The latest advances in screening, treatment, and the prevention of cancer were discussed at the 38th Annual Meeting of the American Society of Clinical Oncology, held in Orlando, Florida from May 18 to 21, 2002. More than 25,000 cancer specialists, research scientists, and other health care professionals from around the world met to discuss important developments including the establishment of guidelines for adjuvant hormonal therapy in women with hormone receptor positive (HR+) operable breast cancer, based on findings from a landmark clinical trial; novel targeted therapies in patients with advanced cancers; a new method of delivery of $\beta$-radiation to unresectable liver cancer; new chemotherapeutic combinations for ovarian cancer and colorectal cancer; combination immunotherapy for advanced non-Hodgkin’s lymphoma; and new approaches for relieving drug-related adverse effects, such as loss of bone mineral density and chemotherapy-induced anemia.

Tamoxifen as Standard Adjuvant Hormonal Treatment

Speaker: Eric P. Winer, MD, Director of the Breast Oncology Center, Dana Farber Cancer Institute, and Associate Professor of Medicine, Harvard Medical School, Boston, Massachusetts.

Assessing the use of aromatase inhibitors as adjuvant therapy for women with hormone receptor positive (HR+) breast cancer, an American Society of Clinical Oncology panel stated that, based on data from the ongoing ATAC (Arimidex and Tamoxifen Alone or in Combination) trial, the panel considered the results of the trial and the extensive supporting data to be very promising, but insufficient to change the standard practice at this time. A five-year course of adjuvant tamoxifen remains the standard therapy for women with HR+ breast cancer.

The ATAC trial is a randomized, double-blind, multicenter trial involving 9,366 postmenopausal women with operable breast cancer, randomly assigned to anastrozole (Arimidex, AstraZeneca) 1 mg or placebo, tamoxifen (Nolvadex, AstraZeneca) 20 mg or placebo, or a combination of tamoxifen 20 mg and anastrozole 1 mg, once daily for five years. The primary endpoints of the study are recurrence-free survival and tolerability.

Early results, presented in December 2001, indicated an improvement in disease-free survival and a reduction in adverse events with anastrozole compared to tamoxifen, leading to an evidence-based technology assessment to determine whether the routine use of anastrozole or any of the aromatase inhibitors in the adjuvant breast cancer setting was appropriate for broad-based conventional use in clinical practice. The outcomes of interest included breast cancer-specific survival, overall survival, and net health benefit.

There are a number of significant considerations, however, concerning the ATAC findings. First, although the differences in disease-free survival are statistically significant, they are very small, and there was no advantage in the combination arm. Second, the median follow-up of patients is 33 months, with only one-third of patients having a follow-up of more than three years. Tamoxifen requires five years of therapy to see maximal benefits, and it is not known whether five years of anastrozole would be better or worse than tamoxifen. And although the number of short-term side effects is the same or less with anastrozole, there is an excess of fractures and musculoskeletal problems that could be exacerbated over a longer follow-up period. There also are no long-term toxicity data, and the effects of profoundly lowering estrogen levels are unknown. Finally, there are no confirmatory trials to date, although some are ongoing; so there is nothing with which to compare the ATAC’s findings.

Oral EGF Receptor Inhibitor for Advanced, Refractory NSCLC

Speaker: Ronald B. Natale, MD, Acting Medical Director, Cedars-Sinai Comprehensive Cancer Center, Beverly Hills, California.

Targeted therapy with the investigational oral epidermal growth factor (EGF) receptor inhibitor ZD1839 (Iressa, Astra Zeneca) was able to shrink tumors in some patients with advanced non-small cell lung cancer (NSCLC) who were resistant to treatment with more than two prior chemotherapeutic regimens containing platinum and docetaxel. This therapeutic approach also resulted in a clinically significant response in disease-related symptoms and quality of life (QOL) in almost all patients with radiologic responses and over half of the patients with stable disease.

Initially, a randomized, double-blind, phase II study (IDEAL 2) was designed to investigate safety, tumor response, and disease-related symptom response of daily oral ZD1839 250 mg/day or
500 mg/day in 216 patients with refractory, locally advanced or metastatic NSCLC. The trial was originally supposed to last two months but some patients were still on ZD1839 at 18 months. Disease-related symptoms were measured weekly using the Lung Cancer Subscale (LCS) of the FACT-L questionnaire, and QOL was measured monthly using FACT-L.

The overall symptom improvement rate was 43.1% for ZD1839 250 mg/day and 35.1% for ZD1839 500 mg/day, with a duration of improvement ranging up to over seven months. Furthermore, a positive correlation was observed between symptom improvement and objective tumor response at both levels. At 250 mg/day of ZD1839, 100% of patients who had an objective tumor response experienced improvement in disease-related symptoms and 81% of patients with stable disease showed symptom improvement. Furthermore, 86% of patients who had an objective response and 52% of those with stable disease had an improvement in QOL, much of which was maintained at day 90. In addition, not only was there a substantial improvement in symptoms, but the improvement occurred very rapidly, within nine to 10 days. Finally, improvement in disease-related symptoms was also associated with an increase in median progression-free and overall survival, compared to those who did not show improvement. In patients treated with ZD1839 250 mg/day, the median survival for patients with symptom improvement had not been reached after a median follow-up of 9.2 months, compared to 3.7 months for patients without improvement; with ZD1839 500 mg/day, the median overall survival times were 8.1 and 3.8 months, respectively. Similar results were recorded for progression-free survival (PFS).

Antiangiogenic Agent for Solid Tumors
Speaker: Virginia K. Langmuir, MD, Senior Clinical Scientist, Genentech, Inc., South San Francisco, California.

Successful long-term therapy with the novel anti-angiogenic agent bevacizumab (Avastin, Genentech), a humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF), is possible in patients with advanced solid tumors.

To reach these conclusions, a subset of 35 cancer patients with advanced cancer (17 colorectal, 12 non-small cell lung, five breast, and one prostate) who had received single-agent bevacizumab therapy or bevacizumab plus chemotherapy for at least one year were evaluated. Overall, 302 patients received bevacizumab therapy in one of six phase I and II trials. These 35 patients had received more than one year of treatment.

Twenty-three of those patients who received bevacizumab therapy for more than a year had an off-treatment observation period and then resumed treatment with bevacizumab when their disease progressed. Of these individuals, 22 patients (96%) had a best response of stabilization of disease (SD) or better during the first course of bevacizumab and 13 patients (57%) had SD or better during the second course.

Interestingly, 71% of patients who received more than one year of bevacizumab were still alive and, while the median survival of these patients has not yet been reached, it is at least 27.5 months and up to 43 plus months. This compared to a life expectancy of approximately one year in all of the patients enrolled in the phase I/II bevacizumab trials, because of the advanced nature of their disease.

90Yttrium-Labeled Glass Microspheres for Unresectable HCC
Speaker: Brian I. Carr, MD, Professor of Medicine, Director of the Liver Tumor Service, and Head of the Starzl Transplant Institute, University of Pittsburgh, Pittsburgh, Pennsylvania.

Glass beads that release highly targeted β-rays from 90yttrium (Therasphere, MDS Nordion) represent an effective and relatively non-toxic treatment option for patients with unresectable and unreplantable advanced-stage hepatocellular carcinoma (HCC) and cirrhosis.

To assess the efficacy and safety of this treatment approach, 36 unresectable HCC patients with cirrhosis and without baseline liver decompensation were treated with the 90yttrium-labeled glass microspheres delivered by catheter directly into the liver through a lobar hepatic artery. Each treatment is designed to deliver 125 to 150 Gray (Gy) per kg of liver. Re-treatments are given at not less than 60-day intervals, and a maximum of two treatments to each liver lobe is planned. Because β-radiation from the glass microspheres travels only 2.5 mm in liver tissue, the tumor-killing power is focused and the chance of damaging healthy tissue is reduced.

Tumor responses to treatment were assessed by CT (computer tomography) scans in 31 evaluable patients. Six patients exhibited a partial response (PR), 18 patients had SD, and disease progression was reported in seven patients. Although Kaplan-Meier estimates for patient survival were 71.4% for patients with Okuda stage-I patients, median survival for these Okuda stage-I patients treated with 90yttrium-labeled glass microspheres had not been reached at over 18 months of follow-up; these results approached that of patients undergoing surgical resection.

New Chemotherapeutic Combination for Ovarian Cancer
Speaker: Paul A. Vasey, MD, Medical Oncologist, Cancer Research UK Clinical Trials Unit, Beatson Oncology Center, Glasgow, Scotland, United Kingdom.

In a longer-term update of the Scottish Randomized Trial in Ovarian Cancer (SCOTROC) study, the chemotherapeutic combination of docetaxel (Taxotere, Aventis) and carboplatin (Para- platin, Bristol-Myers Squibb) demonstrated less neurotoxicity and was equally effective as the standard treatment of paclitaxel (Taxol, Bristol-Myers Squibb) and carboplatin when used as first-line treatment in patients with advanced ovarian cancer.

Of the 1,077 patients randomized at the start of the study to either docetaxel and carboplatin or paclitaxel and carboplatin, 1,074 were available for survival comparison, with the median follow-up of the surviving patients being 23 months; 95% were followed for at least 17 months. Median progression-free survival was 15.1 months in the docetaxel/carboplatin arm and 15.4 months in the paclitaxel/carboplatin arm. At 24 months,
the survival rate was 65.4% for patients treated with docetaxel and carboplatin and 69.8% for those on paclitaxel and carboplatin.

Using the ovarian-specific QOL questionnaire, patients treated with docetaxel and carboplatin reported significantly less joint pain and muscular tenderness than those treated with paclitaxel and carboplatin (33% vs. 48%) and less weakness in the legs or arms (33.9% vs. 47.7%). In addition, significantly less hair was observed (80% vs. 74%). Also, according to a structural neurological assessment tool, patients treated with docetaxel and carboplatin reported markedly less significant symptoms of neurotoxicity, such as tingling in the hands and numbness in fingers or toes during treatment, compared to those treated with paclitaxel/carboplatin. This difference was still evident at least 14 months after randomization.

**New First-Line Combination for Metastatic Colorectal Cancer**

**Speaker:** Josep Tabernero, MD, Medical Oncologist, Hospital Vall d’Hebron, Barcelona, Spain.

Capecitabine (Xeloda, Roche), an oral tumor-activated chemotherapeutic agent, when administered in combination with oxaliplatin (Eloxatin, Sanofi Synthelabo), a new platinum-based chemotherapeutic agent, is being recommended as first-line therapy for patients with metastatic colorectal cancer.

In an international, multicenter, phase II trial, 96 patients with confirmed, measurable, metastatic colorectal cancer were treated with capecitabine 1000 mg/m² twice daily on days one to 14, plus oxaliplatin 130 mg/m² as a two-hour infusion on day one, comprising a 21-day cycle. Treatment was administered until disease progression or for 11 cycles in patients with tumor response or SD, after which time continuation of treatment was allowed.

To date, 20 months after study start and at the end of the minimum follow-up period of 12 months after the last patient was enrolled, the results show an objective response rate of 55%, with two complete responses and 51 PRs. An additional 32% of the patients had stable disease. The median duration of tumor response was 8.9 months. Notably, disease stabilization has lasted more than three months in all 31 patients achieving this outcome. Median time of progression-free survival is 7.6 months, with 13 patients yet to progress and three patients still undergoing treatment. Median overall survival is more than 16 months, with 57 patients still alive.

The impressive anti-tumor activity observed in this study confirms that capecitabine could replace infusional 5-fluorouracil and leucovorin as the standard combination partner for oxaliplatin in first-line therapy for colorectal cancer. This simplified regimen also has the added advantage of requiring only one clinic visit for oxaliplatin administration every three weeks, thereby substantially improving convenience over present standard regimens.

**Combination Immunotherapy for Advanced NHL**

**Speaker:** Deborah Hurst, MD, Senior Director of Clinical Development, Chiron Corporation, Emeryville, California.

Low-dose interleukin-2 (IL-2) (Proleukin, Chiron), when administered in combination with rituximab (Rituxan, Genentech/IDEC) produces positive clinical responses in patients with advanced non-Hodgkin’s lymphoma (NHL), augmenting the antitumor activity of rituximab via expansion and activation of natural killer (NK) cells.

To establish the maximum tolerated dose (MTD), evaluate antitumor responses, and attempt to correlate clinical response with an increase in NK cell number and NK-mediated functional activity, 31 patients with relapsed or refractory stage III or IV advanced B-cell NHL, after a median of four previous treatment courses, were enrolled into two dose-ranging studies. These studies were designed to determine the MTD for IL-2 given either daily (study 1) or three times per week (study 2) by subcutaneous self-injection during weeks two to five in combination with a fixed dose of 375 mg/m² of rituximab during weeks one to four. Study 1 included 17 evaluable patients tested with daily doses ranging from 2.0 to 7.5 million international units (MIU) of IL-2, whereas study 2 included 13 evaluable patients who were given doses of IL-2 at 4.5 MIU, 10 MIU, 14 MIU, and 18 MIU, three times per week.

Combination immunotherapy with IL-2 and rituximab proved to be safe and well-tolerated. The MTD of IL-2 given with rituximab was 6 MIU once daily and 14 MIU when administered three times per week. Overall, 12 patients responded in the two study groups, with five partial responses reported with the 6 MIU once-daily dose of IL-2 and in seven out of 10 patients who completed treatment with an IL-2 dose of 10 MIU or greater given three times weekly.

In study 2, the dose-response of NK cell count increases after subcutaneous IL-2 treatment three times per week. Furthermore, the NK cell counts, following treatment with this combination immunotherapeutic approach, correlate at week 10 with the tumor response, with this killing activity being maintained beyond treatment in those patients who respond.

**Nonsteroidal Antiandrogen in Prostate Cancer Treatment**

**Speaker:** Paul R. Sieber, MD, Urologist, Urological Associates of Lancaster Ltd., Lancaster, Pennsylvania.

Bicalutamide (Casodex, AstraZeneca) treatment administered to men with localized or locally advanced prostate cancer, for whom immediate hormonal ablation is indicated, maintains bone density, whereas those receiving medical castration experienced a progressive loss of bone density during the two-year study period. Furthermore, although the men in the medical castration group had initial muscle mass deterioration, those treated with bicalutamide reported no such problem.

To evaluate changes in bone mineral density and fat-free mass during bicalutamide treatment or medical castration, 103 men with T1 to T4 prostate cancer, for whom immediate hormonal ablation was indicated, were randomized to bicalutamide 150 mg daily or medical castration and followed over two years. Primary endpoints were lumbar spine and hip bone mineral density and fat-free mass at the 96-week follow-up. At the 24, 48, 72, and 96-week assessments, bone mineral density was maintained relative to baseline in bicalutamide-treated patients. In contrast, a progressive 4% to 5% loss, compared to
baseline, was seen over the two-year observation period in the men who received medical castration. Also, in the medical castration group, the fat-free mass initially fell by almost 4%, a significant difference from baseline. This was not the case in the patients treated with bicalutamide, which suggests that there was no deterioration in muscle mass for bicalutamide-treated patients.

**Novel Erythropoietic Agent for Anemia in Cancer**

**Speaker:** Dusan Kotasek, MD, Medical Oncologist, Ashford Cancer Centre, Ashford, Australia.

Results from a multicenter, international dose-finding study point out that darbepoetin alfa (Aranesp, Amgen), a new erythropoietic agent with a longer serum half-life and greater in vivo biological activity than standard recombinant human erythropoietin (rHuEPO), can be safely and effectively administered much less frequently than rHuEPO for the treatment of anemia in patients with solid tumors receiving chemotherapy.

Because many chemotherapy regimens are administered once every three weeks or once every four weeks, an erythropoietic agent administered on a similar schedule to chemotherapy would facilitate the treatment of anemia and fatigue in these cancer patients. A study, therefore, was carried out to assess the efficacy and safety of darbepoetin alfa given subcutaneously once every three weeks or once every four weeks, compared to placebo, for 12 weeks. A total of 405 anemic patients receiving chemotherapy were randomly assigned to placebo or darbepoetin alfa every three weeks (4.5–15 mcg/kg) (249 patients) or placebo or darbepoetin alfa every four weeks (9–18 mcg/kg) (156 patients), in a four-to-one randomization ratio favoring darbepoetin alfa.

At 12 weeks follow-up, hematopoietic responses between 51% and 71% were seen up to the 12 mcg/kg doses, whether darbepoetin alfa was given once every three weeks or once every four weeks. Thereafter, there appeared to be a plateau in the response. The response in the placebo group was 31%. In addition, there was a trend toward a more rapid response with higher doses of darbepoetin alfa, in terms of hemoglobin, and the need for transfusions was universally lower in the darbepoetin alfa groups. Finally, there was no loss of dose efficacy with less frequent administration for a darbepoetin alfa dose of 6.75 mcg/kg every three weeks and 9 mcg/kg every four weeks; both schedules were well-tolerated.