erbitux, ImClone) to platinum-based therapy, was conducted in order to determine whether efficacy of chemotherapy plus cetuximab in this setting could be predicted by candidate biomarkers. Results of the study were presented in July by Pirker and colleagues at the 14th World Conference on Lung Cancer (WCLC), held in Amsterdam. Formalin-fixed paraffin-embedded (FFPE) tumor tissue of patients from the FLEX study were used to extract genomic DNA, which was screened for KRAS codon 12 and 13 and epidermal growth factor receptor (EGFR) kinase domain mutations, with polymerase chain reaction (PCR)-based assays. Tumor EGFR expression was assessed prospectively with immunohistochemistry in 1,121 patients. The researchers then determined a cut-off point (200 or more on a scale of 0–300) for high EGFR expression, which was determined retrospectively according to response rates. In their review of the FLEX data, the researchers found that 345 patients (31%) had tumors with a score of at least 200, the cut-off selected for a high level of EGFR expression, and the other 776 patients (69%) had a low score of less than 200. Patients with high EGFR expression fared better on cetuximab plus chemotherapy than on chemotherapy alone, regardless of histology. The median overall survival in this high-expression group treated with cetuximab plus chemotherapy was 12 months, compared with 9.6 months for patients treated with chemotherapy alone (HR, 0.73; *P*=.011). One-year survival was higher in the combina-

tion group than in the chemotherapy group (50% vs 37%), as was 2-year survival (24% vs 15%). In the 776 patients with lower EGFR expression, the addition of cetuximab produced no survival changes compared with patients who received the control treatment regimen. Cetuximab's enhanced efficacy in high EGFR expressors occurred in both the 135 patients with an adenocarcinoma and in the 144 patients with a squamous cell carcinoma. Cetuximab also had significantly better performance measures by tumor response rate in those with high EGFR expression, with a two-fold higher response rate with cetuximab compared with controls (*P*=.002), There was a statistically significant 22% drop in time-to-treatment-failure (*P*=.026) with cetuximab compared with controls. Duration of PFS was not significantly improved in high expressors. No increased rate of safety issues occurred in the high expressors who received cetuximab, including no increased rate of skin or subcutaneous disorders.

Accelerated Approval of Vincristine Sought for Use in Adult Philadelphia Chromosome–Negative Acute Lymphoblastic Leukemia Patients

A new drug application has been filed with the US Food and Drug Administration (FDA) for vincristine sulfate liposomes injection (Marqibo, Talon Therapeutics); its accelerated approval is sought for the treatment of adult Philadelphia chromosome–negative acute lymphoblastic leukemia (ALL) patients. At present, there are no standard regimens in this poor-prognosis patient population, and currently available third-line, single-agent therapies are highly toxic and induce responses in only 4% of patients or less. Results from the pivotal phase II, multinational RALLY (Safety and Efficacy of Marqibo in Relapsed Acute Lymphoblastic Leukemia) trial showed compelling evidence of single-agent, anti-leukemic activity in advanced, heavily pretreated, adult ALL patients in second or greater relapse or those who had progressed after at least 2 lines of antileukemia therapy. Patients received vincristine sulfate liposomes injection weekly at a dose of 2.25 mg/m^2 (without dose cap). There was a 35.4% overall response rate (ORR); a complete response (CR) or CR with incomplete blood count recovery (CRi) occurred in 20% of patients. There were no unexpected toxicities, and side effects were considered predictable and manageable. Results of the RALLY trial were presented by O'Brien and coworkers at the 2010 meeting of the American Society of Clinical Oncology.

Panel Votes for Brentuximab's Accelerated Approval in the Treatment of Lymphomas

On July 14, the FDA's Oncologic Drugs Advisory Committee voted for the accelerated approval of brentuximab vedotin for treatment of patients with Hodgkin lymphoma that has relapsed after autologous stem cell transplant and for patients with relapsed or refractory systemic anaplastic large-cell lymphoma (ALCL). Both of these patient groups have lymphomas that express the CD30 antigen. The push for approval is based on results from 2 similar studies presented at the 2010 meeting of the American Society of Hematology. The Hodgkin lymphoma study SG035-0003 was a phase II, single-arm trial, where 102 patients (median age, 31 years) with relapsed or refractory progressive Hodgkin lymphoma and prior autologous stem cell transplant received a median of 9 cycles of brentuximab. There was a 75% ORR, with a 6.7-month median duration. There was a 34% CR rate, with a median duration of 20.5 months. A partial remission was achieved in 40% of patients. The most commonly reported treatment-related adverse event was peripheral neuropathy, which occurred in 47% of patients. A larger, randomized, double-blind phase III study is being conducted in order to confirm these results. The FDA is due to make a decision regarding the approval of brentuximab by August 30. The committee's approval vote was also supported by data gathered from a nearly identical single-arm study of brentuximab in 58 patients with relapsed or refractory systemic ALCL, known as SG035-0004. The ORR in this study was 86%, with a median duration of 12.6 months. A CR was seen in 57% of patients, with a 13.2-month median duration; 29% of patients experienced a partial remission. The median PFS was 13 months. Similar to the Hodgkin lymphoma study, peripheral neuropathy was the most common treatment-related adverse event, which occurred in 48% of patients. If approved, Seattle Genetics plans to market brentuximab vedotin as Adcetris.

Germline Mutations Identified in 3 Genes Are Linked to Barrett's Esophagus and Esophageal Adenocarcinoma

Orloff and coworkers conducted a study in order to identify risk alleles or mutated genes associated with Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC) predisposition. Results of the study were published in the July 27 issue of *JAMA*. A series of genetic studies were performed over the course of 5

years; included in these analyses were 21 concordantly affected sibling pairs with BE/EAC and 11 discordant sibling pairs, and data from 176 white patients with BE/EAC and 200 ancestry-matched controls. Data from 19 BE/EAC tissues yielded 12 candidate genes that were considered a priority for mutation analysis. Genes that showed mutations in cases but not in controls were further screened in 58 cases. Three major genes—macrophage scavenger receptor 1 (MSR1), activating signal cointegrator 1 complex subunit 1 (ASCC1), and collagen triple-helix repeat-containing 1 (CTHRC1)—were associated with BE/EAC (P<.001 for each gene). There were 13 patients (11.2%) with BE/EAC who carried germline mutations in *MSR1*, *ASCC1*, or *CTHRC1*; the most frequently mutated gene was *MSR1*, with 8 of 116 (proportion, .069; 95% CI, 0.030–0.130; P<.001) cases with c.877C>T (p.R293X). Germline *MSR1* mutations were also found in 2 of 58 cases in an independent validation series (proportion, 0.035; 95% CI, 0.004–0.120; P=.09). Cyclin D1 (CCND1) upregulation in peripheral-protein lysate was found to be the result of *MSR1* mutation; increased nuclear expression of CCND1 was shown in immunohistochemistry of BE tissues in *MSR1* mutation carriers. The researchers stated that larger studies are needed to explore the risks associated with these mutations.