

## Phase III Study Compares Efficacy of Azacitidine with That of Conventional Care Regimens in the Treatment of Higher-Risk Myelodysplastic Syndromes

A phase III international, multicenter, controlled, parallel group, open-label trial, conducted by Fenaux and colleagues and reported in the March 1 issue of *Lancet Oncology*, found that treatment with azacitidine (Vidaza, Celgene) increases overall survival in patients with higher-risk myelodysplastic syndromes relative to conventional care. The study randomized patients (with a block size of 4) 1-to-1 to receive azacitidine (75 mg/m<sup>2</sup>/day x 7 days every 28 days) or conventional care (best supportive care, low-dose cytarabine, or intensive chemotherapy as selected by investigators). Patients were stratified by the French/American/British and international prognostic scoring system classifications. The study's primary endpoint was overall survival, and efficacy analyses were performed on the intent-to-treat population (ITT). Between February 13, 2004 and August 7, 2006, 358 patients were randomized to received azacitidine (n=179) or conventional care (n=179). Eighteen patients (4 in the azacitidine group, 14 in the conventional care group) did not receive study drugs, but were included in the ITT analysis. Median overall survival was 24.5 months for the azacitidine group and 15.0 months for the conventional care group after a median follow-up of 21.1 months (hazard ratio [HR]=0.58; 95% confidence interval [CI], 0.43–0.77; stratified log rank *P*=.0001). At the last follow-up, 82 patients in the azacitidine group and 113 patients in the conventional care group died. Based on Kaplan-Meier estimates, at 2 years, 50.8% (95% CI, 42.1–58.8) of patients in the azacitidine group were alive compared to 26.2% (95% CI, 18.7–34.3) of patients in the conventional care group (*P*<.0001). Safety findings showed that the most common grade 3/4 adverse events were peripheral cytopenias.

## Phase III trial of Sutent in Pancreatic Cancer Terminated Early Due to Positive Results

On March 12, Pfizer terminated a phase III trial for sunitinib (Sutent), SUN 1111, after the data safety monitoring board claimed that the drug showed significant benefit in a rare form of pancreatic cancer known as pancreatic islet cell tumor. The current treatment options

for patients with this cancer are palliative and of limited activity, and the sunitinib trial is one of the first phase III studies to show efficacy. The study, which was started in March 2007, compared sunitinib to best supportive care, with a planned enrollment of 340 patients and an estimated end date of March 2011. There was clear evidence that sunitinib significantly prolonged progression-free survival compared to best supportive care. The study was commenced based on earlier results from a phase II study, in which 68% of patients with advanced pancreatic endocrine tumors had stable disease after treatment. Forty-one patients began at least 5 cycles of treatment (approximately 6 months). The median time to progression among the 66 patients in the phase II study was 7.7 months, the 1-year survival rate was 81.1%, and the overall objective response rate was 16.7%. The problem with localized therapies for this rare cancer is that only the tumors that are reached with a catheter or probe can be treated. However, a systemic therapy such as sunitinib may be able to reach all affected tissue. Pfizer will be discussing its filing options with the FDA, but in the meantime it plans to report data at an upcoming meeting.

## Thalidomide Improves Myeloma Survival After Stem Cell Transplant

According to a report in the March 9 issue of *Journal of Clinical Oncology* by Dr. Andrew Spencer and colleagues from the Alfred Hospital in Melbourne, Australia, consolidating low-dose thalidomide (Thalomid, Celgene) and prednisolone can improve survival in patients with multiple myeloma who have undergone autologous stem cell transplantation (ASCT). The addition of thalidomide to the treatment regimen increased the 3-year progression-free survival by almost 20% (from 23% to 42%; *P*<.001). The researchers analyzed 269 patients who received high-dose melphalan conditioned ASCT and who were randomized to receive prednisolone maintenance therapy alone or in combination with 12 months of thalidomide consolidation. The investigators who assessed the survival of these patients also found an increase in overall survival at 3 years in the thalidomide group compared to the control group (86% vs 75%; *P*=.004). In patients who experienced a relapse, there was no evidence that prior thalidomide treatment decreased the efficacy of salvage therapy. In regard to safety, neurologic adverse events

(Continued on page 221)

were more frequent in patients receiving thalidomide; there was no difference in thromboembolic event rates between treatment groups. Based on the study findings, the researchers recommend that 12 months of thalidomide consolidation in combination with prednisolone maintenance therapy be offered to patients with multiple myeloma undergoing initial single high-dose melphalan conditioned ASCT as part of first-line therapy, regardless of ASCT response.

### **Scientists Identify Potential Target That May Provide a New Approach to Melanoma Treatment**

Researchers at the National Cancer Institute (NCI) have released a new study, reported in the March 9 issue of the *Journal of Clinical Investigation*, which found a specific protein that is involved in inhibiting the development and metastasis of melanoma tumors in mouse and human skin models. Increased expression of the protein, SOX9, may also increase the sensitivity to retinoic acid, an agent used to treat other types of cancer. The SOX9 protein is a transcription factor, which is expressed in adult tissues, such as the brain, heart, and kidneys. Transcription factors, such as SOX9, are important regulators of essential biologic processes because they are able to control the expression of genes. Previous studies with SOX9 found that the protein is involved in regulating the differentiation of normal melanocytes, the cells in which melanoma originates, as well as in inhibiting the proliferation of human melanoma cells. The study, led by Dr. Thierry Passeron of NCI's Center for Cancer Research, analyzed the expression of SOX9 protein in normal human skin samples and in samples of nevi, primary, and metastatic melanoma tumors that had spread to other tissues. The researchers observed the highest expression of SOX9 in normal cells and a progressive reduction in expression as cells transitioned from the precancerous state to the most advanced stages of cancer. Subsequently, the investigators inserted the SOX9 gene into human melanoma cells and compared them to melanoma cells without the inserted gene. This analysis showed that cells without SOX9 formed tumors, whereas cells with SOX9 did not. These findings were also seen in mice injected with melanoma cells that either contained the inserted gene or did not. The researchers then determined that

the melanoma cells inserted with SOX9 gene were sensitive to retinoic acid, showing a dramatic reduction in proliferation compared to the cells without the gene. They also investigated whether the SOX9 protein could be activated or its expression increased, and found that melanoma cells exposed to prostaglandin D2 also had enhanced SOX9 activity. The results of this study have brought insight into the cellular changes that occur during the development of melanoma cells and have put forward a new therapeutic approach to melanoma.

### **Motexafin Gadolinium Combined with Whole Brain Radiotherapy Prolongs Time to Neurologic Response in Non-small Cell Lung Cancer**

Results of a phase III study reported by Mehta and colleagues in the March 15 issue of *International Journal of Radiation Oncology, Biology, Physics* showed that motexafin gadolinium (MGd) significantly prolonged the interval to neurologic progression in patients with non-small cell lung cancer with brain metastases who were receiving whole brain radiotherapy (WBRT). The international, randomized, phase III study randomized patients to WBRT with or without MGd. The primary endpoint, interval to neurologic progression, was determined by a centralized Events Review Committee who was blinded to the treatment. Investigators enrolled 554 patients; 275 were randomized to WBRT and 279 to WBRT plus MGd. Analysis showed that WBRT plus MGd, compared to WBRT alone, improved the interval to neurologic progression (15 months vs 10 months;  $P=.12$ ; HR=0.78) and the interval to neurocognitive progression ( $P=.057$ ; HR=0.78). The patients who received WBRT required more salvage brain surgery or radiosurgery than did the patients who received WBRT and MGd (54 vs 25 salvage procedures;  $P<.001$ )

Treatment with MGd was well tolerated, with 92% of intended doses administered. The most frequently reported MGd-related grade 3 or higher adverse events were liver function abnormalities (5.5%), asthenia (4%), and hypertension (4%). A statistically significant interaction between geographic region and MGd treatment effect and between treatment delay and MGd treatment effect was also observed. Researchers concluded that MGd produced a favorable trend in neurologic outcome with acceptable toxicity.