By Stacey Small

Survival Benefits of Platinum-Based Doublet Chemotherapy in Elderly Patients With NSCLC

In a multicenter, open-label, randomized phase III trial, Quoix and colleagues compared a carboplatin and paclitaxel doublet chemotherapy regimen with monotherapy in elderly patients with advanced non–small-cell lung cancer (NSCLC). A total of 451 patients between ages 70 and 89 years with locally advanced or metastatic NSCLC and World Health Organization performance status scores of 0–2 were enrolled. There were 226 patients who received 5 cycles (2 weeks on treatment, 1 week off treatment) of vinorelbine or gemcitabine monotherapy. Doublet chemotherapy, consisting of 4 cycles (3 weeks on treatment, 1 week off treatment) of carboplatin (on day 1) plus paclitaxel (on days 1, 8, and 15) was administered in 225 patients. The median overall survival was 10.3 months among patients treated with combination chemotherapy and 6.2 months among patients treated with monotherapy (hazard ratio [HR] 0.64; 95% confidence interval [CI], 0.52–0.78; $P<.0001$). The 1-year survival was 44.5% (95% CI, 37.9–50.9%) in the doublet chemotherapy arm and 25.4% (95% CI, 19.9–31.3%) in the monotherapy arm. Toxicities occurred more frequently in the doublet chemotherapy arm versus the monotherapy arm, including decreased neutrophil count (48.4% vs 12.4%, respectively) and asthenia (10.3% vs 5.8%, respectively). The study was published in the September issue of *The Lancet*. Despite the increased toxicities of platinum-based doublet chemotherapy, the results suggest that elderly patients with advanced NSCLC can be considered for the same aggressive therapy as younger patients; additional research is warranted.

CHEK2 Mutations and Family History in Predicting Risk of Breast Cancer

In order to investigate the relationships among *CHEK2* mutations, family history of breast cancer, and the risk of breast cancer, Cybulksi and associates conducted a prospective study that included 7,494 BRCA1 mutation–negative patients with breast cancer and 4,346 control women. Family history of breast cancer in first-degree and second-degree relatives was considered. Study participants were genotyped for 4 founder mutations in *CHEK2*. A total of 227 patients with breast cancer (3%) and 37 controls (0.8%) had a truncating *CHEK2* mutation (odds ratio [OR], 3.6; 95% CI, 2.6–5.1). Women who had a first- or second-degree relative with breast cancer had a higher OR (OR, 5.0; 95% CI, 3.3–7.6) than those with no family history of the disease (OR, 3.3; 95% CI, 2.3–4.7). The OR was 7.3 (95% CI, 3.2–16.8) if both a first- and second-degree relative had breast cancer. Assuming a 6% baseline risk of breast cancer (the general population risk in Poland), the lifetime risk of breast cancer for a woman with a *CHEK2* mutation was estimated to be 20% if there was no family history of breast cancer, 28% if a second-degree relative had breast cancer, 34% if a first-degree relative had breast cancer, and 44% if both a first- and second-degree relative had breast cancer. The study was published in the August 29 online issue of the *Journal of Clinical Oncology*. Although gene mutations and baseline risks of breast cancer differ across countries, these results suggest that *CHEK2* gene mutations do contribute to some cases of breast cancer, and that risk may be particularly high for women who have both a *CHEK2* gene mutation and a family history of the disease.

Overall Survival Significantly Increased With Radium-223 Chloride in Castration-Resistant Prostate Cancer

Results of the preplanned interim analysis of the ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer) trial were presented in September at the European Multidisciplinary Cancer Congress in Stockholm, Sweden (Abstract 1LBA). The trial was an international, randomized, double-blind, placebo-controlled, phase III study of radium-223 chloride (Alpharadin, Bayer HealthCare Pharmaceuticals) plus best standard of care compared with a placebo plus best standard of care in men with metastatic, castration-resistant prostate cancer (mCRPC). A total of 922 enrolled patients who had either failed prior docetaxel-based chemotherapy or were not eligible to be treated with docetaxel-based chemotherapy received up to 6 intravenous treatments with radium-223 chloride or placebo, with a 4-week period between each treatment. Results of the preplanned interim analysis were strong enough to prematurely stop the trial. The study met its primary endpoint of overall survival; radium-223 improved overall survival by 44% compared to placebo (median of 14 months vs 11.2 months, respectively; HR, 0.695; $P=.00185$). The time to first skeletal-related event significantly improved from 8.4

months with placebo to 13.6 months with radium-223 (HR, 0.61; *P*=.00046). Levels of total alkaline phosphatase (ALP) were normalized in 33% of men treated with radium-223 versus 1% of men who received a placebo. Treatment with radium-223 improved time to prostate-specific antigen (PSA) progression by 49% compared to placebo (HR, 0.671; *P*=.00015). Radium-223 chloride is not yet approved in the United States or Europe, but it was granted fast track designation by the US Food and Drug Administration (FDA) in August 2011.

SF3B1 Gene Mutations in Patients With Myelodysplastic Syndromes Linked to Better Overall Survival

Mutations of the *SF3B1* gene were found in a significant proportion of patients with myelodysplastic syndromes (MDS), according to a presentation by Papaemmanuil and associates at the 2011 European Multidisciplinary Cancer Congress. There was also a relationship between the gene mutation and ring sideroblasts in bone marrow, which makes *SF3B1* the first gene to be closely associated with a particular feature of MDS. Targeted sequencing of *SF3B1* was conducted in 2,087 samples (from blood, bone marrow, or primary tumor cells) from patients with a variety of myeloid and other common cancers. Somatic mutations of *SF3B1* were present in 20.3% of MDS patients, 5.3% of patients with AML, and 2.9% of patients with myeloproliferative neoplasms. In patients with MDS whose disease was defined by the presence of ring sideroblasts, 64.6% of them had the *SF3B1* mutation. Researchers also found that the gene mutation was present in 1–5% of patients with other common cancers, such as breast cancer, multiple myeloma, and kidney cancer. Available data for 123 patients with MDS showed that 34 of them had the *SF3B1* mutation. Compared to those without the mutation, these patients had a milder form of MDS and significantly better overall survival, and they were less likely to survive without their MDS developing into leukemia. Due to the fact that mutations in the *SF3B1* gene tended to be correlated with a better prognosis, the findings suggest the possibility of screening patients for the mutation and then adjusting treatment strategies accordingly.

Preoperative Chemotherapy Plus Radiation Improves Survival in Rectal Cancer: 3-Year Follow-Up

Chances of survival increased to 88% in rectal cancer patients who were treated with capecitabine in combination with 5 weeks of radiation before surgery, according to 3-year follow-up data from the ACCORD (Action Clinique Coordonnées en Cancérologie Digestive) 12/0405-PRODIGE 2 trial. Gerard and colleagues presented the 3-year follow-up data on October 3 at the annual meeting of the American Society for Radiation Oncology (ASTRO). A total of 598 patients with locally advanced rectal cancer were randomly assigned to receive either Cap45 (capecitabine and radiation at 45 Gy) or Capox50 (capecitabine and oxaliplatin plus radiation at 50 Gy). Compared to the Cap45 treatment regimen, patients who were treated with the Capox50 regimen did not have significantly increased chances of the cancer returning, nor did they have a significant increase in the chance of survival at 3 years after treatment. Adverse events were greatly increased in the Capox50 arm due to oxaliplatin, which also failed to increase the likelihood of local tumor sterilization. When the radiation dose was increased from 45 Gy to 50 Gy in 5 weeks, it was effective, well tolerated, and did not extend the duration of treatment. The study investigators found that preoperative treatment with capecitabine and 5 weeks of radiation at 50 Gy (Cap50 regimen) was safe and reduced the chances of cancer returning to 5% or less.